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Zhengtu Li

The first affiliated hospital of Guangzhou Medical University

Shaoqiang Li

The first affiliated hospital of Guangzhou Medical University

Youwei Wang

Sichuan Academy of Medical Science

Yongkang Liao

The first affiliated hospital of Guangzhou Medical University

Hui Chen

Shenzhen Bao an District Songgang Peoples Hospital

Jing Cheng

The first affiliated hospital of Guangzhou Medical University

Ye Lin

The first affiliated hospital of Guangzhou Medical University

Zhaoming Chen

The first affiliated hospital of Guangzhou Medical University

Kangjun Sun

Jiaangsu Medomics Medical Technology Co. Ltd, Nanjing

Min Zhang

The first affiliated hospital of Guangzhou Medical University

Mindie Wang

The first affiliated hospital of Guangzhou Medical University

Xinni Wang

The first affiliated hospital of Guangzhou Medical University

Xinyan Yang

The first affiliated hospital of Guangzhou Medical University

Wensheng Cai

Maruzen Yushodo Kabushiki Kaisha

Yangqing Zhan

The first affiliated hospital of Guangzhou Medical University

Shiyue Li

The first affiliated hospital of Guangzhou Medical University

Nanshan Zhong

The first affiliated hospital of Guangzhou Medical University

Feng Ye (✉ tu276025@gird.cn)

The first affiliated hospital of Guangzhou Medical University

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Title page

Rapid screening diagnosis of SARS-CoV-2 infection with IgM-IgG combined antibody test using peripheral blood

Zhengtu Li^{1*}, Shaoqiang Li^{1*}, Youwei Wang^{2*}, Yongkang Liao¹, Hui Chen³, Jing Cheng¹,
Ye Lin¹, Zhaoming Chen¹, Kangjun Sun⁴, Min Zhang¹, Mindie Wang¹, Xinni Wang¹,
Xinyan Yang¹, Wensheng Cai⁴, Yangqing Zhan¹, Shiyue Li¹, Nanshan Zhong¹, Feng
Ye^{1#}

¹State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China

²Department of Clinical Laboratory, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu 610072, China

³Shenzhen Bao'an District Songgang Peoples' Hospital, Shenzhen 518105, China

⁴Jiangsu Medomics Medical Technology Co., Ltd, Nanjing 210061, China

* Contributed equally

Corresponding to:

Prof. Feng Ye, the First Affiliated Hospital of Guangzhou Medical University of Guangzhou Medical University, 151 Yanjiang Xi Road, Guangzhou, Guangdong 510120, China. Tel.: +86-20-83062898; Fax: +86-20-83062898. E-mail: tu276025@gird.cn, or yefeng@gird.cn.

Running Title:

Rapid screening diagnosis for SARS-CoV-2 infection

Key points:

1. There were higher sensitivity and specificity of the rapid IgM-IgG combined antibody test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using peripheral blood as a point-of-care testing (POCT) assay.
2. The POCT assay also can detect IgM and IgG antibodies of SARS-CoV-2 in asymptomatic carriers.
3. The POCT assay can be used for rapid screening of SARS-CoV-2 infection.

Abstract

Background: Rapid and convenient screening for identification of SARS-CoV-2 infected individuals are key to prevent and control this pandemic.

Methods: The peripheral blood samples were collected from coronavirus disease 2019 (COVID-19) patients and asymptomatic carriers to evaluate the test characteristics of the IgM-IgG combined assay for SARS-CoV-2 compared to that of serum samples and enzyme-linked immunosorbent assay (ELISA). Close contacts, healthcare workers and workforces were recruited and screened using this assay.

Results: The sensitivity of the rapid IgM-IgG combined antibody test for SARS-CoV-2 using peripheral blood (used as a POCT) was 97.0% and the specificity was 99.2%, which was consistent with the result obtained using serum sample (consistency is about 100%). Furthermore, this POCT assay also can detect IgM and IgG antibodies of SARS-CoV-2 in asymptomatic carriers, with 19 of the 20 RT-PCR confirmed asymptomatic carriers testing positive. Therefore, this POCT assay was used for population screening of SARS-CoV-2 infection diagnosis. First, it found 4 positive close contacts among the 10 cases, and there were three IgM positive cases and one IgG positive case among them. It is worth noting that the IgM positive cases also tested positive for the nucleic acid of the SARS-CoV-2. Second, there was one IgM positive assay among the 63 healthcare workers, but RT-PCR of SARS CoV-2 was negative. Third, for workforces screening, there were no positive cases.

Conclusions: The IgM-IgG combined antibody test of SARS-CoV-2 can be used as a POCT for rapid screening of SARS-CoV-2 infection.

Keywords: COVID-19; IgM-IgG antibody; peripheral blood; rapid screening

Background

COVID-19 has spread rapidly around the world since its outbreak in December 2019, leading to more than 10 million cases in over 160 countries up to 29 June 2020, furthermore, the WHO reassessment of global risk was deemed to be very high.[1] And the biggest challenge for effective prevention and control of COVID-19 pandemic was how to quickly and accurately identify both symptomatic and asymptomatic carriers of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in the general population. Currently, viral nucleic acid real-time polymerase chain reaction (RT-PCR) has been the diagnostic standard for the SARS-CoV-2 infection.[2, 3] However, the current RT-PCR assays have many limitations: 1). although RT-PCR is rapid and sensitive/specific, it has a long turnaround time and is operationally complicated, often taking upwards of 2-3 hours to produce results; 2) RT-PCR testing requires certified laboratories, expensive equipment and highly-trained technicians to perform the assay; 3) RT-PCR may produce false negative results,[4, 5] and there are considerable differences in sensitivity of RT-PCR for different specimens.[6] As a result, RT-PCR is not suitable to be a POCT test for rapid screening of SARS-CoV-2 infection.

Blood specific antibodies, including IgM and IgG of SARS-CoV-2, have also been used for the diagnosis of SARS-CoV-2 infection.[2, 3] Specific antibody testing for SARS-CoV-2 has been as an ideal choice for the diagnosis of COVID-19 as it is simple to conduct and has both a quick turnaround time and high sensitivity. It is widely accepted that IgM provides the initial humoral immune response during viral infections, prior to the generation of the adaptive, high affinity IgG antibodies that are important for long term immunity and immunological memory.[7] The acute antibody response to SARS-CoV-2 infection is similar to many other acute viral infections.[8, 9] After the body has been infected with SARS-CoV-2, IgM antibodies are produced, such that increases in the level of IgM are markers of a recent infection. The production of IgG antibodies occurs later in the disease course and is an indicator of previous infections. The simultaneous detection of IgM antibody and IgG antibody can distinguish acute and previous infections[8]. Thus, the rapid detection of both IgM and IgG antibodies

will add value to the diagnosis and treatment of COVID-19. In our previous study, we have designed a rapid IgM-IgG combined antibody test kit for diagnosis of SARS-CoV-2 infection. It also has been that the test can be performed rapidly (<15 min) and conveniently using peripheral blood samples to detect SARS-CoV-2 infection.[10] However, there were some limitations in our previous study: 1) insufficient number of COVID-19 cases using peripheral blood sampling 2) lack of data to confirm that it can be used for asymptomatic carriers diagnosis, 3) and for as a POCT detection, and screening for SARS-CoV-2 infection. Therefore, we designed and carried out this study to address these limitations using IgM-IgG combined antibody test.

Methods

Study oversight and design

A flowchart outlining the milestones in the study is shown in Figure 1.

Targeted testing

COVID-19 patients, confirm by RT-PCR positive of SARS-CoV-2 and whose clinical and virological characteristics will be reported in other papers, were recruited in the study to determine the efficacy of IgM-IgG combined antibody test. The group included both symptomatic individuals, who have clinical symptoms of cough, fever, myalgias, or shortness of breath, and the onset time more than seven days before antibody tested, and asymptomatic carriers who confirmed by RT-PCR positive of SARS-CoV-2.

Population screening

Population screening focused on the following three groups of individuals: 1) close contacts either symptom-free or had mild symptoms, but had contact with confirmed COVID-19 patients. 2) Healthcare workers who took care of COVID-19 patients for extended periods of time. 3) Workforces who had recent exposure to high-risk areas and needed to be ruled out SARS-CoV-2 infection before returning to work. Before IgM/IgG test, all participants were required to self-quarantine for more than 14 days either after last contact with confirmed COVID-19 patients or come from high-risk areas.

Participants positive for SARSCoV-2 were required to self-quarantine, then they were retested by RT-PCR assay for SARS-CoV-2. If the RT-PCR results were positive, they continued to be quarantined and treated until they were RT-PCR negative.

IgM and IgG antibody of SARS-CoV-2 was detected

Peripheral blood testing

Just prior to testing, the pouched device was opened, and an alcohol disinfected finger from the study subject was pricked with a disposable needle. Approximately one drop of blood (about 15 μ L) was squeezed out and pipetted into the sample port to which 2-3 drops (70-100 μ L) of dilution buffer was added to drive capillary action along the strip. Results were obtained 10-15 minutes later (Fig. 2).

ELISA assay

Anti-Human IgM (μ -chain specific) antibody or N protein of SARS-CoV-2 (IgG) was used as the coating. The plasma obtained from patients was diluted at 1:100 for testing. HRP labeled N protein of SARS-CoV-2 (IgM) or anti-human IgG (H + L) antibody labeled with HRP was used as the secondary antibody. The colorimetric reaction was induced by adding TMB and terminated by using H_2SO_4 . Detection of the substrate was carried out via spectrometry by measuring the OD450. The positive and negative control were set at the same time.

Real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay

Clinical specimens were tested with RT-PCR assay kits certified by the Chinese government (Kaijie biotechnology co., LTD, Shanghai, China). The detailed product information, specifically the detection sequence of SARS-CoV-2, could not be fully obtained due to proprietary technology. However, it is known that the detection target of RT-PCR for SARS-CoV-2 focuses on NP and ORF1ab genes, and a positive result requires both gene tests to be positive. The detection operation was conducted in accordance with the instructions of the products.

Statistical analysis

The sensitivity, specificity, the overall coincidence rate and Kappa statistical test which was used for the interobserver consistency are calculated according to the following

formulas

$$1) \text{Sensitivity} = \frac{\text{TP (True positive)}}{\text{TP+FN (False negative)}} \times 100\%$$

$$2) \text{Specificity} = \frac{\text{TN (True negative)}}{\text{FP (False positive)} + \text{TN}} \times 100\%.$$

$$3) \text{The overall coincidence rate is expressed by the } \frac{\text{TP+TN}}{\text{TP+FP+FN+TN}} \times 100\% \text{ ratio}$$

$$4) \text{Kappa consistency was calculated by } \frac{\text{PA-Pe}}{1-\text{Pe}}, \text{ in which } \text{PA} = \frac{\text{TP+TN}}{\text{TP+FP+FN+TN}}, \text{ Pe} =$$

$$\frac{(\text{TP+FP})(\text{TP+FN})+(\text{FN+TN})(\text{FP+TN})}{(\text{TP+FP+FN+TN}) \times (\text{TP+FP+FN+TN})}.$$

Results were accepted as either poor ($\text{kappa} < 0.20$), fair ($\text{kappa} = 0.21-0.40$), moderate ($\text{kappa} = 0.41-0.60$), good ($\text{kappa} = 0.61-0.80$), very good ($\text{kappa} = 0.81-0.90$), and excellent ($\text{kappa} > 0.91$)

Results

IgM-IgG combined antibody test showed a higher sensitivity and specificity for SARS-CoV-2 in confirmed COVID-19 patients using peripheral blood

In order to evaluate whether the IgM-IgG combined antibody test can detect specific antibodies of SARS-CoV-2 using peripheral blood, samples from confirmed COVID-19 (RT-PCR positive of SARS-CoV-2), non-COVID-19 patients (RT-PCR negative of SARS-CoV-2) and healthy were recruited.

A total of 85 cases were tested: 33 confirmed COVID-19 patients, 23 non-COVID-19 patients and 29 healthy subjects. The IgM/IgG tested time of confirmed COVID-19 patients was average 35 ± 8.5 days post-symptom onset (Supplementary Table 1), and it was average 2.1 ± 0.9 days post-symptom onset for non-COVID-19 patients. Furthermore, 19 of 33 confirmed COVID-19 patients were IgM positive (sensitivity 57.6%), and the test was most negative in both non-COVID-19 and healthy individuals (specificity 98.5%). The IgG antibody test results showed a sensitivity of 97.0% and a specificity of 99.2%, with 32 of the 33 COVID-19 patients tested positive (Table 1). These operations used peripheral blood.

We also evaluated the differences in test characteristics of the IgM-IgG combined antibody assay between peripheral blood and serum samples, as well as between the combined antibody assay and ELISA. As shown in Table 2, the overall coincidence rate

between peripheral blood and serum samples was 100% for IgM and IgG antibody testing. Furthermore, compared to ELISA assay, the overall coincidence rate was 80% (16 out of 20) for the IgM-IgG combined antibody test. Among the 16 patients, 4 patients were both IgM and IgG positive, 5 were IgM positive and IgG negative, 7 were IgM negative and IgG positive (Fig. 3).

IgM-IgG combined antibody test of SARS-CoV-2 also showed a positive diagnosis for asymptomatic carriers using peripheral blood

This study recruited 20 asymptomatic carriers who had no clinical symptoms or travel history of high-risk area. They were permanent residents in Sichuan province, China. However, they had close contact with confirmed COVID-19 patients in their community within 14 days and were positive for SARS-CoV-2 by RT-PCR. Subsequently, they got the IgM and IgG antibodies tested at 5.8 ± 2.87 days (4-14 days) after the initial positive PCR assay using peripheral blood samples. The total positive rate was 95% as compared to RT-PCR. The positive rate of single IgM and IgM-IgG combined were higher than that of single IgG, 95% v.s. 95% v.s. 30%, respectively (Table 3). The results verified that the IgM-IgG combined antibody test can be used to diagnose asymptomatic SARS-CoV-2 carriers.

IgM-IgG combined antibody test can be used as a screening test for SARS-CoV-2 infection

The above results proved that the IgM-IgG combined antibody test can test the IgM and IgG antibody of SARS-CoV-2 in 10-15 minutes using peripheral blood as a POCT. Furthermore, this POCT assay can test the antibody in symptomatic and asymptomatic individuals confirmed by RT-PCR. Therefore, we suggest that this POCT assay can be used for screening diagnosis of SARS-CoV-2 infection in publication. In order to illustrate its screening characteristics, three distinct groups of individuals were included in this study (Fig. 4A). The first group were 10 subjects who have an explicit contact history with confirmed COVID-19 patients without proper protective gear, among whom, 3 cases (30%) were IgM positive but asymptomatic, as well as the RT-PCR retesting of SARS-CoV-2 also was positive. And 1 case (33.3%)

was reported IgG positive but RT-PCR negative. Those RT-PCR positive patients received standard treatment afterwards(Fig. 4B). The second group were 63healthcare workers who were in closecontact with COVID-19 patients but wore standard personal protective gear, among whom one showed positive (2.12%). Re-testing using RT-PCRassayfor SARS-CoV-2 showed negative for this individual although, she was advised to quarantinefor her previous close contact with confirmed COVID-19 patients (Fig. 4B). The third group were 298workforcesfrom high-risk areas. All subjects tested negative and were considered noninfectious and cleared to return to work (Fig. 4B).

Discussion

We evaluated the rapid screening diagnosis of SARS-CoV-2 infection with IgM-IgG combined antibody test using peripheralblood based on previous validated study [10]. We affirmed that therapid IgM-IgG combined antibody test for SARS-CoV-2using peripheralblood(used as a POCT) presented high sensitivity and specificity compared with serum samples and ELISA. Furthermore, the POCTassay can be used to test the IgM and IgGantibody of SARS-CoV-2 in both symptomatic and asymptomatic individuals. Therefore, we recommend this POCT assay as a screening tool for those potentially exposed to SARS-CoV-2 in a hope to actmore efficiently in the prevention and control of this pandemic.

The current techniques to detect SARS-CoV-2 can be classified into four types based on methodology: pathogen culture, antigen testing, nucleic acid testing and antibody testing. Pathogen culture has traditionally been considered as the goldstandard for viral detection for more than 70years.[11] However, it has limited use because of its slow turnaround time when rapid pathogen detection is required.[12]Although nucleicacid amplification tests including RT-PCR are rapid, highly sensitive and specific,[13, 14]PCR testing requires certified laboratories, expensive equipment, and well-trained technicians, taking 2-3 hours to obtain results. Furthermore, RT-PCR may yield false negative results.[4, 5]Metagenomic

next-generation sequencing (NGS) has been widely used as an emerging detection technology, but it requires the sequencing process to be completed before analysis can begin.[15] Metagenomic NGS also requires cumbersome instruments and a dedicated laboratory. Antigen testing may be able to fit screening, however there are no commercially available products yet. In this occasion, the IgM-IgG combined antibody test of SARS-CoV-2 can be used to address current needs.[10] We were able to verify the utility of this bedside antibody test in detecting the IgM and IgG antibodies of SARS-CoV-2 using peripheral blood (Fig. 2). The results can be obtained within 15 minutes with high sensitivity and specificity (Table 1), which is consistent with the previous study.[16] The results obtained from peripheral blood were highly consistent with those from serum samples, which implies that the sampling process can be optimized. The above findings suggest that the rapid IgM-IgG combined antibody test can be employed as a POCT for screening COVID-19 patients. [17]

It has been well established that the initial production of IgM after a viral infection is followed by IgG, which confers long term immunity and immunological memory.[7] According to other coronavirus infections such as SARS-CoV-1, IgM antibodies can be detected in blood samples 3-6 days after the initial infection and IgG after 8 days.[18, 19] In COVID-19 patients, IgM are typically produced within 7 days after the onset of illness, but IgG single positive and IgM-IgG double positive can appear in the acute and convalescence periods (1-35d).[16] Zhao et al found that less than 40% of patients had detectable antibodies within 7 days of disease onset, and this portion increased to 100% after 15 days from initial onset, of which 94.3% was detected for IgM and 79.8% for IgG.[8] Herein, we found that the detection sensibility was lower in individual IgM antibody test than individual IgG or IgG-IgM combined antibody test when the testing time was later from onset (Table 1; average 35 ± 8.5 days). However, the detection sensibility of individual IgM and IgG-IgM combined antibody test will be higher than individual IgG when the testing time was early from onset (Table 3; average 5.8 ± 2.87 days). Additionally, we found that the detection sensibility was higher in IgG-IgM combined antibody test than in individual IgG or IgM antibody

test.[10] Therefore, combined with the production of IgM and IgG antibody, we recommend the IgM-IgG combined antibody test will be better used.

The IgM and IgG antibodies of COVID-19 serve as an indicator of infection. Based on the current understanding of the disease process in China, the Chinese clinical guideline considers the detection of antibodies a diagnostic option for COVID-19.[2] Besides, we believe the rapid IgM-IgG combined antibody test of SARS-CoV-2 may play an important role in screening individuals with potential exposure to the virus, particularly the asymptomatic carriers. Relevant reports indicate asymptomatic carriers can still transmit the virus to others individuals.[20, 21] Therefore, large scale screening for asymptomatic carriers combined with early detection, quarantine, prevention, and treatment will be crucial to control this epidemic.[22] Fortunately, we found that the rapid IgM-IgG combined antibody test of SARS-CoV-2 could serve as a better testing tool for asymptomatic carriers (Table 3). It is showed that asymptomatic carriers of COVID-19 are highly contagious, and people in close contact with them are susceptible to infection. Therefore, it is important to identify and isolate of asymptomatic carriers of COVID-19, more testing and more follow-up, which is benefit to the prevention and control of the epidemic.[23-25] Interestingly, the rapid IgM-IgG combined antibody test of SARS-CoV-2 has better practical application for the screening of asymptomatic patients, and guided isolation therapy in advance (Fig. 4).

There are limitations to use rapid IgM-IgG combined antibody test of SARS-CoV-2 as a screening tool. Firstly, there will be false negative results as its lower sensitivity compared to that of ELISA (Table 2). Secondly, since IgM and IgG are produced later (usually 3-5 days after onset) in the disease course, early negative results do not rule out an infection. Third, false positive of IgM and IgG antibody testing should not be ignored. Therefore, multiple detection methods can be used to improve the diagnostic accuracy when necessary.

Conclusion

The rapid IgM-IgG combined antibody test for SARS-CoV-2 provides high sensitivity

and specificity using peripheral blood samples as a POCT, which can also be used to detect the antibodies in asymptomatic carriers of the SARS-CoV-2 virus, Therefore, it can be used as a POCT tool to screen the high-risk populations.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; POCT: point-of-care testing assay; COVID-19):coronavirus disease 2019;ELISA: enzyme-linked immunosorbent assay; RT-PCR: real-time polymerase chain reaction; NGS: next-generation sequencing.

Declaration

Consent for publication:

Not applicable.

Ethics approval and consent for participate:

This observational study was obtained ethical approval from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Ethical number: 2020-36),and the informed consent was obtained from each participant.

Availability of data and material:

The data that support the findings of this study are available from the corresponding author on reasonable request. Participant data without names and identifiers will be made available after approval from the corresponding author. After publication of study findings, the data will be available for others on request. The research team will provide an email address for communication once the data are approved for sharing with others. A proposal containing a detailed description of study objectives and statistical analysis plan will be needed for evaluating the reasonability of request for our data. The corresponding author will make a decision based on these materials. Additional materials may also be required during the process.

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Competing interests:

The authors report no conflicts of interest.

Authors' contributions:

FY, SQL, YWW and ZTL conceived and designed the study, had full access to all data, and took responsibility for the data accuracy and integrity. CJ, YL, ZMC, MZ, KJS, WSC and MDW contributed to the population screening. YWW and ZMC contributed to the RT-PCR test. FY and ZTL contributed to the statistical analysis. The remaining authors contributed to the management and treatment of patients. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version of the manuscript.

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Figure legends

Figure 1. Study Design for Targeted Testing and Population Screening. In this study, targeted testing for coronavirus disease 2019 (COVID-19) was applied to those with symptoms as well as asymptomatic carriers, as well as for screening for the contact tracing, medical workers, and company staff, who were high-risk populations.

Figure 2. Operating procedure of detecting antibody in peripheral blood. The procedure was simple and convenient, and results can be obtained within 15 minutes.

Figure 3. Comparing the detection characteristics between ELISA and the rapid antibody test. The quadrate (earthy yellow) represents the ELISA assay and the circle represents the rapid antibody test. IgM antibody testing is depicted in red and IgG antibody testing is depicted in orange-yellow.

Figure 4. Population screening with rapid IgM-IgG combined antibody test for SARS-CoV-2 in peripheral blood. A was a picture showed the screening site. B shows the screening results, including Close contacts, healthcare workers and workforces.

Tables

Table 1. The detection sensibility and specificity of SARS-CoV-2 IgM-IgG combined antibody test using peripheral blood

Variable			PCR			Sensibility	Specificity
			Positive	Negative	Total		
IgM	COVID-19	Positive	19	0	19	57.6%	98.5%
		Negative	14	0	14		
	Non-COVID-19	Positive	0	2	2		
		Negative	0	99	99		
	Healthy person	Positive	0	0	0		
		Negative	0	29	29		
	Total		33	130	163		
	IgG	COVID-19	Positive	32	0		
Negative			1	0	1		
Non-COVID-19		Positive	0	1	1		
		Negative	0	100	100		

IgM /IgG	Healthy person	Positive	0	0	0	97.0%	97.7%	9
		Negative	0	29	29			
		Total	33	130	163			
	COVID-19	Positive	32	0	32			
		Negative	1	0	1			
	Non-COVID- 19	Positive	0	3	3			
		Negative	0	98	98			
	Healthy person	Positive	0	0	0			
		Negative	0	29	29			
		Total	33	130	163			

Noting: 1) The IgM and IgG tested time was average 35 ± 8.5 days post symptom onset.

2) IgM/IgG means IgM positive or/and IgG positive.

Table 2. The comparing between peripheral blood and serum of venous blood of SARS-CoV-2 IgM-IgG combined antibody test

Variable			Serum of venous blood			The overall coincidence
			Positive	Negative	Total	
peripheral blood	IgM	Positive	13	0	13	100%
		Negative	0	29	29	
		Total	13	29	42	
	IgG	Positive	30	0	30	100%
		Negative	0	12	12	
		Total	0	12	42	

Table 3. IgM-IgG combined antibody detection of SARS-CoV-2 in asymptomatic carriers

Variable	Asymptomatic carriers		
Male sex, no. (%)	8/20 (40)		
Mean age (years)	25.2±12.79		
Nationality	China		
Place of residence	Sichuan province		
Any epidemic area travel, no. (%)	0/20 (0)		
Known contact with infected person, no. (%)	20/20 (100), cluster cases		
The time contacting	No clear		
Symptoms reported, no. (%)	0/20 (0)		
RT-PCR positive, no. (%)	20/20 (100)		
Antibody testing, no. (%); using peripheral blood	IgM (+) 19/20 (95)	IgG (+) 6/20 (30)	IgM or IgG (+) 19/20 (95)
The time to take results	10-15 min		
Time distance from RT-PCR positive (days)	5.8±2.87		

Figures

Figure 1

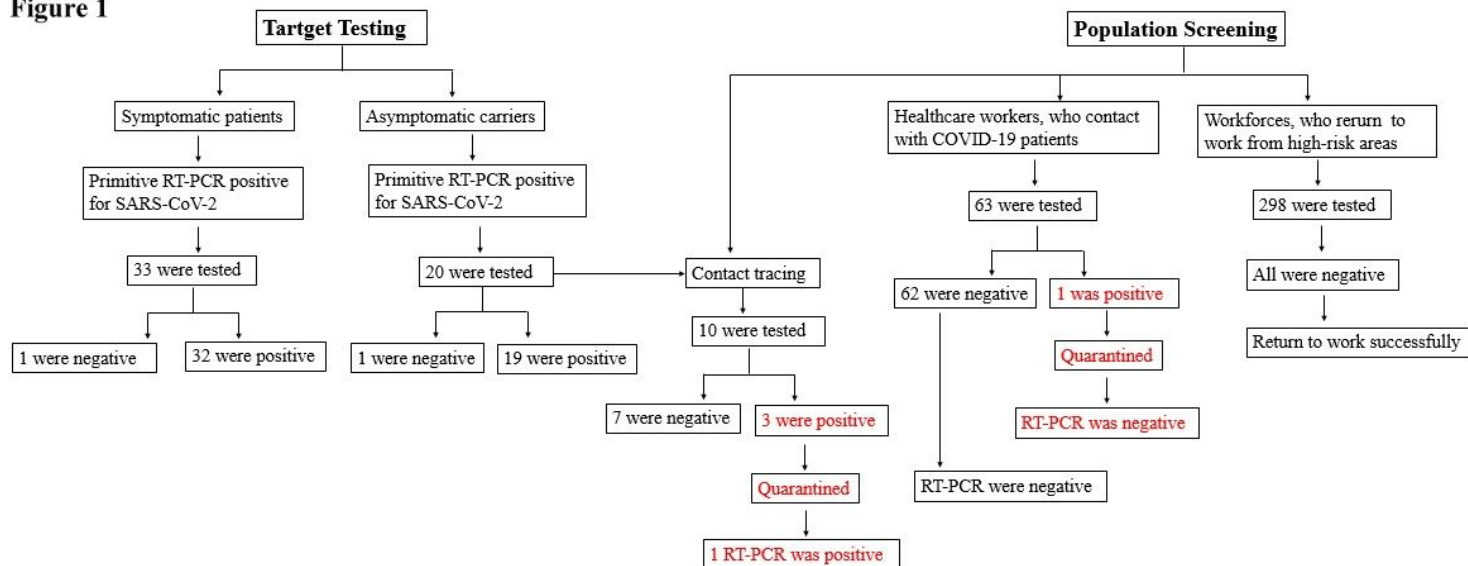


Figure 1

Study Design for Targeted Testing and Population Screening. In this study, targeted testing for coronavirus disease 2019 (COVID-19) was applied to those with symptoms as well as asymptomatic carriers, as well as for screening for the contact tracing, medical workers, and company staff, who were high-risk populations.

Figure 2

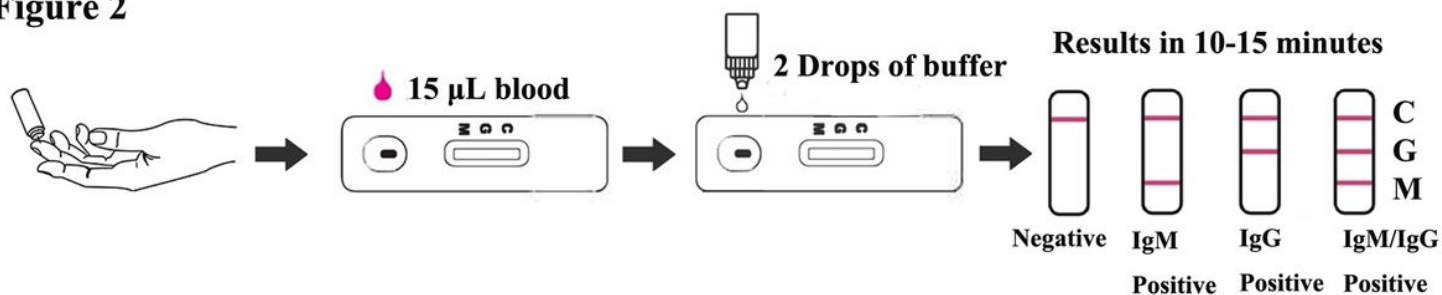


Figure 2

Operating procedure of detecting antibody in peripheral blood. The procedure was simple and convenient, and results can be obtained within 15 minutes.

Figure 3

Total: 20

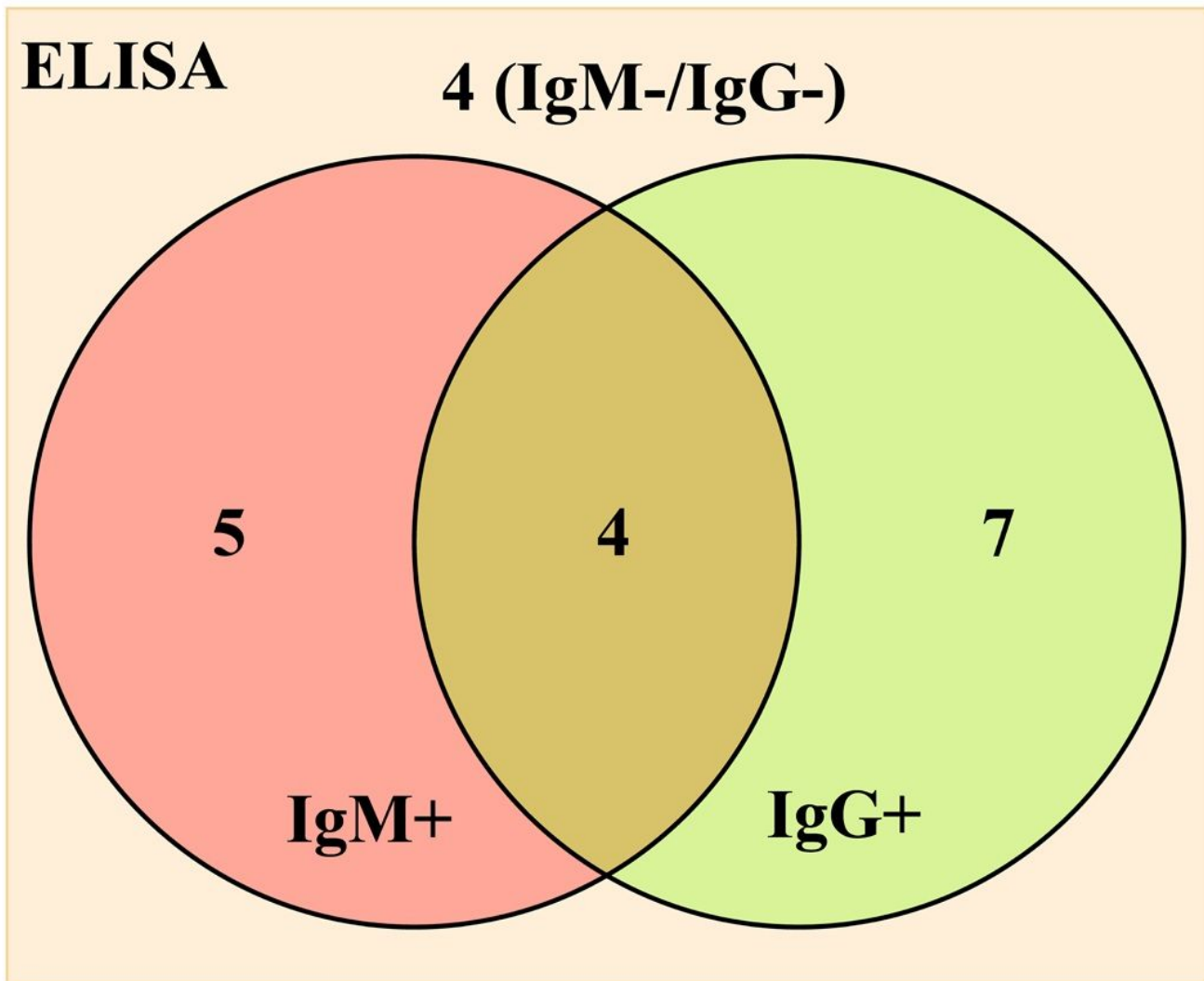


Figure 3

Comparing the detection characteristics between ELISA and the rapid antibody test. The quadrate (earthy yellow) represents the ELISA assay and the circle represents the rapid antibody test. IgM antibody testing is depicted in red and IgG antibody testing is depicted in orange-yellow.

Figure 4

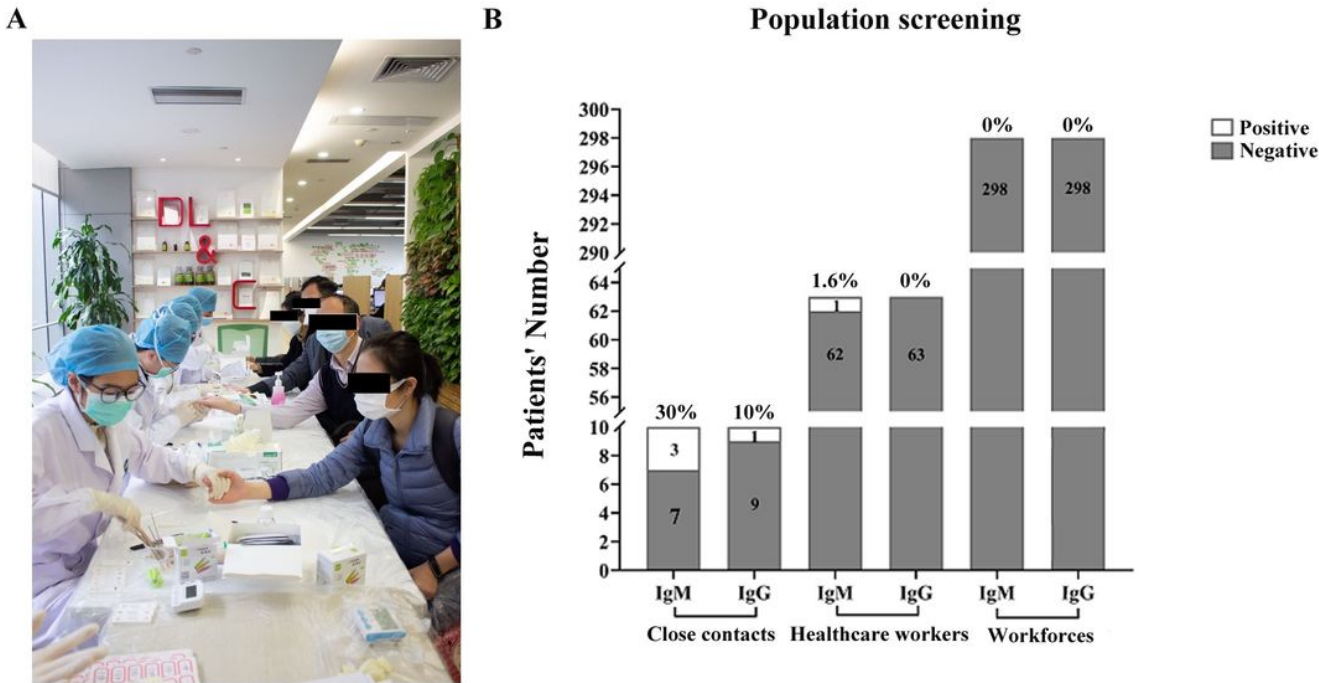


Figure 4

Population screening with rapid IgM-IgG combined antibody test for SARS-CoV-2 in peripheral blood. A was a picture showed the screening site. B shows the screening results, including Close contacts, healthcare workers and workforces.

Supplementary Files

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- [SupplementaryTable.docx](#)