

Rapid immunoassay and clinical evaluation of the SARS-CoV-2 antibody assay on the real express-6 analyzer

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Abstract

We developed a rapid and simple magnetic chemiluminescence enzyme immunoassay on the Real Express-6 analyzer, which could simultaneously detect immunoglobulin G and immunoglobulin M antibodies against SARS-CoV-2 virus in human blood within 18 min, and which could be used to detect clinical studies to verify its clinical efficacy. We selected blood samples from 185 COVID-19 patients confirmed by polymerase chain reaction and 271 negative patients to determine the clinical detection sensitivity, specificity, stability, and precision of this method. Meanwhile, we also surveyed the dynamic variance of viral antibodies during SARS-CoV-2 infection. This rapid immunoassay test has huge potential benefits for rapid screening of SARS-CoV-2 infection and may help clinical drug and vaccine development.

KEYWORDS

antibody, immunoassay, rapid, SARS-CoV-2

1 | INTRODUCTION

Near the end of 2019, many cases of unexplained pneumonia occurred in Wuhan City, Hubei Province. The illness spread quickly throughout the city and eventually over the entire country.¹ By early January 2020, it was confirmed that it was an acute respiratory infection that was caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the disease being named coronavirus disease 2019 (COVID-19).² However, the virus soon found its way around the world, and by the beginning of March 2020, the World Health Organization (WHO) officially labeled the disease as a pandemic.³ As of April 2021, SARS-CoV-2 had spread to 223 countries, and there have been 147 539 302 confirmed cases of SARS-CoV-2, including 3 116 444 deaths.⁴ SARS-CoV-2 occurred by human-to-human transmission and mostly affected elderly and immunocompromised persons.⁵ The rapid spread of SARS-CoV-2 has caused considerable damage to public health and the economy.^{6,7} In

the absence of treatment for this virus, accurate and rapid diagnosis of SARS-CoV-2 is the cornerstone of the efforts to control the epidemic, and save people's lives. Currently, the detection of viral nucleic acid real-time polymerase chain reaction (RT-PCR) has become the current standard diagnostic method for the diagnosis of COVID-19.^{8,9} However, the performance of RT-PCR depends on many factors, such as the sample collection skill, sample type, different disease progression, and the quality and consistency of the PCR assay used.^{10,11} Therefore, there is an urgent need for a rapid, simple to use, sensitive, and accurate test to identify infected patients of SARS-CoV-2 to prevent virus transmission.

Early diagnosis, isolation, and treatment are essential to cure the disease and control the epidemic. Antibody detection is of great significance in the diagnosis of infected patients, and helps to identify the stage of the infectious.¹² Based on these, we developed a magnetic chemiluminescence enzyme immunoassay test product, which could detect IgG and IgM simultaneously in human blood within

18 min. Here, we retrospectively described 456 serum samples through IgG/IgM antibody detection. All samples are from HwaMei Hospital, University of Chinese Academy of Sciences. This study may provide a reference for the clinical profile of SARS-CoV-2 patients confirmed by antibody detection, and further to investigate the potential relationship between immune antibodies and disease progression.

2 | METHODS

2.1 | Data collection

A total of 456 samples presented to the hospital with laboratory-confirmed SARS-CoV-2 infection in HwaMei Hospital, University of Chinese Academy of Sciences, Zhejiang, China, by April 2, 2020. The diagnosis of SARS-CoV-2 was based on guidelines issued by the National Health Commission of the People's Republic of China and the interim guidance from the World Health Organization. All enrolled patients were confirmed to be infected with SARS-Cov-2 by RT-PCR of samples taken from upper nasopharyngeal swabs. Information was collected on dates of illness onset, clinical characteristics, chest computed tomographic (CT) scan. The 456 blood samples collected during the hospitalization were tested for IgG and IgM levels against SARS-CoV-2. Control blood samples from normal people with non-epidemiological history. The plasma samples were separated after centrifugation at 3000 rpm for 5 min, and then frozen and stored at -70°C .

2.2 | Antibody detection

The SARS-CoV-2 antibodies (IgG and IgM) of the subjects were detected using the SARS-CoV-2 IgG/IgM test kit by Ningbo Institute of life and Health Industry, University of Chinese Academy of Sciences. The IgG and IgM detection was developed based on a magnetic chemiluminescence enzyme immunoassay. Antibody levels are presented as the measured chemiluminescence values divided by the cutoff. The cutoff value for a positive result sample with IgG and IgM concentration more than equal to 278.8 and 6.6 U/ml are considered positive. The tests were conducted on an automated magnetic chemiluminescence analyzer (The Real Express-6) according to the manufacture's instructions. All tests were performed under strict biosafety conditions. The dynamics of antibodies with the disease progression were analyzed.

2.3 | Stability of the SARS-CoV-2 antibody test kit

To establish the stability of the kit, two samples were stored for 0, 1, 4, 7, 15, 21, 28, and 60 days at room temperature, $2-8^{\circ}\text{C}$ and -20°C . We redetected the IgG and IgM concentrations of known positive and negative plasma samples with the SARS-CoV-2 antibody test kit.

2.4 | Precision of the SARS-CoV-2 antibody test kit

A negative samples pool, approximately 30 ml, was prepared by combing leftover antibody-negative samples ($\text{IgG} < 278.8 \text{ U/ml}$, $\text{IgM} < 6.6 \text{ U/ml}$). Similarly, critical positive ($278.8 \text{ U/ml} < \text{IgG} < 320 \text{ U/ml}$, $6.60 < \text{IgM} < 7.59 \text{ U/ml}$), medium/strong ($\text{IgG} > 320 \text{ U/ml}$, $\text{IgM} < 7.59 \text{ U/ml}$) positive pool, approximately 30 ml, were prepared by diluting a positive clinical sample with a partial negative sample. Aliquots of 400 μl were prepared from each pool and frozen at -20°C . Two controls and three samples containing different concentrations of analysis were assayed in duplicate, with two runs per day, one lot of reagent for each run, and two replicates per run. Repeatability and Between-Lot precision study was performed by assaying each sample and one lot of reagent 10 times. A between-day precision study was performed by thawing out each respective aliquot to room temperature and running over 20 days. The mean and SD were calculated for each sample, and the coefficient of variation (CV) was determined as $\text{CV} (\%) = (\text{SD} \times 100) / \text{mean}$.

2.5 | Cross-reactivity of the SARS-CoV-2 antibody test kit

In total, some samples from patients with Influenza A virus antibodies, Influenza B virus antibodies-positive samples, Parainfluenza virus antibodies-positive samples, respiratory syncytial virus antibodies-positive samples, Adenovirus antibodies-positive samples, EBV VCA IgG-positive samples, EBV VCA IgM-positive samples, CMV IgG-positive samples, CMV IgM-positive samples, *Mycoplasma pneumoniae* IgM-positive samples, *Chlamydia pneumoniae* IgM-positive samples, and ANA-positive samples were analyzed by SARS-CoV-2 antibody and colloidal gold test kit to assess the extent of cross-reactivity.

2.6 | CT examination and image analysis

The patients underwent chest CT examinations on admission. All CT images were reviewed independently by two experienced radiologists. The image features included lesion distribution, local or bilateral patchy shadowing, lesion density, and interstitial abnormalities. Additionally, the CT scan was obtained every 5 days or in case of deterioration during hospitalization.

2.7 | Statistical analyses

Statistical analyses and graphical presentations were conducted with GraphPad Prism version 7.0 (GraphPad Software, Inc.). Categorical variables are expressed as numbers (%) and were compared by Fisher's exact test. The IgG and IgM antibody responses in individual patients groups were determined by Student's test. The predictive

power of different variables was assessed using the receiver operating characteristic curve (ROC). $p < 0.05$ were considered statistically significant.

3 | RESULTS

3.1 | The sensitivity and specificity studies

To test the detection sensitivity and specificity of the SARS-CoV-2 antibody test, a total of 456 samples were tested: 185 (positive) clinically confirmed (including PCR test) SARS-CoV-2-infected samples and 271 (negative) non-SARS-CoV-2-infected samples. ROC analysis was performed and demonstrated that the IgG and IgM levels could be used to distinguish patients with SARS-CoV-2 positive from patients with normal individuals through the area under the ROC curve (AUC) of 0.968 and 0.949. The sensitivity and specificity of an IgG level were estimated to be 91.8% and 96.7%. Furthermore, the sensitivity and specificity of an IgM level were estimated to be 87.5% and 94.5% (Figure 1).

3.2 | The stability studies

To evaluate the stability of the SARS-CoV-2 antibody test kit, we tested the IgG and IgM levels of two samples ($n = 2$) at three different temperatures (Figure 2). When stored at room temperature, these samples were stable for 7 days, and their IgG and IgM levels were the same as at room temperature. In addition, the samples were stable for at least 60 days when stored at -20°C , and were consistent with the IgG and IgM levels at the first two temperatures.

3.3 | The cross-reactivity studies

The cross-reactivity study for SARS-CoV-2 IgG and IgM test kits were designed to evaluate potential cross-reactants and were shown in Table 1. The cross-reaction of the IgG and IgM test kit with Influenza A virus antibodies was 8.33%, which was lower than of colloidal gold 25.00%, whereas the IgG presented a cross-reaction of 0.00% with respiratory syncytial virus antibodies, and lower than the colloidal gold and IgM 6.67%. The cross-reaction of both IgG and IgM were 11.76% with EBV VCA IgM, and lower than the colloidal gold 17.65%. Similarly, the cross-reaction of the IgG and IgM were 10.00% and 0.00% for the CMV IgG, when compared with that of colloidal gold 20.00%. In addition, the cross-reaction of both IgG and IgM were 7.14% and 14.29% for the *C. pneumoniae* IgM, which were significantly lower than that of colloidal gold 21.43%. Taking together, these results indicate the low cross-reactivity between the IgG and IgM, when compared with the colloidal gold.

3.4 | Precision study of SARS-CoV-2 IgG and IgM test kit

To investigate the precision of the SARS-CoV-2 IgG and IgM test kit, we detected three aspects: repeatability, between-lot, and between-day. The results are summarized in the following Table 2. The negative control sample on each of two lots with two runs per day and two measurements per run, showing a mean concentration of IgG and IgM were 126.696 U/ml and 5.610 U/ml (CV = 0.00%), and the detection rate was 100%. For repeatability, the repeatability precision analysis was repeated 10 times, showing a mean concentration of IgG and IgM were 293.787 U/ml (CV = 2.82%) and 7.599 U/ml (CV = 5.99%) for the critical positive, and the concentration of IgG and IgM were 4966.105 U/ml (CV = 2.37%) and 192.099 U/ml (CV = 3.11%) for the medium/strong positive. Moreover, for the between-lot, yields of the CV of IgG and IgM were 1.23% and 0.84% for critical positive, and the CV of IgG and IgM were 1.24% and 1.70% for the medium/strong positive. Similarly, in the between-day assay, the CV of IgG and IgM were 0.75% and 1.81% for critical positive, and the CV of IgG and IgM were 0.38% and 0.97% for medium/strong positive. In general, the CV of the positive groups of the indices was below 4%. A lower CV is closely related to higher repeatability or reproducibility.

3.5 | Antibody level and Chest CT features

The patients were hospitalized on February 5, 2020, after 3 days' fever. Longitudinal antibody changes in one representative patient of the types of seroconversion are shown in Figure 3A. One patient with confirmed COVID-19 was followed up until discharge. The patient achieved seroconversion of IgG or IgM within 22 days after symptom onset. We found that the IgG seroconversion was earlier than that of IgM. In the pooled analyses on all involved patients, the average

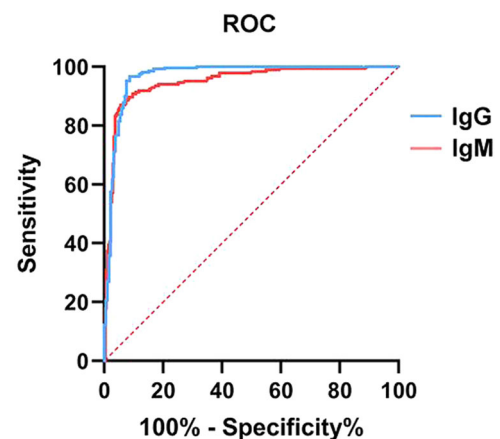


FIGURE 1 Receiver operating characteristic curves for prediction of SARS-CoV-2 by IgG and IgM levels. IgG, immunoglobulin G; IgM, immunoglobulin M; ROC, receiver operating characteristic curve

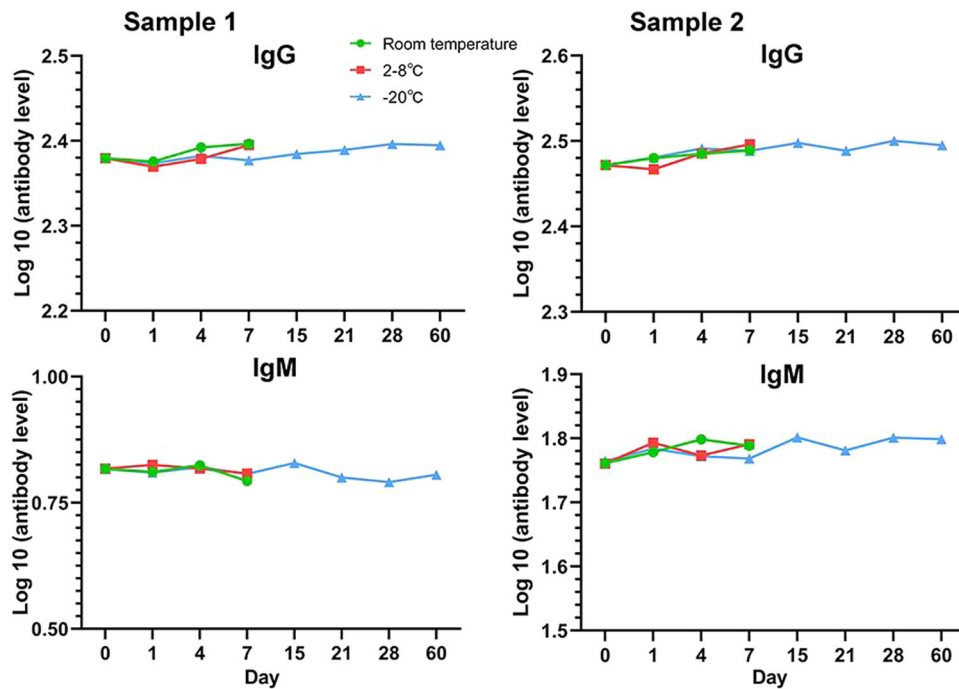


FIGURE 2 Divided the serum of the two samples into three equal parts and stored them at three different temperatures. The specimens were subjected to SARS-CoV-2 serologic testing on days 0–60 after collection. IgG, immunoglobulin G; IgM, immunoglobulin M

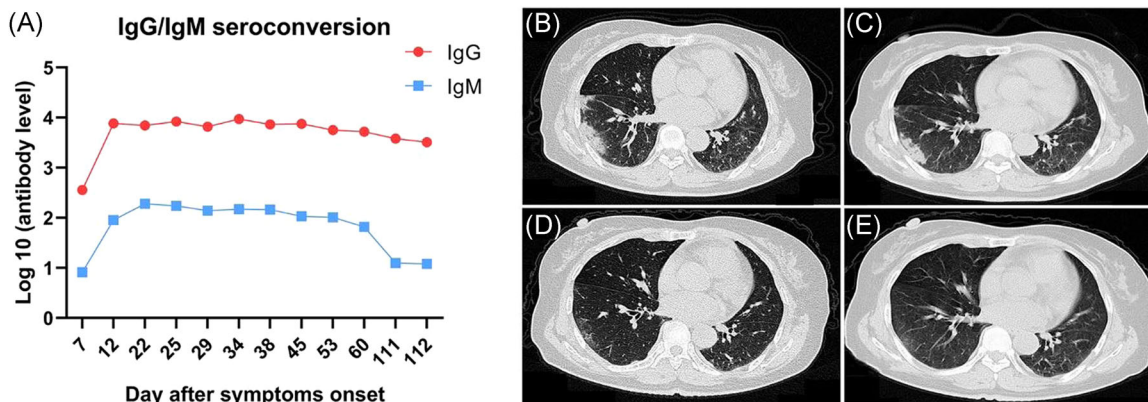


FIGURE 3 Antibody seroconversion time and chest CT image of a 66-year old woman with COVID-19 pneumonia. (A) The day of seroconversion for one patient is plotted. (B–D) The CT scan was obtained from February 5, 2020, to 27, 2020 after the onset of COVID-19 symptoms. CT, computed tomography

antibody levels showed a marked increase since about 7 days after onset and continuously elevated during the next 14 days. In addition, consolidation on chest CT. (Figure 3B) Chest CT on admission showed multiple patches of fuzzy shadows in both lungs, especially in the lower lungs (February 5, 2020). (Figure 3C) After 5 days' treatment, chest CT images showed some lesions were absorbed (February 10, 2020). (Figure 3D) CT scan on February 21, 2020, showed lesions at the upper lobe of bilateral lungs were substantially absorbed. Meanwhile, (Figure 3E) CT scan on February 27, 2020, showed that the lesion was easily absorbed as in (Figure 3D). In summary, the level of antibody detection is consistent with CT results.

4 | DISCUSSION

In this study, the median age was 53 years (ranging from 16 years to 90 years, and 52.74% of the patients were male. To investigate the efficacy of the SARS-CoV-2 IgG/IgM test kit, samples from 185 SARS-CoV-2 participants who were nucleic acid-positive and 271 healthy control were analyzed. The positive samples showed a much higher level of IgG, compared with normal controls. An analysis of the ROC curve for IgG demonstrated an optimal cut-off value of 278.8 U/ml ($p < 0.001$, sensitivity of 91.8% and specificity of 96.7%). The AUC was 0.968. For IgM, the results showed that the AUC reached 0.949 ($p < 0.001$). The optimal cutoff value was 6.6 U/ml,

TABLE 1 Cross-reactivity of non-SARS-CoV-2 viruses

Serum	No. of cases	IgG test kit		IgM test kit		colloidal gold	
		No. of positive	Positive rate (%)	No. of positive	Positive rate (%)	No. of positive	Positive rate (%)
Influenza A virus antibodies	12	1	8.33	1	8.33	3	25.00
Influenza B virus antibodies	12	0	0.00	1	8.33	2	16.67
Parainfluenza virus antibodies	10	1	1.00	0	0.00	2	20.00
Respiratory syncytial virus antibodies	15	0	0.00	1	6.67	1	6.67
Adenovirus antibodies	16	0	0.00	1	6.25	1	6.25
EBV VCA IgG	9	0	0.00	1	11.11	2	22.22
EBV VCA IgM	17	2	11.76	2	11.76	3	17.65
CMV IgG	10	1	10.00	0	0.00	2	20.00
CMV IgM	10	0	0.00	2	20.00	2	20.00
<i>Mycoplasma pneumoniae</i> IgM	14	0	0.00	2	14.29	3	21.43
<i>Chlamydia pneumoniae</i> IgM	14	1	7.14	2	14.29	3	21.43
ANA	20	1	5.00	2	10.00	2	10.00

TABLE 2 Precision study of the SARS-CoV-2 antibody assay

Sample	Mean (U/ml)		N	Repeatability (CV%)		Between-Lot (CV%)		Between-Day (CV%)	
	IgG	IgM		IgG	IgM	IgG	IgM	IgG	IgM
Negative	126.696	5.610	80	NA	NA	NA	NA	NA	NA
Critical positive	293.787	7.599	80	2.82%	5.99%	1.23%	0.84%	0.75%	1.81%
Medium/strong positive	4966.10-5	192.09-9	80	2.37%	3.11%	1.24%	1.70%	0.38%	0.97%

with sensitivity and specificity values of 87.5% and 94.5%, respectively. The stability of the SARS-CoV-2 IgG/IgM test kit is better and less affected by temperature. In the cross-reaction, we used the SARS-CoV-2 IgG/IgM test kit and the colloidal gold to detect the IgG and IgM levels of 10 viruses. We found that the positive rate of the IgG/IgM kit was lower, which was lower than the colloidal gold result. For precision, the negative detection rate of negative samples was 100%, the positive detection rate of borderline positive samples was more than 95%, and the positive detection rate of medium/strong positive samples was 100% and $CV \leq 15\%$. Meanwhile, the IgG positive rate was always higher than IgM, and this phenomenon was also observed in a study by Zhang et al.¹³ Based on the above, we analytically and clinically evaluated the qualitative and report that it performs reliably, precisely, consistent with manufacturer specifications

Currently, virus nucleic acid RT-PCR, CT imaging, and hematology parameter are the primary tools for clinical diagnosis of the infection.¹⁴ Chest CT has been proposed as an ancillary approach for screening individuals with suspected COVID-19 pneumonia during the epidemic period and monitoring treatment response according to the dynamic radiological changes.¹⁵

Although detection of the RNA by either RT-PCR or sequencing is the gold standard for COVID-19 diagnosis, it still suffers from some limitations such as being labor-intensive and time-consuming.^{16,17} Testing the SARS-CoV-2 specific antibodies in the blood of patients is a good choice for rapid, simple, and highly sensitive diagnosis of SARS-CoV-2.¹⁸ Serologic tests could provide much-needed insight into the adaptive immune response against SARS-CoV-2, the exposure history of an individual, transmission patterns, and potential donors of convalescent plasma.¹⁹ Therefore, we also study the dynamic variance of viral antibodies during SARS-CoV-2 infection. We found that the IgG seroconversion was earlier than that of IgM and this is similar to Long et al.²⁰ On the contrary, the antibody levels increased rapidly during the first two weeks. Studies have found that IgM antibodies appear about 2 weeks after infection, while IgG antibodies last for months or even years.²¹ Another study showed that the IgM antibody appeared within 1 week after SARS-CoV-2 infection, and this antibody was present in the body for 1 month or even longer, the IgG antibody is usually produced in about 10 days.¹² In addition to the diagnosis value, our study revealed a strong negative correlation between clinical severity and

antibody levels 2 weeks after illness onset. The results suggested that antibodies may have begun to clear the virus. The human antibody response which is crucial for the clearance of the initial virus infection has been widely used to help diagnose virus infection.²² The IgM and IgG could be used to understand the epidemiology of SARS-CoV-2 infection and to help to determine the level of humoral immunity in patients.²³ Indeed, being able to receive information about the antibody concentration and time kinetics of humoral response is very important for diagnostic, prognostic, and therapeutic applications.

In summary, the new rapid SARS-CoV-2 IgG/IgM antibody test kit could detect IgG and IgM, it could be used for both early diagnosis and for monitoring during treatment. However, our study has several limitations. First, most of the serum samples we collect are mainly taken around 14 days after the onset of symptoms. Due to the lack of initial samples of virus infection, there may be an impact on the sensitivity and specificity of the initial samples. Second, limited to this study, we only selected one patient, and it is necessary to investigate the relationship between the dynamic change of antibody and the course of COVID-19 in a large sample size study.

5 | CONCLUSION

We developed a rapid SARS-CoV-2 IgG/IgM antibody test using magnetic chemiluminescence enzyme immunoassay technology. The detection time is less than 18 min to generate results and determine whether SARS-CoV-2 infection has occurred recently. The results of this study show that the test is sensitive and specific, and the operation is simple and fast. Then we investigated possible cross-reactivity with other corona-virus and influenza viruses, and also compared antibody levels at different stages of SARS-CoV-2 infection. This rapid test has huge potential benefits for rapid screening of SARS-CoV-2 infection and may help clinical drug and vaccine development.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Ting Cai designed the study, Zhang Shun analyzed the data and drafted the manuscript. Yingjun Ning, Yejing Rong, Yaxing Nie, Zi Xiong, Rui Li, Tong Jin contributed to the acquisition of subjects and data. Zhang Shun contributed to the analysis and

interpretation of data. Ting Cai has primary responsibility for the final content.

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