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Review

The role of serum specific- SARS-CoV-2 antibody in COVID-19 patients

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 2019 (COVID-19), has rapidly spread, resulting in considerable casualties and serious economic loss worldwide. Disease severity and related symptoms markedly vary among individuals. A large number of patients present atypical symptoms, which represent a big challenge for early diagnosis and prompt infection source isolation. Currently, COVID-19 diagnosis predominantly depends on nucleic acid tests (NAT) for SARS-CoV-2 in respiratory specimens, but this method presents a high rate of false negative results. Therefore, serum antibody measurement has been rapidly developed as a supplementary method with the aim of improving diagnostic accuracy. Further, serum antibody levels might help to identify the infection stage, asymptomatic carriers, and patients with diverging severities and to monitor convalescent plasma therapy. In the current review, we aim to present comprehensive evidence to clarify the utility of SARS-CoV-2 antibodies in COVID-19 patients as a reference for use in the clinic.

1. Introduction

The novel coronavirus infection was first reported at the end of December 2019 in Wuhan, China. Later, the cause of pneumonia cases of unknown etiology was confirmed to be a new coronavirus infection. The World Health Organization (WHO) named it coronavirus disease 2019 (COVID-19), and the responsible virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is characterized by rapid transmission, atypical clinical symptoms, and the potential to be easily misdiagnosed. In particular, the numerous asymptomatic carriers are major obstacles for prevention and control.

Currently, the gold standard for COVID-19 diagnosis is the nucleic acid test (NAT) for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR). However, due to factors such as sample quality, personnel handling, testing equipment, and many others, this detection method may result in a number of false negatives. In hospital in Wuhan, 4880 patients with respiratory infection symptoms or close contact with COVID-19 patients were tested using RT-PCR, finding positive NAT rates in nasopharyngeal swabs, sputum, and bronchoalveolar lavage were 38.25%, 49.12%, and 80%, respectively [1]. The low positive rates in nasopharyngeal swabs and sputum samples might be due to the localized involvement in the lung at the disease stage [2]. Although the positive detection rate with sample from the lower respiratory tract is high, obtaining these samples is difficult, especially for outpatients, and there is a risk of infection and/or virus diffusion during the sampling process. Serological antibody tests are fast processing, convenient, obtainable, and highly sensitive. For the aforementioned reasons, serum antibody tests have been rapidly developed as a supplemental tool in COVID-19 diagnosis. Additionally, serum antibodies are important for assessing the severity of COVID-19, helping diagnose asymptomatic SARS-COV-2 infections, and in screening the best convalescent plasma donors.

In order to provide a reference for clinicians, we have reviewed the role of serum specific SARS-CoV-2 antibodies in patients with COVID-19.

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2. Antibody types commonly employed for COVID-19 diagnosis

Immunoglobulin (Ig) M, IgA, and IgG are the antibody types most commonly used in COVID-19 diagnosis. IgM mediates the primary immune response, and the detection of specific IgM indicates a recent infection. Serotype IgA is a monomer that mainly exists in the serum and participates in humoral immunity. IgG is the most abundant isotype (75%–80%), has the longest half-life (20–23 days) in the serum and extracellular fluid, and is the main antibody involved in the secondary immune response.

Li et al [3] found that after SARS-CoV-2 infection in humans, specific antibodies can be produced in 15 days. Specific IgM and IgA can be detected in 3–6 days, and IgM can rise to its highest levels 8–14 days after symptom onset. While the IgA level continues to rise for 0–14 days following symptom onset and thereafter ceases to increase. IgG can be detected 14 days after symptom onset, with level rising during days 8–21, and stabilizing after 21 days, and remains present in the later stages of infection [3]. Liu et al. found an increase in IgM titers on day 4 after SARS-CoV-2 infection, reaching a peak approximately on day 20, whereas IgG could be identified on day 7 after infection, peaking around day 25 [4]. Xu et al. found that the cumulative seropositivity rates for IgM and IgG were 44% and 56% on day 7 after symptom onset, respectively, and reached more than 95% on day 20 and day 16, respectively, with both IgM and IgG antibody levels remaining above the threshold on day 28, a different observation from the time of antibody appearance and persistence in other studies [5].

Compared with specific IgM and IgG, IgA has not shown obvious advantages in the diagnosis of SARS-COV infection [6]. In influenza virus infections, protective secretory IgA can be found in asymptomatic or mildly symptomatic cases [7]. IgA measurements have been shown to be more sensitive than IgM in detecting hepatitis B virus infection, with levels being associated with the severity of liver disease [8]. In patients infected with SARS-CoV-2, IgA and IgM appeared for a similar time period, and IgA titers and detection rate were higher than those of IgM [3]. These characteristics differ from those of SARS-CoV infection. A study by Yu et al. [9] showed that the first IgA seroconversion day was 2 days after initial symptoms onset in COVID-19 patients, and that of IgM and IgG was 5 days after onset, the level of specific IgA were significantly higher than those of IgM. Padoan et al. [10] found that the IgA response appears and grows early, peaks at week 3, and is stronger and more persistent than the IgM response. Jääskeläinen et al. [11] also found that IgA testing could be useful together with IgG in COVID-19 patients with atypical symptoms or suspected cases with negative NAT. Therefore, IgA may be useful for diagnosing patients with acute stage infection or asymptomatic carriers. Presently, the detection of IgM and IgG isotypes is widely applied in clinical practice, but the diagnostic value of IgA in COVID-19 has not received enough attention and requires further research.

IgM and IgG have a reciprocal relationship; therefore, the simultaneous detection of IgM and IgG antibodies is more suitable for COVID-19 patients at an unclear infection stage. In a study evaluating the sensitivity and specificity of IgG/IgM combined antibodies, the combined antibodies showed superiority to IgM or IgG tests alone [12]. Not only can combined antibody detection improve diagnostic accuracy and infection control, but it can also be employed to assess disease progression and monitor long-term dynamic.

3. Efficacy of SARS-CoV-2 specific antibodies

The diagnostic efficacy of SARS-COV-2 specific antibodies varies greatly according to various research results, most likely due to the different antibody detection methods, specific proteins targeted, and various products. Cassaniti et al. used VivaDiag COVID-19 IgM/IgG Rapid Test lateral flow immunoassay for rapid COVID-19 diagnosis, and found that [13] the VivaDiag COVID-19 IgM/IgG Rapid Test has a sensitivity of 18.4%, specificity of 91.7%, negative predictive value (NPV) of 26.2%, and positive predictive value (PPV) of 87.5%. Jin et al. used a chemiluminescence immunoassay to detect IgM and IgG and found that compared with molecular detection, the sensitivity of serum IgM and IgG antibodies for COVID-19 diagnosis was 48.1% and 88.9%, respectively, and the specificity was 100% and 90.9%, respectively [14]. Shen et al. evaluated the diagnostic performance of colloidal gold immunochromatography in the detection of SARS-CoV-2 specific IgM/IgG combined antibodies in suspected COVID-19 cases, and found that the sensitivity and specificity in this population were 71.1% and 96.2%, respectively [15]. Spicuzza, et al. [16] evaluated the diagnostic efficacy of IgM/IgG combined antibodies for COVID-19 by rapid immunochromatography and found that considering the molecular test as the gold standard for diagnosis, the sensitivity and specificity of the antibody test were 83% and 93%, respectively. Xiang et al. [17] based on the recombinant SARS-CoV-2 Nucleocapsid (N)-protein to detect SARS-CoV-2 antibodies after 3-40 days of symptoms onset by enzyme linked immunosorbent (ELISA), the results show that in suspected COVID-19 patients, the sensitivity, specificity, PPV, NPV and consistency rate were 87.5%, 100%, 100%, 95.2% and 96.4%, respectively for IgM, and 70.8%, 96.6%, 85.0%,89.1% and 88.1% for IgG. Despite the different results, all authors agreed that antibody detection, whether sarS-CoV-2 specific IgM and IgG alone or IgM-IgG in combination, could be a beneficial supplement to NAT (Table 1).

Table 1
Interpretation of serum SARS-CoV-2 specific antibody tests.

Nucleic acid	IgM	IgG	Interpretation of Results
Positive	Negative	Negative	The patient may be in the incubation period of SARS-CoV-2 infection, which is generally 2 weeks.
	Positive	Negative	The patient may be in the early stages of SARS-CoV-2 infection.
	Negative	Positive	The patient may be in the middle or late stages of SARS-CoV-2 infection or has recurrent infection. When IgG antibody is increased by 4 times or more in the convalescent phase compared to the acute phase, a recurrent infection can be diagnosed.
	Positive	Positive	The patient may be in the active phase of SARS-CoV-2 infection.
Negative	Positive	Negative	The patient is highly likely to be in the acute phase of SARS-CoV-2 infection. A false negative of the nucleic acid test and a false positive of the IgM test should be considered possible.
	Negative	Positive	The results may be due to previous SARS-CoV-2 infection, that has resolved or the virus has been cleared from the body.
	Positive	Positive	This may indicate recent SARS-CoV-2 infection, and that the patient has recovered and the virus has been cleared from the body, but the IgM is not low enough to detect the lower limit, or it may indicate that nucleic acid test is a false negative, and the patient is in the active period of SARS-CoV-2 infection.
	Negative	Negative	Healthy people not infected with SARS-CoV-2.

4. Usefulness of serum antibody detection in asymptomatic COVID-19 patients

Asymptomatic SARS-CoV-2 carriers are uncertain factors in the prevention and control of the current epidemic. Asymptomatic COVID-19 infection has no clinical symptoms (such as fever, cough, or sore throat) and no radiological changes to the lung, yet NAT is positive for SARS-CoV-2. In a recent study for COVID-19 patients, the viral load of upper respiratory tract samples was similar for both asymptomatic and symptomatic patients, suggesting that the potential for viral

transmission by asymptomatic or mildly symptomatic patients is comparable to that of symptomatic patients [18]. Therefore, early screening and isolation of asymptomatic carriers is of great significance for controlling the spread of the epidemic. Currently, the screening of asymptomatic infected persons mainly relies on NAT, but its false positive rate leads to a serious underestimation of the proportion of asymptomatic infected persons. In Spain, 5% of the population is serologically positive, and one-third of these people do not report symptoms [19]. Guangzhou reported that 44% of people infected with SARS-CoV-2 were asymptomatic [20]. In a study by Huang et al. the proportion of patients with asymptomatic infections was 20.8% [21]. Dong et al suggested that conducting large-scale serological studies on SARS-CoV-2 specific IgG could improve the ability to predict the epidemiological characteristics of asymptomatic infections [22].

Serological detection has certain specificity in asymptomatic SARS-CoV infections. Two studies on China's wildlife market in Guangzhou showed that 14.86% of the staff had been exposed to SARS-CoV but did not show obvious clinical symptoms [23,24]. Similarly, the Middle East respiratory syndrome coronavirus (MERS-CoV) infection may be asymptomatic or cause a mild influenza-like disease [25]; in that situation, serological antibody tests were performed in groups at a high or low risk of MERS-CoV infection, where in the high-risk group comprised individuals in close contact with confirmed cases, and the low-risk included blood samples collected from blood donors within a five-year period (2012–2016) [26]. The results showed that the ratio of serum antibodies was increased in the high-risk group, which confirmed the significance of IgG in MERS and highlighted the complementary effect of IgM and IgG detection. Studies on Ebola virus also reached similar conclusions. In a study of 24 asymptomatic individuals, 11 produced specific IgM and IgG against the Ebola virus, indicating clear serological changes in asymptomatic individuals [27].

Several studies suggest that asymptomatic SARS-CoV-2 carries are in the incubation period and have the ability to transmit the virus [28–30]. The mean shedding time (19 days) was significantly longer in asymptomatic individuals than in symptomatic ones [21], suggesting that asymptomatic patients may have a different immune response to SARS-COV-2 infection. Meanwhile, IgG levels in the symptomatic group were significantly higher than those in the asymptomatic group in the acute and early convalescent phase [21]. Chen et al. revealed that serological testing is useful for the identification of asymptomatic or subclinical infections of SARS-CoV-2 among those in close contact with COVID-19 patients [31]. The study by Long [32] also showed that serological antibody testing helps diagnose RT-PCR negative patients with suspected and asymptomatic infections and is essential for the accurate estimation of COVID-19 prevalence. Lei [33] also observed that NAT binding to specific IgM can significantly improve detection sensitivity compared with NAT alone. Therefore, screening asymptomatic patients for serum antibodies can effectively identify the source of infection and control further COVID-19 outbreaks.

5. Usefulness of serum antibody detection in COVID-19 patients with different severity

Although serological antibody tests can serve as a diagnostic tool, there is also evidence that the levels of antibodies are representative indicators of COVID-19. Quantification of antibody levels in patients with varying COVID-19 severity is essential to assess patient prognosis. A single-center, retrospective cohort study showed that [34] for IgM titers $\geq$ 50 AU/ml, patients with severe/critical COVID- 19 are at a higher risk of clinical adverse events; therefore, the reduction in IgM titers in severe/critical cases may be indicative of a better prognosis. Hou et al. [35] found that in COVID-19 patients, severe and critical cases had higher IgM levels than mild cases, whereas the IgG levels in critical cases were lower than those in both mild and severe cases. Caturegli et al. [36] showed that SARS-CoV-2 antibodies predict the odds of developing acute respiratory distress syndrome, with a 62% increase in incidence for every 2-fold increase in IgG. Similar results could be obtained with a test for neutralizing antibodies. Liu L et al [37] suggested that ICU patients had an accelerated and augmented neutralizing antibody response compared to non-ICU patients, which was associated with disease severity. Our previous research [38] also found that IgA and IgG levels were higher in severe and critical COVID-19 patients than in moderate ones, while IgM levels were did not differ between the two groups. The relationship between SARS-CoV-2 specific antibodies and the severity and prognosis of COVID-19 has not been conclusively established, but existing studies support the view that the higher the level of antibodies, the more severe is the disease and the poorer is the prognosis. Therefore, quantitative detection of serum antibodies may have potential significance for evaluating the severity and prognosis of COVID-19. However, it may be necessary to include more COVID-19 patients as well as studies including antibodies against different proteins to derive further conclusions.

6. Application of serum antibody detection in convalescent plasma treatment for COVID-19 patients

Recovery plasma contains specific polyclonal antibodies, which have been used in the treatment of SARS, MERS, Ebola, and other infectious diseases. Several studies have shown that in patients with SARS, those who received recovery plasma treatment had shorter hospital stays and lower mortality than those who did not [39–41]. In addition, convalescent plasma infusion is considered the most promising treatment for MERS-CoV infection [42,43], and convalescent plasma collected from Ebola patients was recommended in 2014 as an empirical treatment during outbreaks. Because of the comparable virological and clinical characteristics among SARS, MERS, and COVID-19 [44], convalescent plasma may be effective for the treatment of COVID-19. Some reports have shown that plasma therapy can effectively reduce the symptoms and mortality of patients with SARS-CoV-2 infection when there is no specific treatment for COVID-19[45–47], and convalescent plasma transfusion has shown good safety results in hospitalized patients with COVID-19 [48].

Neutralizing antibodies are antibodies against viral surface antigens, which can bind to the free virus in the body to prevent it from being absorbed and invade cells. IgM, IgG, and IgA possess neutralizing antibody activity, and IgG, especially specific IgG in Receptor Binding Domain (RBD) of Spike (S) protein, plays an important role in plasma therapy during the recovery period due to its high content in body fluid, high specificity, and long-term existence after recovery. A study on plasma therapy for five severe COVID-19 patients showed good therapeutic effect and [47] the selected plasma donors were required to meet the following conditions: at least 10 days without symptoms during the recovery period, a titer of serum SARS-CoV-2 specific IgG antibody higher than 1:1000 (detected by ELISA), a neutralizing antibody titer higher than 40, and same-day infusion into the patients with COVID-19 receiving treatment. The titers of the specific IgG and IgM in the RBD and the neutralizing antibody against SARS-CoV-2 were 1800–16200 and 80–480, respectively, as determined using ELISA. After infusion, patients should be continuously monitored for at least 1 week to ensure a time-dependent increase in IgM and IgG levels.

Convalescent plasma therapy may result in increased antibody dependence, which may lead to more severe disease only in a subset of genetically susceptible patients [49]; therefore, special attention should be paid to the timing of plasma therapy. In order to improve the body's humoral immune response, reduce the repeated stimulation of killer T cells on the human immune system, and avoid a cytokine storm, patients should receive infusions when they have not produced IgG antibodies. Presently, the National Health Commission of China recommends collecting plasma within two weeks after the recovery period [50]. A study indicates that the S-RBD-specific IgG antibody reaches high levels four weeks after the onset of COVID-19 symptoms; therefore, the researchers recommended that donors should wait four weeks after

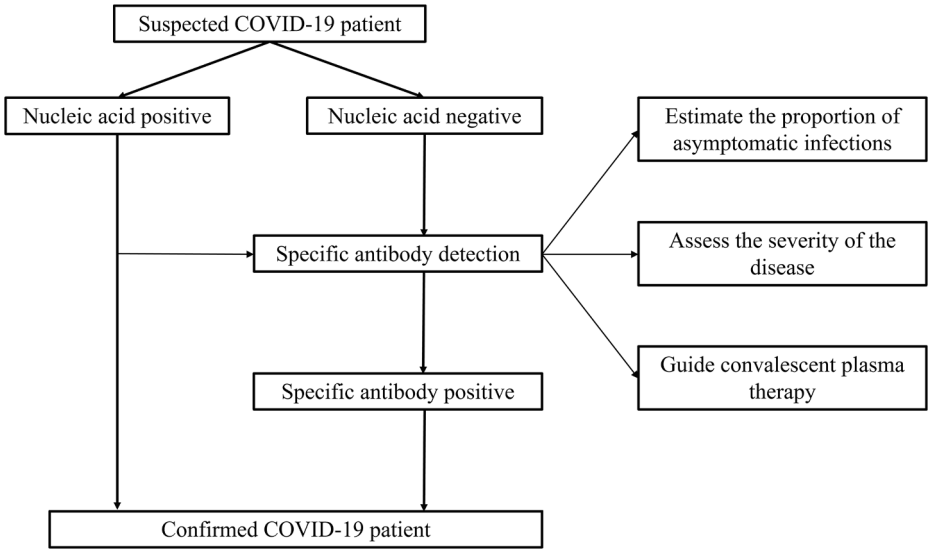

Fig. 1. Diagnostic procedures for COVID-19 and the role of SARS-CoV-2 specific antibody.

symptoms' onset before considering donating plasma [51]. In the process of plasma treatment, dynamic screening of specific antibodies is required for both donors and patients.

7. Practicability and limitations of serum antibody detection

Generally, when patients have suspected symptoms of COVID-19 and the NAT for SARS-CoV-2 is negative, SARS-CoV-2 specific IgM/IgG antibodies can be used as diagnostic standard for COVID-19 (Fig. 1). First, in suspected or clinically diagnosed patients with COVID-19 at the initial visit (negative or no NAT), if a single serum specific-antibody is positive, COVID-19 infection can be highly suspected. Multiple and diversified local NAT and verification tests must be conducted, and the antibody should be rechecked after one week. If the NAT is positive or the antibody significantly elevated, COVID-19 infection can be diagnosed. Second, in close contacts without clinical symptoms, if the antibody is positive, the close contacts may carry the virus; multiple and diversified local NAT and verification tests must be conducted, and the antibody rechecked after one week. If the NAT is positive or the antibody is significantly increased, infection can be diagnosed.

For patients diagnosed with COVID-19 via NAT, continuous quantitative antibody detection during the course of the disease can provide doctors with information about the changes in their antiviral immune status. This facilitates a deeper understanding of the correlations among antibody response, viral load, and other laboratory indicators as well as correlations with clinical outcomes, such as risk and prognosis of critically ill patients. Moreover, since antibody levels can also assess the severity of the disease, this information can help guide clinical treatment.

For rehabilitation patients, volunteers with high-titer antibodies may be screened through quantitative antibody detection for the development of therapeutic recovery plasma to ensure the efficacy of recovery plasma in critically ill patients.

However, antibody detection also has limitations and may produce false-positive results. The detection of specific IgM and IgG false-positives often occurs for the following reasons [52–55]: (1) Cross-reaction of the coating antigen with SARS-CoV or other subgenus coronaviruses. There is a cross-reaction between SARS-CoV-2 and the angiotensin-converting enzyme 2 (ACE2) receptor of the S protein of SARS-CoV. The cross-reaction of N protein and S-protein of coronavirus - occurs within the same subgenus, but also between different subgenera. (2) Some weak positives will be considered as false positives because of the various cut-off values of different detection methods and reagents. Current detection methods include colloidal gold immunochromatographic assay, fluorescence immunochromatography, ELISA, and chemiluminescence. The colloidal gold method involves judging of the positive and negative results by observing the color with the naked eye. As there is no cut-off value, the results may be related to the subjective evaluation of the operator. In the other methods, the positive cut-off value needs to be set (Table 2). (3) Endogenous or exogenous interfering substances in the patient samples that can lead to false-positive results. Endogenous interfering substances generally include rheumatoid factors, heterophilic antibodies, a complement while exogenous interference may occur due to hemolysis, bacterial contamination, long storage time, and incomplete coagulation.

On the premise of ensuring the quality of blood samples, $\geq$2 dynamic antibody tests can not only effectively avoid the false positive results caused by some interfering factors but also capture the dynamic changes of IgM/IgG conducive to COVID-19 diagnosis.

It must be emphasized that the antibodies currently being tested are

Table 2
Comparison of common detection methods of SARS-CoV-2 serum antibodies.

	Colloidal gold immunochromatographic assay	Fluorescence immunochromatography	Enzyme-linked immunosorbent assay (ELISA)	Chemiluminiscence
Sensitivity	Low	Middle	Middle	High
Detection time	10 ~ 20 min	10 ~ 20 min	2 ~ 3 h	0.5 ~ 1 h
Detection throughput	Low	Low	High	High
Procedure	Easy	Easy	Complex	Easy
Equipment	No	Minitype device	Enzyme marker and plate washer	Chemiluminescence apparatus
Output way	Naked eye	Instrument	Instrument	Instrument
Report form	Qualitative/semi-quantitative	Quantitative	Qualitative/quantitative	Quantitative

Table 3
Main studies and findings.

Utility of antibodies	Authors	Findings
Asymptomatic COVID-19 patients	Zou et al. [18]	The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients.
	Long et al. [21]	The mean shedding time (19d) was significantly longer in asymptomatic individuals than in symptomatic individuals; IgG levels in the symptomatic group were significantly higher than those in the asymptomatic group in the acute and early convalescent phase.
	Dong et al. [22]	Clinical manifestations range from asymptomatic cases to patients with mild and severe symptoms, with or without pneumonia. Laboratory detection of the viral nucleic acid can yield false-negative results, and serological testing of virus-specific IgG and IgM antibodies should be used as an alternative for diagnosis.
	Chen et al. [31]	Serological testing is useful for the identification of asymptomatic or subclinical infection of SARS-CoV-2 among close contacts with COVID-19 patients.
	Long et al. 32]	Serological antibody testing helps diagnose RT-PCR-negative patients with suspected and asymptomatic infections and is essential for the accurate estimation of COVID-19 prevalence.
	Lei et al. [33]	Nucleic acid test binding to specific antibody IgM can significantly improve detection sensitivity compared with NAT alone.
COVID-19 patients with different severity	Liu et al. [34]	Severe/critical patients with COVID-19 have a higher risk of clinical adverse events when IgM titer $\geq$ 50 AU/ml.
	Hou et al. [35]	Severe and critical cases had higher IgM levels than mild cases, whereas the IgG level in critical cases was lower than those in both mild and severe cases. Quantitative detection of IgM and IgG antibodies against SARS-CoV-2 quantitatively has potential significance for evaluating the severity and prognosis of COVID-19.
	Caturegli et al. [36]	SARS-CoV-2 antibody predicts odds of developing acute respiratory distress syndrome, with a 62% increase in incidence for every 2-fold increase in IgG.
	Liu et al. [37]	ICU patients had an accelerated and augmented neutralizing antibody response compared to non-ICU patients, which was associated with disease severity.
convalescent plasma treatment in COVID-19 patients	Shen et al. [47]	The titers of specific IgG and IgM in the receptor binding domain and neutralizing antibody against SARS-CoV-2 were 1800–16200 and 80–480, respectively, as determined by ELISA. The patients should be monitored continuously for at least one week after infusion to ensure a time-dependent increase in IgM and IgG levels.
	Fleming et al. [49]	While convalescent plasma has the potential to benefit a large number of patients, its overall safety and the appropriate timing of administration need further study.

not equivalent to neutralizing antibodies. In China, there are three kinds of antibody detection kits for SARS-CoV-2 on the market: S protein, RBD on S-protein and N-protein. Different detection methods, products, and antibodies to different proteins have differing sensitivities and specificities [56]. Antibodies against the S-protein have a higher specificity, while those against the N-protein have a higher sensitivity [57]. To engage the host cell receptor human-ACE2, the S-protein undergoes dramatic conformational changes to expose the RBD and key residues for receptor binding [58]. Considering the critical role of RBD in initiating SARS-CoV-2 invasion into host cells, it is a vulnerable target for neutralizing antibodies. Theoretically, the neutralizing antibody binds to RBD on the S-protein, but it may also bind to other domains; therefore, the screening of neutralizing antibodies needs to be verified by neutralizing the live virus at the cellular level. However, it is important to note that the detection of antibodies, especially IgG, does not indicate a certain immunity to SARS-CoV-2, but only a present or past infection.

8. Conclusion

Since RT-PCR can produce a false-negative result in viral NAT, especially in nasopharyngeal swabs, COVID-19 should be diagnosed using a combination of NAT and clinical symptoms [59]. However, COVID-19 does not show the same typical clinical symptoms as those observed in individuals infected with SARS, MERS, and Ebola virus. In particular, there are a large number of asymptomatic SARS-CoV-2 carriers. Antibody detection is a useful adjunct to RT-PCR detection and can improve the accuracy of COVID-19 diagnosis, thus providing an effective complement to NAT for the diagnosis of SARS-CoV-2 infection. Further, antibody detection has clinical significance for determining the stage of infection and identifying asymptomatic carriers, evaluating the severity of disease, and evaluating the progress of plasma treatment during the recovery period (summarized in Table 3).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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