

# World Journal of *Clinical Cases*

*World J Clin Cases* 2023 April 6; 11(10): 2123-2362



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

April 6, 2023

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**INSTRUCTIONS TO AUTHORS**

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<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Clinical application of SARS-CoV-2 antibody detection and monoclonal antibody therapies against COVID-19

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**Specialty type:** Medicine, research and experimental

**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): E

**P-Reviewer:** Kumar I, India; Nassar G, France; Wijaya JH, Indonesia

**Received:** December 7, 2022

**Peer-review started:** December 7, 2022

**First decision:** January 5, 2023

**Revised:** January 17, 2023

**Accepted:** March 10, 2023

**Article in press:** March 10, 2023

**Published online:** April 6, 2023



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## Abstract

The purpose of this study was to investigate the clinical application of severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) specific antibody detection and anti-SARS-CoV-2 specific monoclonal antibodies (mAbs) in the treatment of coronavirus infectious disease 2019 (COVID-19). The dynamic changes of SARS-CoV-2 specific antibodies during COVID-19 were studied. Immunoglobulin M (IgM) appeared earlier and lasted for a short time, while immunoglobulin G (IgG) appeared later and lasted longer. IgM tests can be used for early diagnosis of COVID-19, and IgG tests can be used for late diagnosis of COVID-19 and identification of asymptomatic infected persons. The combination of antibody testing and nucleic acid testing, which complement each other, can improve the diagnosis rate of COVID-19. Monoclonal anti-SARS-CoV-2 specific antibodies can be used to treat hospitalized severe and critically ill patients and non-hospitalized mild to moderate COVID-19 patients. COVID-19 convalescent plasma, highly concentrated immunoglobulin, and anti-SARS-CoV-2 specific mAbs are examples of anti-SARS-CoV-2 antibody products. Due to the continuous emergence of mutated strains of the novel coronavirus, especially omicron, its immune escape ability and infectivity are enhanced, making the effects of authorized products reduced or invalid. Therefore, the optimal application of anti-SARS-CoV-2 antibody products (especially anti-SARS-CoV-2 specific mAbs) is more effective in the treatment of COVID-19 and more conducive to patient recovery.

**Key Words:** SARS-CoV-2 antibody; Detection; COVID-19; Monoclonal antibody; Clinical application

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**Core Tip:** Immunoglobulin M testing can be used for early diagnosis of coronavirus infectious disease 2019 (COVID-19). Immunoglobulin G testing can be used for the late diagnosis of COVID-19 and the identification of asymptomatic patients. The combination of antibody and nucleic acid testing has improved the diagnosis rate of COVID-19. The continuous emergence of mutated strains of the novel coronavirus, especially omicron, enhances its immune escape ability and infectivity, making the effects of authorized products reduced or invalid. The specific monoclonal antibodies against severe acute respiratory distress syndrome coronavirus-2 authorized by the United States Food and Drug Administration are more beneficial for the treatment of COVID-19 and patient recovery.

**Citation:** Sun J, Yang ZD, Xie X, Li L, Zeng HS, Gong B, Xu JQ, Wu JH, Qu BB, Song GW. Clinical application of SARS-CoV-2 antibody detection and monoclonal antibody therapies against COVID-19. *World J Clin Cases* 2023; 11(10): 2168-2180

**URL:** <https://www.wjgnet.com/2307-8960/full/v11/i10/2168.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v11.i10.2168>

## INTRODUCTION

Since the coronavirus infectious disease 2019 (COVID-19) pandemic began in 2019, it has had a devastating impact on communities across the globe. So far, severe acute respiratory distress syndrome coronavirus-2 (SARS-CoV-2) has mutated several times with the identification of the following variant strains: Alpha (B.1.1.7) was first discovered in the United Kingdom in late December 2020; Beta (B.1.351) was first reported in South Africa in December 2020; Gamma was first reported in Brazil in early January 2021; Delta (B.1.617.2) was first reported in India in December 2020; Omicron (B.1.1.529) was first reported in South Africa in November 2021 and quickly spread to countries around the world due to its increased infectivity. Omicron's spike protein has exhibited more than 30 changes that enhanced viral capacity for immune escape. Studies have shown that Omicron shows a 13-fold increase in viral infectivity, and is 2.8 times more infectious than the delta variant, and previously approved monoclonal antibodies (mAbs) against SARS-CoV-2 are less effective against this variant. Furthermore, vaccines against SARS-CoV-2 are less effective in prevention of Omicron infection, and treatment is more challenging[1]. For these reasons, Omicron has become a major variant of concern in many countries, and many mutants of this strain have been identified (*e.g.*, BA.1, BA.2, BA.3, BA.4, BA.5, and XBB.1.5). The XBB.1.5 mutant is becoming increasingly frequent in the United States, and is still defined as an Omicron lineage variant[2]. It remains to be seen whether this specific mutant strain will worsen the ongoing COVID-19 pandemic.



As of January 13, 2023, there have been over 660 million confirmed COVID-19 cases and over 6.7 million deaths reported to the World Health Organization (WHO)[3]. The timely and accurate diagnosis of COVID-19 is necessary for controlling the spread of the virus, initiating prompt treatment, and rehabilitating patients. The primary method for diagnosing COVID-19 is *via* detection of SARS-CoV-2 RNA using polymerase chain reaction (PCR). However, the accuracy of PCR analysis depends on many factors, such as the quality of the reagents, the quality and method of sample collection (oropharynx, nasopharynx, lower respiratory tract, and swabs), and the skill level of the operator. Changes in the above factors may lead to either false negative or false positive results. PCR has many additional limitations: long testing time (average 2–3 h); complex technology; easy contamination of samples; high cost; and requirement for a laboratory with strict biosafety certification and trained technicians. These issues pose serious challenges in screening for COVID-19, achieving early diagnosis, implementing isolation of infected patients, and starting treatment. As such, new diagnostic tools are urgently needed to help compensate for the shortcomings of PCR[4].

The detection of SARS-CoV-2 specific antibodies (SSAs) can aid in the diagnosis of COVID-19. Additionally, asymptomatic infected people and those with milder symptoms can also be identified, helping to calculate the population infection rate more accurately. Large scale serological maps of a population can also be used in epidemiological investigations to provide a better understanding of the pandemic status, help to control the spread of the virus, and aid in treating patients efficiently. Antibody detection and nucleic acid detection can complement each other and improve the rate of accurate COVID-19 diagnosis. Indeed, serological detection technology has been widely used in the clinic[4].

SARS-CoV-2 induces an excessive and prolonged cytokine/chemokine response, known as a cytokine storm, in some infected individuals, particularly those with severe COVID-19 disease. Cytokine storm can cause acute respiratory distress syndrome or multiple organ dysfunction, which can lead to deterioration or death. Timely control of early cytokine storm with administration of immunomodulators and cytokine antagonists can reduce inflammatory cell infiltration into the lung and limit the disease. Suppressing cytokine storm effectively is important to prevent deterioration in COVID-19 patients and key to preventing death associated with this disease[5].

mAbs are immunoglobulins that are produced from single-cell lineages and have a high affinity for their target cells. When used as antiviral therapy, neutralizing Abs (Nabs) aid in the development of passive antiviral immunity. The viral genome is susceptible to mutation, resulting in the emergence of viral escape variants that render the virus resistant to specific mAbs. Several mAbs were combined into cocktails to improve efficacy and overcome the phenomenon of viral escape. The United States Food and Drug Administration (FDA) has granted emergency use authorization (EUA) for 4 mAbs. As new SARS-CoV-2 variants emerge, the clinical efficacy of previously approved mAbs is being called into question, prompting clinicians and scientists to reconsider and pursue the development of new drugs to treat COVID-19. The FDA has also made numerous updates to previously authorized recommended drugs, rendering them unavailable or making conditional recommendations.

Convalescent plasma (CP), highly concentrated immunoglobulin (HIG), and anti-SSA (ASSA) products have been recommended or conditionally recommended for use in clinical research and healthcare facilities. For patients with mild to moderate COVID-19 who are at risk of progressing to critical illness, the FDA has approved the use of single or combined mAbs. Two mAbs can be combined in some cases to interfere with SARS-CoV-2 for post-exposure prophylaxis. Tocilizumab, an anti-interleukin-6 inhibitor, and baricitinib, a Janus kinase inhibitor, have received EUA from the FDA and are recommended for patients with severe COVID-19 who are receiving corticosteroids[6]. Tocilizumab reduces mortality in critically ill patients and also the number of days without need for artificial organ support; the recommended dose is 8 mg tocilizumab per kg body weight (up to 800 mg) in 1 h intravenous infusion, with a second dose repeated 12 to 24 h later if needed[7]. The combination of interleukin-6 blockers in particular may be more beneficial[8]. Baricitinib, an antiviral drug, is used to treat severe or critical COVID-19 and has been shown to reduce mortality, hospitalization, and the need for mechanical ventilation[9,10]. Corticosteroids are usually only used as a last resort in COVID-19 patients who are critically ill; routine use is generally not advised.

The purpose of this article is to discuss the clinical value of SSA detection technologies and ASSA in the treatment of COVID-19.

## DYNAMIC CHANGES IN SARS-COV-2 SPECIFIC ANTIBODIES

Antibodies are reactive substances (immunoglobulins) produced by the immune system to combat invading pathogenic microorganisms and can bind to specific pathogens. SSAs are mainly composed of immunoglobulin M (IgM) and immunoglobulin G (IgG) Abs. IgM Abs are produced during the early stages of infection and can enhance the ability of the innate immune system to phagocytose, agglutinate, and kill pathogens. IgG is the main type of Ab in plasma (approximately 75%) and is involved in Ab-dependent cellular phagocytosis and complement-mediated cytotoxicity against bacterial and viral infections. Abs positivity is indirect evidence of infection caused by pathogenic microorganisms.



Detecting the levels of IgM and IgG can also reveal the immune function of the body, which is an important factor contributing to public health and has great clinical significance.

After infection by a pathogen, certain steps associated with the production of Abs can be used to diagnose and treat disease. In a COVID-19 study involving 34 adults, Abs were assessed starting at 2 wk after disease onset. After 3 wk, the Ab tests of all patients were positive. The average levels of IgG and IgM were 112.40 AU/mL and 322.80 AU/mL (reference range < 10 AU/mL), respectively. After 4 wk, the level of IgM began to decline, and an average value of 147.92 AU/mL was recorded; the average level of IgG increased to 157.01 AU/mL. After 5 wk, the average level of IgM continued to fall, reaching 78.03 AU/mL, and 2 patients were negative for IgM; the IgG levels of all patients increased, reaching an average of 163.56 AU/mL. At the end of week 7, the study was terminated. Two patients were negative for IgM, and the average IgM level dropped to 21.83 AU/mL; all patients were positive for IgG, and their average titer increased to 167.16 AU/mL. A high level of IgM indicates that the infection is in the acute phase, and relatively high IgM levels lasting longer than 1 mo indicate a longer viral replication time. IgG Abs appear later than IgM Abs, persist longer, and are present at a higher level, indicating that the humoral immune response acts to defend the host against SARS-CoV-2 infection[11].

A study by Lee *et al*[12] showed that IgM was detected on the day 5 of infection, and the longest duration of detection was 42 d after the onset of disease. In another patient, IgG was also detected by day 5 after the onset of disease. In most cases, once positive, IgG remains positive. The duration of PCR positivity is related to the Abs response and clinical manifestations. In patients with detectable symptoms and IgM Abs positivity, nucleic acid-based tests can quickly become negative[12]. Another study analyzed 38 cases of COVID-19 and found the highest level of viral RNA in sputum samples (92.3%) in the early stage of the disease (7 d after disease onset); the next highest viral RNA level was detected in pharyngeal swabs (69.2%). In this study, Abs were detected in fewer positive cases (IgM 23.0% and IgG 53.8%). Abs titers increased to 50.0% (IgM) and 87.5% (IgG) after 8 d, and Abs detection was found to be easier than viral RNA detection. After 15 d, the detection rate of viral RNA was 52.2%, indicating that Abs detection could be useful for auxiliary diagnosis. For patients who have achieved clearance of the virus, PCR testing is not suitable. The initial immune response is marked by an increase in the IgM level and the detection of IgM indicates that the infection is recent; as such, IgM can be used for the early diagnosis of COVID-19. IgG is produced after IgM and persists longer; it is a diagnostic indicator of a secondary infection or previous exposure[13].

Timilsina *et al*[14], described an electrochemical device that can rapidly and quantitatively detect Abs against SARS-CoV-2 in clinic. This method was shown to be simple to use, economic, sensitive (100% sensitivity and specificity), and fast (10 min). Furthermore, it required blood samples of only 1.5 µL, and Abs could even be detected in dry blood spots. This test can be operated on-site and *via* remote application, and may have great promise in the future of COVID-19 testing[14].

The monumental achievement in creating an effective vaccine against SARS-CoV-2 presents a new challenge for Abs testing: can Abs produced by vaccination be distinguished from those produced by the real virus? How long do the Abs from the vaccine last? The answers to these questions are key to preparing for any future wave of the COVID-19 pandemic[15]. A schematic diagram of the dynamic changes in human antibody production after the initial infection (Figure 1).

Zamani *et al*[16] studied the kinetics of seroconversion in 118 hospitalized patients with COVID-19 (Table 1). The authors demonstrated the kinetics of seroconversion in COVID-19 patients, and showed that 83.5% of IgM and 36.8% of IgG patients who were originally positive were found to be negative within 3 mo after the onset of symptoms. These findings suggest that the retention time of anti-SARS-CoV-2 Abs could be used as a reference for SARS-CoV-2 prevention, control, and vaccine administration. No correlation was found between Abs titers and patient age at any time point. In addition, mean Abs levels at different times after the onset of clinical symptoms also did not exhibit a predilection for either sex.

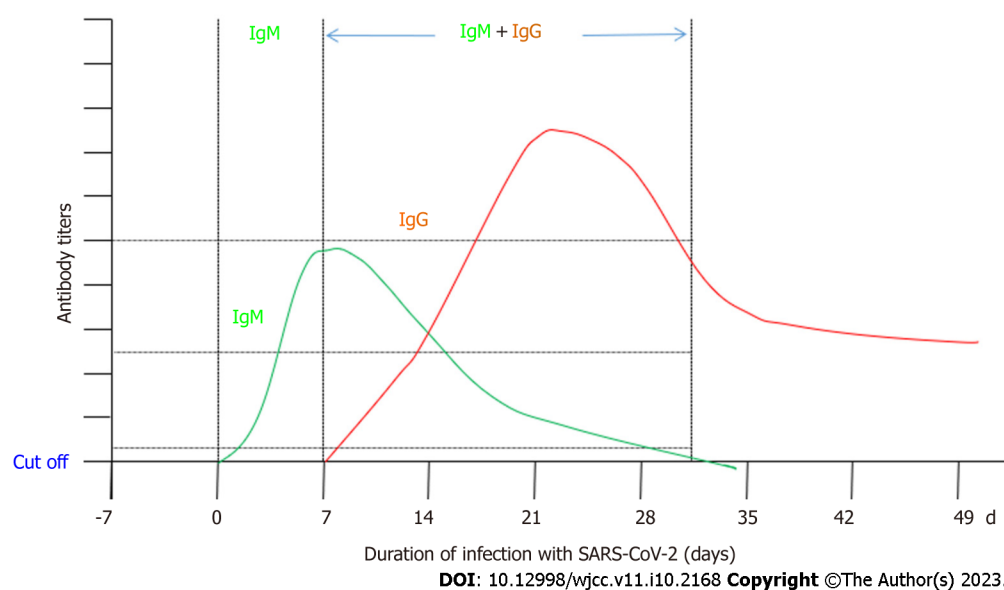
## ROLE OF SARS-COV-2 SPECIFIC ANTIBODIES IN COVID-19 SCREENING AND DIGNOSIS

Wu *et al*[17] performed COVID-19 screening on 1021 workers in the Recovery Work Group (RG) and 381 patients in the COVID-19 Non-Hospital Group (NHG), totaling 1402 subjects. Screening included nasopharyngeal swab nucleic acid detection, chest computed tomography (CT), and IgM and IgG Abs detection. In NHG, one case of nucleic acid was positive, as were IgM and IgG. Other patients' CT chest radiographs were normal, and the nucleic acid tests were negative. After being diagnosed with COVID-19, the positive patient was "cured." He was transferred to a hospital specializing in COVID-19 treatment after testing positive again. In RG, 98 (98/1021, 9.60%) patients were IgG positive, IgM negative, and nasopharyngeal swab PCR negative. In NHG, 39 cases (39/380, 10.3%) of nasopharyngeal swab samples were positive for IgG, negative for IgM, and negative by PCR. These findings suggest that 137 (98 + 39) patients had previously been infected with SARS-CoV-2. The IgG-positive patients had no suspicious symptoms and no history of COVID-19. None of these cases had previously been tested by PCR. In other words, the patients had recovered from asymptomatic infections discovered only through Abs screening[17].

**Table 1 Seropositive rates of severe acute respiratory distress syndrome coronavirus-2-specific immunoglobulin G and immunoglobulin M at various time points after symptom onset**

Days after symptom onset	IgM positivity rate (%)	IgG positivity rate (%)
0–5	44/118 (37.3)	71/118 (60.2)
6–15	36/55 (65.5)	44/55 (80.0)
16–25	48/70 (68.6)	56/70 (80.0)
26–35	26/56 (46.4)	2/56 (75.0)
36–95	17/95 (17.9)	56/95 (58.9)

IgG: Immunoglobulin G; IgM: Immunoglobulin M.

**Figure 1 Schematic diagram of the dynamic changes in antibody production after initial infection with severe acute respiratory virus-2.**  
Due to differences in data from analytical studies, these data are considered approximations only.

To determine the diagnostic efficacy of IgM and IgG Abs in suspected cases, Abs tests were conducted in 52 patients whose symptoms or CT imaging characteristics met the COVID-19 criteria but who had multiple consecutive negative PCR results. IgG or IgM Abs were positive in 4 patients. Reasonable speculation led to a diagnosis of COVID-19. Similarly, to determine the diagnostic efficacy of IgG and IgM tests for asymptomatic infections, the team conducted Ab screening in 164 close contacts, 16 of whom were positive for IgM or IgG. Among the 148 patients excluded by PCR 1 mo before the screening process, 7 were also positive for the Abs. These individuals had never experienced any symptoms, indicating that they were asymptomatic carriers who could not have been diagnosed by nucleic acid detection. Thus, increasing the frequency of IgM and IgG Abs testing could help to confirm the diagnosis of suspected cases and screen for asymptomatic individuals[18].

A comprehensive study found that the earliest IgM Abs appear within 5–7 d after infection with SARS-CoV-2[13]. Abs testing can provide results within 15 min, and the technique is simple and convenient, which is helpful for the rapid screening of febrile patients. In infected individuals, during the incubation period of the virus before the development of the disease, IgM is not produced and cannot be detected. Hence, the detection of Abs alone is not suitable for early screening. Abs testing can only play an auxiliary diagnostic role; the maintenance time of IgM is short, and IgM disappears by the end of the infection. IgM positivity is the only basis for the early diagnosis of an infection. IgG is produced 10–15 d after infection and is present for a long period after the disease course has ended. Furthermore, IgG can persist in the body, even in the blood, for a lifetime. A positive IgG Ab test can indicate a pathogenic infection. When the same pathogen is encountered, the specific IgG binds to the pathogen, reducing its activity and preventing it from binding to human cells. IgG can also rapidly activate the innate immune system, shortening immune response time and avoiding or reducing the recurrence of the disease. Abs detection is a practical method for conducting an epidemiological survey after an outbreak, despite the reported 10%–15% deviation. It has high sensitivity and can serve as a

valid metric for a long time after a disease is no longer present in an individual. Moreover, Abs detection can very accurately identify asymptomatic infected individuals and thereby helps determine the actual scale of the pandemic[17,18].

In a study of 173 patients, plasma samples ( $n = 535$ ) were collected for the detection of total anti-SARS-CoV-2 Abs, IgG, and IgM. The dynamics of the antibody levels during disease progression were also analyzed. The seroconversion rates of IgG, IgM, and Abs were 64.7%, 82.7%, and 93.1%, respectively. The median seroconversion times of IgM, IgG, and Abs were 14 d, 12 d, and 11 d, respectively. One week after disease onset, the prevalence of antibodies in studied patients was less than 40%. From 15 d after onset, the prevalence increased starkly to 79.8% (IgG), 94.3% (IgM), and 100.0% (Abs). The detectability of RNA decreased from 66.7% (58/87) at day 7 to 45.5% (25/55) between 15 d and 39 d after the disease onset. Even in the early stages, the combined application of RNA and Abs detection can significantly improve the diagnosis rate of COVID-19 ( $p < 0.001$ )[19]. When rapid PCR testing for SARS-CoV-2 was not available, another study concluded that using rapid antigen-Abs combined testing improved detection accuracy, with a sensitivity of 91.2% and a specificity of 98.9%. The results of antigen and Abs testing can be used as a reliable substitute for PCR testing[20]. Clinical significance of the combined detection of SSA and SARS-CoV-2 RNA (Table 2).

## ROLE OF ANTI-SARS-COV-2 SPECIFIC ANTIBODIES IN THE TREATMENT OF COVID-19

### *Therapeutic effect of convalescent plasma on COVID-19*

Immunological studies have shown that Abs in CP can recognize antigenic determinants of pathogens, including those of viruses. These Abs can neutralize the virus, reduce the viral load, and prevent or cure disease. In other words, Abs can trigger and participate in a self-repairing process in the body. By providing Nabs, CP is a form of passive immunotherapy. The benefits of CP infusion in related diseases were first studied in the 20<sup>th</sup> century[21]. In the absence of specific treatments for emerging infectious diseases, CP therapy remains an important treatment method[22]. CP has been shown to be effective in treating patients with influenza A (H1N1)[23], severe acute respiratory syndrome[24], and Middle East respiratory syndrome[25].

On August 23, 2020, the United States FDA approved the emergency use of CP as a potential COVID-19 treatment. Plasma therapy, according to the FDA, can effectively reduce the severity or the duration of COVID-19 disease in some hospitalized patients, and the known potential benefits far outweigh the product's risks[26]. With the continuous emergence of SARS-CoV-2 variants, previously effective treatment methods have been called into question. Several other observational studies and randomized controlled trials have recently been reviewed by experts from the National Institutes of Health (NIH) in the United States[27-29]. In these studies, the efficacy of CP against COVID-19 was investigated in both outpatient and inpatient settings. The FDA updated the EUA of CP to treat COVID-19[30] on November 28, 2021. Only CP with high titers of SARS-CoV-2 Abs is thought to be effective in patients with COVID-19 who are immunocompromised (*i.e.* those who have recently received radiation, chemotherapy, or who have immunodeficiency disease) or have received immunosuppressive therapy[29], and the potential benefits to patients may outweigh the known potential risks. However, infusion of CP in immunocompetent COVID-19 patients is unlikely to be clinically beneficial, and its use in these patients is not advised.

The WHO treatment guidelines only recommend the use of CP in the research and clinical trial settings[31]. However, based on subgroup data analysis from several observational studies and randomized controlled trials[27-29], the NIH treatment guidelines still recommend that CP be used for COVID-19 patients with secondary or primary humoral immunodeficiency (*e.g.*, with agammaglobulinemia, hematological malignancies, solid organ transplant, or other immunodeficiency)[32,33]. In a subset of immunocompromised patients, some findings suggest that CP may provide benefits such as improved survival and/or more days without organ support when compared to placebo [odds ratio 1.51; 95 percent confidence interval(CI): 0.80–2.92][29].

In clinical practice, a high titer CP with a volume of 200 mL can be considered first, and the need to increase the dose can be determined based on the individual patient scenario. Past and current studies have demonstrated real-world clinical efficacy for the treatment of COVID-19 with CP[34-36]. This suggests that high-level randomized controlled trials (RCTs) should be designed in the future to investigate the potential therapeutic effects of CP in the treatment of COVID-19.

The Infectious Diseases Society of America and the FDA have also re-evaluated CP for use in outpatients at risk of progression due to the lack of antiviral drugs, as the polyclonal nature of CP can render SARS-CoV-2 variants less able to escape immune defenses[37,38].

### *Therapeutic effect of highly concentrated immunoglobulin on COVID-19*

HIG is a high-titer Abs preparation made up of anti-SARS-CoV-2 mAbs from multiple CP donors that is more concentrated than anti-SARS-CoV-2 Specific antibodies (ASSAs) from a single donor (the SARS-CoV-2 Abs titer is several times higher)[39]. The preparation may work by inhibiting the virus and altering inflammation. Varicella zoster immunoglobulin has been used for varicella post-exposure

**Table 2 Clinical significance of combined detection of severe acute respiratory distress syndrome coronavirus-2-specific antibodies and RNA**

No.	Antibody assay		Nucleic acid detection	Clinical significance
	IgM	IgG		
1	+	+	+	During the active infection period, the body has a certain resistance to COVID-19 (persistent IgG has been produced)
2	+	-	+	The patient may be in the middle of the SARS-CoV-2 infection. The body's immune response produces IgM antibodies early in the disease course. IgG has not yet been produced, or the IgG level has not reached the limit of detection
3	-	+	+	The patient may be in the middle or late phase of the disease or may have a recurrent infection of SARS-CoV-2
4	-	-	+	This is the COVID-19 "window period", which usually lasts 2 wk
5	+	+	-	The patient is in the recovery phase of COVID-19. The virus has been cleared from the body, and IgM and IgG are positive. Alternatively, this may indicate that the nucleic acid test result was a false negative, and the patient is in the active phase of infection
6	+	-	-	IgM positivity indicates that the patient may be in the early stage of infection. Suspicious nucleic acid test results require repeated sampling and verification
7	±	-	-	This indicates that the patient is in the early stage of viral infection, and the viral load is very low. The patient is in the acute stage of COVID-19, and the body has not yet produced IgG. Alternatively, the result for IgM may have been an error caused by the presence of rheumatoid factor. One week later, the examination and diagnosis must be repeated based to evaluate for changes in IgM and IgG
8	-	+	-	The patient may have been infected with the virus in the past and has recovered; the virus has been cleared from the body. IgG can last for a long time, possibly even for life
9	-	-	-	The individual is healthy or in the incubation period of infection

IgM: Immunoglobulin M; IgG: Immunoglobulin G; COVID-19: Coronavirus infectious disease 2019; SARS-CoV-2: Severe acute respiratory distress syndrome coronavirus-2.

prophylaxis (PEP) in high-risk individuals, and cytomegalovirus immunoglobulin has been shown to be effective and safe for the prevention of post-transplant cytomegalovirus infection. However, clinical data on the treatment of COVID-19 with HIG are currently lacking[40].

### ***Therapeutic effect of anti-SARS-CoV-2 specific antibodies against COVID-19***

Spike protein (S), nucleocapsid protein, membrane protein, envelope protein, and auxiliary and nonstructural proteins are all encoded by the SARS-CoV-2 genome. S1 and S2 are thorn protein subtypes. S1 binds to angiotensin-converting enzyme 2 receptors on host cells. It causes S2 to change conformation, fuses the viral and host cell membranes, and allows the virus to enter human cells[41]. Binding of spike protein by mAbs decreases SARS-CoV-2 infectivity, resulting in a therapeutic effect. Indeed, ASSAs have shown clinical efficacy in the treatment of SARS-CoV-2 infection[42].

### ***Anti-SARS-CoV-2 monoclonal antibody for pre-exposure prophylaxis of SARS-CoV-2 infection***

Experts recommend intramuscular tixagevimab plus cilgavimab (Evusheld) as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (age ≥ 12 years and weight ≥ 40 kg) who have not been exposed to COVID-19. In patients with moderate to severe immunocompromise, the immune response to the COVID-19 vaccine may be insufficient, or vaccination with any available COVID-19 vaccine may not be complete[43]. Omicron mutant sensitivity to tixagevimab plus cilgavimab has been shown to be moderately reduced, but the regimen was still beneficial for PrEP prevention of infection by Omicron strains.

### ***Anti-SARS-CoV-2 monoclonal antibodies for post-exposure prophylaxis of SARS-CoV-2 infection***

Casirivimab plus imdevimab and bamlanivimab plus elexsevimab are not recommended for PEP of SARS-CoV-2[42] in countries and regions where Omicron variant strains are prevalent as these strains are not susceptible to these drugs. Prior to Omicron, the FDA issued a EUA for this regimen, allowing PEP in people who are at high risk of SARS-CoV-2 infection and have a high risk of developing severe COVID-19 disease. This protocol should be made available for PEP of the individuals listed above in non-Omicron endemic countries and regions.

### ***Anti-SARS-CoV-2 monoclonal antibodies for outpatient COVID-19 patients***

To treat outpatients (age ≥ 12 years and weight ≥ 40 kg) with mild to moderate COVID-19 and high risk of clinical progression, the use of sotrovimab 500 mg as a single intravenous infusion within 10 d of symptom onset is recommended. Sotrovimab retains *in vitro* activity against Omicron variants and is



believed to benefit Omicron-infected patients clinically[44].

Experts do not recommend casirivimab plus imdevimab or bamlanivimab plus etesevimab because Omicron is not susceptible to these drugs. However, because the FDA issued EUA prior to the Omicron epidemic, these regimens can be used in countries and regions where Omicron is not endemic. The use of casilimab plus imdevimab has also been halted in the United States due to Omicron variant insensitivity[45]. Casilimab 600 mg plus imdevimab 600 mg administered as a single intravenous infusion were approved by the FDA prior to the spread of Omicron and is approved for the treatment of patients with mild to moderate COVID-19. The use of this protocol is supported by results from a phase 3 double-blind, randomized, placebo-controlled trial in outpatients with mild to moderate COVID-19[46]. This regimen can still be used in places where non-Omicron variants are prevalent.

### **Anti-SARS-CoV-2 monoclonal antibodies for COVID-19 hospitalized patients**

In one study, 583 outpatients with mild to moderate COVID-19 were studied. Two hundred ninety-one subjects were randomly assigned to receive sotrovimab (500 mg IV) and 292 subjects received placebo. On day 29, the primary endpoint was the proportion of hospital stays longer than 24 h or death from any cause. Three patients (1%) in the sotrovimab group and 21 patients (7%) in the placebo group required hospitalization or died as a result of disease progression (relative risk reduction, 85%; 97.24%CI: 44-96;  $P = 0.002$ ). On day 29, 1 patient in the placebo group died after being admitted to the intensive care unit. Adverse events were reported in 17% of patients in the sotrovimab group and 19% of patients in the placebo group during the safety assessment; the incidence of serious adverse events was lower in the sotrovimab group than in the placebo group (2% and 6%, respectively). Sostovizumab reduced the risk of COVID-19 exacerbations in high-risk patients with mild to moderate COVID-19[47].

The use of bamlanivimab plus etesevimab to treat COVID-19 has been halted in the United States because the Omicron variant has poor susceptibility to this mAb *in vitro*[45]. Prior to the emergence of the Omicron variant, the BLAZE-1 phase 3 clinical trial demonstrated that bamlanivimab plus etesevimab benefits patients with mild to moderate COVID-19 at risk of progression to severe disease with or without hospitalization[46]. The main SARS-CoV-2 strain currently introduced to China from abroad is Omicron BA.2. Pfizer's antiviral drug Paxlovid (nirmatovir plus ritonavir) is recommended for adults and adolescents aged 12–17 years old, weight  $\geq 40$  kg. Paxlovid is given in cases of mild disease within 5 d of onset according to China's Protocol for Prevention and Control of Novel Coronavirus Infection (10<sup>th</sup> Ed)[48].

### **Anti-SARS-CoV-2 monoclonal antibodies for hospitalized patients with severe or critical COVID-19**

ASSA are not currently approved for use in hospitalized patients with severe COVID-19; however, these products may see use in such patients through an expanded access plan. Casirivimab plus imdevimab is conditionally recommended for COVID-19 patients with severe or critical illness, and may also benefit seronegative patients. According to the RECOVERY trial, a credible subgroup effect suggests that casirivimab plus imdevimab may reduce mortality and days requiring mechanical ventilation in patients with seronegative status[31].

Relevant literature is summarized in Table 3[49-54]. Many therapeutic mAbs that were previously effective became ineffective in the face of the Omicron variant; studies of these are not included.

### **Safety of monoclonal antibodies in clinical application**

In most studies, adverse events with the use of therapeutic mAbs were not serious (*e.g.*, nausea, diarrhea) and were mostly self-limiting. The most common adverse events were mild reactions, chills, headache, injection site pain, and bronchospasm. Serious adverse events were rare, and observed instances of shortness of breath may be associated with exacerbations of COVID-19 itself[37].

### **Limitations of this article**

SARS-CoV-2 has been raging for nearly 3 years. In the past 2 years, the mutation of SARS-CoV-2 has become more and more frequent, and transmission speed is also faster, especially with the Omicron variant. Fortunately, Omicron is becoming less toxic. The mutation of the virus reduces the efficacy of existing therapeutic drugs, which can now only be applied in some special circumstances. This is the case of the use of CP or mAbs in the treatment of COVID-19. The FDA's EUAs for many drugs are require constant updates. As human efforts cannot keep up with the speed of Omicron mutation, we should redouble our efforts to proactively discover the pattern of SARS-CoV-2 mutation and finally defeat the novel coronavirus.

## **CONCLUSION**

SSA detection technology is widely used in clinical practice. It can assist PCR nucleic acid in the diagnosis, screening, and tracking of infection in patients with COVID-19 (including mild and asymptomatic infections). Thus, it is valuable for public health and has many potential clinical applications[55].

Table 3 Sensitivity of Omicron variants to therapeutic monoclonal antibodies

mAb (s)	FDA EUA	Target on S	Omicron variant			
			BA.1	IC <sub>50</sub>	BA.2	IC <sub>50</sub>
Bamla/Etese	Yes	BRD or S	Reduction in activity <i>vs</i> control approximately 1000-fold (highly resistant)	> 10000 ng/mL	Reduction in activity <i>vs</i> control approximately 1000-fold (highly resistant)	> 10000 ng/mL
Casir/Imdev	Yes	BRD	Reduction in activity <i>vs</i> control approximately 1000-fold (highly resistant)	> 10000 ng/mL	Reduction in activity <i>vs</i> control approximately 1000-fold (highly resistant)	> 10000 ng/mL
Sotro	Yes	BRD	Median fold reduction in susceptibility 4.0 (IQR: 2.6 to 6.9)	Median 276 ng/mL (IQR: 163 to 423)	Median fold reduction in susceptibility 17 (IQR: 13 to 30)	Median 1250 ng/mL (IQR: 567 to 1456)
Cilag/Tixag	Yes	BRD	Median fold reduction in susceptibility 86 (IQR: 27 to 151). The FDA recommended that the dosage for each mAb in this combination be increased 300 mg and administered intramuscularly	Median 256 ng/mL (IQR: 170 to 750)	Median fold reduction in susceptibility 5.4 (IQR: 3.7 to 6.9). Nearly complete restoration BA.2 suscepti- bility to cilgavimab	Median 44 ng/mL (IQR: 27 to 73)
Bebte	Yes	BRD	Median fold reduction in susceptibility 1.0 (IQR: 0.7 to 1.4) Bebtelovimab is the only mAb active against the current dominant circulating Omicron variant; in non- hospitalized adults, bebtelovimab may be used as an alternative therapy when no preferred therapy ( <i>e.g.</i> , nirmatrelvir/ritonavir, remdesivir) available	Median 2.6 ng/mL (IQR: 1.8 to 5.0)	Median fold reduction in susceptibility 1.0 (IQR: 0.7 to 1)	Median 4.0 ng/mL (IQR: 0.8 to 5.0)
Regda	No	BRD	Displayed little residual activity	NA	Displayed little residual activity	NA
Amuba	No	BRD	Displayed little residual activity	NA	Displayed little residual activity	NA
Romlu	No	BRD	Retained partial activity	NA	Displayed little residual activity	NA
Adint	No	BRD	Retained partial activity	NA		NA

Adint: Adintrevimab; Amuba: Amubarvimab; Bamla/Etese: Bamlanivimab/Etesevimab; Bebtte: Bebtelovimab; BRD: Spike receptor binding domain; Casir/Imdev: Casirivimab/Imdevimab; Cilag/Tixa: Cilgavimab/Tixagevimab; EUA: Emergency use authorization; FDA: United States Food and Drug Administration; IC<sub>50</sub>: 50% inhibitory concentration; IQR: Interquartile range; mAbs: Monoclonal antibodies; NA: Not available; Regda: Regdanvimab; Romlu: Romlusevimab; S: Spike protein; Sotro: Sotrovimab.

Because of the emergence of Delta and Omicron variants, the use of CP is severely limited. It is only recommended for use in COVID-19 patients with impaired immune function, immunodeficiency, or who are taking immunosuppressants. HIG could theoretically treat COVID-19, but there is currently insufficient data to guide its use. Treatment with ASSAs has made significant progress, and outpatient outcomes are promising. Several clinical trials[27-29] have assessed ASSA's efficacy and safety in the treatment of non-hospitalized COVID-19 patients. Sotrovimab was evaluated in the Phase 3 trial COMET-ICE for the treatment of COVID-19. This mAb treatment is thought to be more effective, and has proven effective in preventing COVID-19[47]. The United States FDA granted a EUA for the use of sotrovimab[56] in May 2021. The BLAZE-1 study investigated the efficacy of intravenous bamlanivimab in the early treatment of COVID-19[57]. Bebtelovimab is the only anti-SARS-CoV-2 mAb active against the current dominant circulating Omicron variant[50]. Monoclonal antibodies can protect unvaccinated people or people exposed to high-risk environments in a prophylactic manner. The effectiveness of mAbs targeting the SARS-CoV-2 spike protein is also promising; however, research must continue to actively pursue new drugs and methods for the accurate and rapid diagnosis and treatment of COVID-19.

## FOOTNOTES

**Author contributions:** Yang ZD and Sun J contributed to conception and design, these authors have contributed equally to this work and share first authorship; Yang ZD, Qu BB, Song GW, Xu JQ and Gong B contributed to administrative support; Song GW and Li L contributed to provision of study materials; Yang ZD, Song GW, Xie X, Li L, Zeng HS and Wu JH contributed to collection and assembly of data; Yang ZD, Sun J, Zeng HS, Gong B, Xu JQ, Qu BB and Xie X contributed to data analysis and interpretation; All authors contributed to manuscript revision and approved the submitted version.

**Conflict-of-interest statement:** All the authors report having no relevant conflicts of interest for this article.

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**S-Editor:** Li L

**L-Editor:** Filipodia

**P-Editor:** Li L

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