

REVIEW

Protective and pathogenic role of humoral responses in COVID-19

Uni Park^{1,2} and Nam-Hyuk Cho^{1,2,3,4,5*}

¹Department of Microbiology and Immunology, College of Medicine, Seoul National University, Seoul 03080, Republic of Korea

²Department of Biomedical Sciences, College of Medicine, Seoul National University, Seoul 03080, Republic of Korea

³Institute of Endemic Disease, Seoul National University Medical Research Center, Seoul 03080, Republic of Korea

⁴Seoul National University Bundang Hospital, Seongnam 13620, Republic of Korea

⁵Wide River Institute of Immunology, Seoul National University, Hongcheon 25159, Republic of Korea

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Since the advent of SARS-CoV-2 in Dec. 2019, the global endeavor to identify the pathogenic mechanism of COVID-19 has been ongoing. Although humoral immunity including neutralizing activity play an important role in protection from the viral pathogen, dysregulated antibody responses may be associated with the pathogenic progression of COVID-19, especially in high-risk individuals. In addition, SARS-CoV-2 spike-specific antibodies acquired by prior infection or vaccination act as immune pressure, driving continuous population turnover by selecting for antibody-escaping mutations. Here, we review accumulating knowledge on the potential role of humoral immune responses in COVID-19, primarily focusing on their beneficial and pathogenic properties. Understanding the multifaceted regulatory mechanisms of humoral responses during SARS-CoV-2 infection can help us to develop more effective therapeutics, as well as protective measures against the ongoing pandemic.

Keywords: COVID-19, SARS-CoV-2, humoral immunity, antibody-escaping variants

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has swept through the world with more than 270 million confirmed cases and about 5 million deaths (<http://covid19.who.int>). Many COVID-19 patients suffer from respiratory symptoms such as cough, sore throat, and shortness of breath, as well as fever, chills, headache, and

diarrhea (<http://korean.cdc.gov/>). Although many of the confirmed cases are asymptomatic or have mild symptoms, less than 20% of patient present with severe pneumonia or acute respiratory syndrome (ARDS), and these cases are often fatal (Sharma *et al.*, 2020; Zhao *et al.*, 2020). Despite the global effort to elucidate the pathogenic mechanisms of COVID-19, the primary culprits of pneumonic progression leading to severe ARDS and death remain unclear.

During viral infection, adaptive immune responses, including T cell-mediated cellular immunity and B cell-mediated humoral immune responses, play an important role in protection from a major illness (Murin *et al.*, 2019). For example, viral antigen-specific antibodies can neutralize the invading pathogens by blocking the cellular entry of SARS-CoV-2 (Dörner and Radbruch, 2007). In addition, long-lived plasma cells generated from activated B cells during virus infection produce antigen-specific antibodies over a long period, even in the absence of viral antigens (Slifka and Ahmed, 1998; Dörner and Radbruch, 2007; Quast and Tarlinton, 2021). These persistent antibody responses against viruses can protect the host from reinfection by the viruses (Slifka and Ahmed, 1998; Hangartner *et al.*, 2006; Dörner and Radbruch, 2007). However, both the levels and durability of antibody responses vary depending on the patient's condition, disease severity, and the type of viral pathogens (Wiseman *et al.*, 2020; Nguyen *et al.*, 2021). Moreover, preformed antibodies can induce pathological side effects such as antibody-dependent enhancement (ADE). This can lead to enhanced viral infection, aberrant induction of inflammation via engagement of Fcγ receptors (FcγR) in phagocytic cells, and priming overt complement activation via the classical pathway during the reinfection of several pathogenic viruses (Morens, 1994; Xu *et al.*, 2021). Antibodies can also pressure the emergence of antibody-escaping variants of the virus, making the current pandemic difficult to control (Lok *et al.*, 2001; Hudu *et al.*, 2015; Magnus *et al.*, 2016; Gao *et al.*, 2020; Roy, 2020; Sitaras *et al.*, 2020).

This review summarizes and discusses current knowledge on the potential role of humoral immune responses in COVID-19, primarily focusing on their beneficial and pathogenic properties (Fig. 1). Understanding the regulatory mechanisms of specific humoral responses in COVID-19 can help us develop more effective therapeutics as well as protective measures against the ongoing pandemic.

*For correspondence. E-mail: chonh@snu.ac.kr; Tel.: +82-2-740-8392;

Fax: +82-2-743-0881

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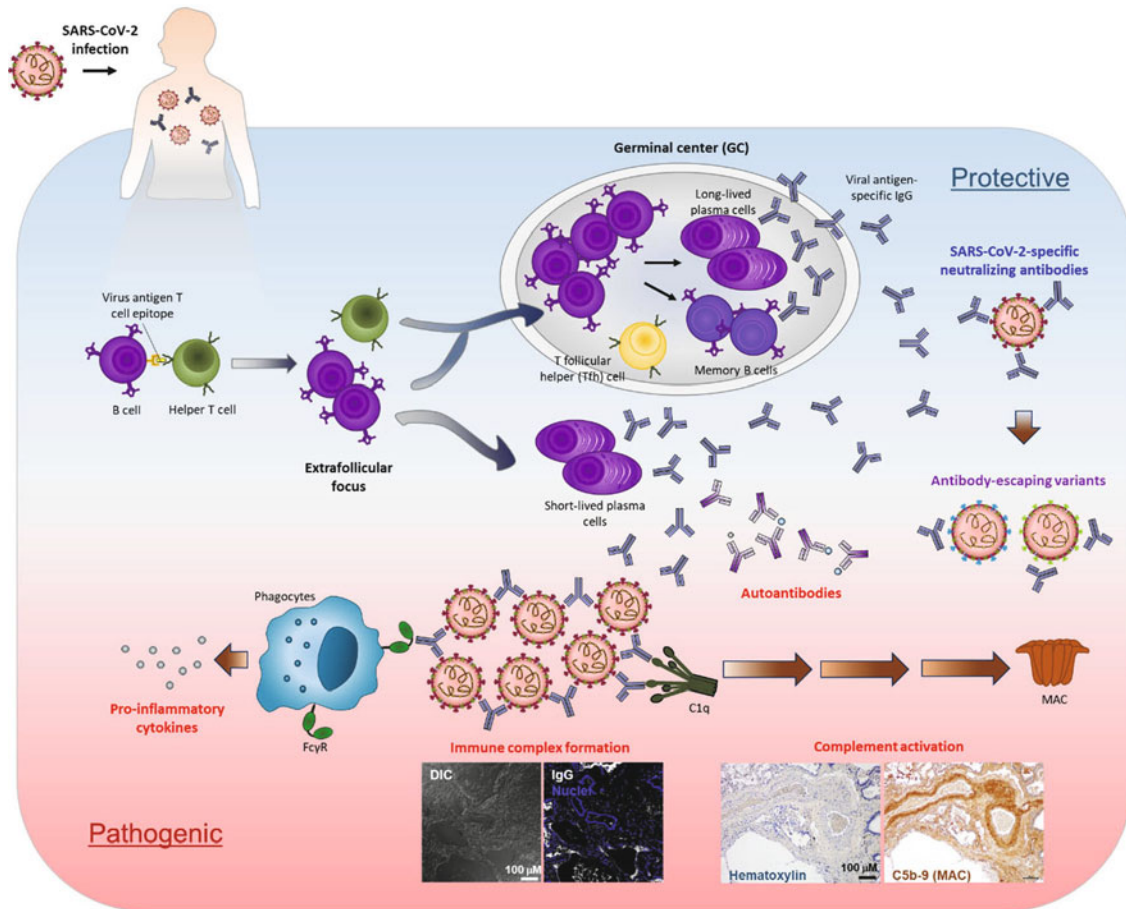


Fig. 1. Protective and pathogenic humoral responses in COVID-19 patients. During SARS-CoV-2 infection, the viral antigen is recognized by and activates both B cells and T cells. The activated B and T cells interact with each other at the interface of B and T cell zones. These interactions yield an extrafollicular focus. In the extrafollicular focus, activated B cells proliferate and differentiate into plasma cells, most of which are short-lived plasma cells. Some helper T cells can differentiate into T follicular helper (Tfh) cells in the extrafollicular focus, which then migrate back into the follicle with some activated B cells. This results in a germinal center (GC) formation. In the GC, activated B cells can differentiate into long-lived plasma cells or memory B cells. The viral antigen-specific antibodies secreted by plasma cells play a protective role by neutralizing viral infection. On the other hand, antibodies can also have a pathogenic effect. Autoantibody reactions against immunomodulatory proteins have been detected in some patients with severe COVID-19. SARS-CoV-2 antigen-specific antibodies can induce immune complex formation by binding viral antigens. The Fc regions of immune complex-forming antibodies interact with Fc γ R expressed by phagocytes; this is, followed by excessive pro-inflammatory cytokine secretion. Viral antigen-specific antibodies also can induce complement activation via the classical pathway. Immune complex and membrane-attack complex (MAC) deposition has been observed in the lungs of patients who have died of COVID-19, suggesting that dysregulated antibody responses are potential pathogenic drivers of COVID-19 progression via the induction of cytokine storms, thrombosis, and coagulopathy. SARS-CoV-2 has continued to evolve to escape host antibody responses, and the emergence of these antibody-escaping variants is among the major challenges in attempts to control this virus.

Differential Antibody Responses Associated with COVID-19 Severity

Since the advent of SARS-CoV-2, researchers have tried to identify primary factors associated with COVID-19 severity. In an acute viral infection, higher viral loads and inefficient viral clearance during the early phase of infection are generally associated with more severe outcomes. In addition, dysregulated and overt inflammation could be an additional pathogenic driver of severe disease progression. For example, during the acute phase of Dengue virus infection, the severity of the disease is primarily determined by the viral load (Morsy *et al.*, 2020). The override of immune reactions or inflammatory responses against Influenza virus or Middle East respiratory syndrome coronavirus (MERS-CoV) can also worsen

the clinical progression of these infections (Min *et al.*, 2016; Myers *et al.*, 2021). Although it is still contested whether SARS-CoV-2 viral loads are positively correlated with disease severity, we and others have reported that the viral loads of SARS-CoV-2 in respiratory specimens may not be associated with disease severity (Fajnzylber *et al.*, 2020; Abdulrahman *et al.*, 2021; Kim *et al.*, 2021c; Knudtzen *et al.*, 2021; Trunfio *et al.*, 2021). Nevertheless, delayed viral clearance has been observed in younger (under 60 years old) patients with severe COVID-19 and in elderly patients regardless of disease severity (Kim *et al.*, 2021b). In addition, dysregulated immune responses or overt inflammation may be more critical risk factors associated with severe COVID-19 progression. Multiple studies on humoral responses in COVID-19 patients showed that clinical parameters or hospitalization periods were gen-

erally correlated with higher quantities of virus-specific antibodies (Mazzoni *et al.*, 2020; Rijkers *et al.*, 2020; Garcia-Beltran *et al.*, 2021; Kim *et al.*, 2021d; Lucas *et al.*, 2021; Vigón *et al.*, 2021). In addition, patients with the severe disease showed more rapid and robust antibody responses than patients with mild cases (Mazzoni *et al.*, 2020; Rijkers *et al.*, 2020; Kim *et al.*, 2021c). This characteristic of COVID-19 contrasts with previous zoonotic coronavirus infections, including MERS and SARS, in which the specific antibody responses were significantly delayed in critical patients compared to moderate patients during the acute phase of infection (Zhang *et al.*, 2006; Min *et al.*, 2016; Ko *et al.*, 2017). A recent systemic and comparative review of antibody responses in COVID-19, MERS, and SARS reported conflicting results across these coronavirus infections (Huang *et al.*, 2020), which may have been due to inconsistent definitions of clinical grades among the studies. Nevertheless, dozens of research papers also reported a positive correlation between antibody levels and survival in COVID-19 patients.

In another study, the positivity of a specific immunoglobulin G (IgG) to the SARS-CoV-2 receptor binding domain (RBD) was a predictor of survival in COVID-19 patients (Secchi *et al.*, 2020). Garcia-Beltran *et al.* (2021) proposed that a higher neutralization potency of antibodies predicts survival and Lucas *et al.* (2021) claimed that patients could recover if the neutralizing antibodies are produced within 14 days of the onset of symptoms. On the other hand, Trinité *et al.* (2021) found that in critical cases, patients produced more rapid and greater quantities of neutralizing antibodies than in asymptomatic or non-critical cases. More robust research with larger data sets and consistent clinical grading is required to define the specific role of antibody responses during the acute phase of primary infection in COVID-19 patients. Nevertheless, it has been generally accepted that convalescent patients who survived severe disease developed higher levels of virus-specific antibodies compared to patients with mild disease regardless of the type of zoonotic coronaviruses (Kim *et al.*, 2021a; Wong and Perlman, 2022). More robust antibody responses and B cell memory could play better protective roles in the future infection of SARS-CoV-2 variants if they provide sufficient neutralizing activity (Kim *et al.*, 2021a).

In the kinetic analysis of humoral immunity in COVID-19 patients, the viral antigen-specific IgG and immunoglobulin M (IgM) seroconversion occurred within two weeks of primary infection and the level of antibodies peaked 3–5 weeks after infection (Long *et al.*, 2020; Feng *et al.*, 2021b). Although most patients showed seroconversion of specific IgM, followed by IgG, seroconversion for IgG and IgM can occur simultaneously (Long *et al.*, 2020). Patients infected with other zoonotic coronaviruses maintain virus-specific antibody levels for many years after infection. SARS-CoV-specific antibodies were reported to persist up to six years post infection (Tang *et al.*, 2011). The seropositivity in recovered MERS patients also persists for up to 4 years and decreases from the fifth year after infection (Cheon *et al.*, 2022). The longevity of specific antibodies to MERS-CoV spike protein depends on the disease severity during the acute phase. Patients who suffered from severe pneumonia were reported to have sustained and higher levels of antibodies, neutralizing activity, and antibody-secreting B cell counts compared to patients who were

asymptomatic or recovered from mild symptoms (Kim *et al.*, 2021a; Cheon *et al.*, 2022). In COVID-19 patients, the longevity of specific antibodies is shorter compared to that of MERS patients. The persistence of antibodies against SARS-CoV-2 RBD, N, or S has been tracked in convalescent patients for more than 1 year. Studies reported that anti-S or N IgG was detected in recovered COVID-19 patients for 6 to 12 months after symptom onset, while anti-S or N IgM levels decreased rapidly from 6 months after symptom onset (Anand *et al.*, 2021; Feng *et al.*, 2021a; Havervall *et al.*, 2021; Wu *et al.*, 2021; Zhang *et al.*, 2021). Neutralizing activity was detected as early as 6 to 17 days after symptom onset (Suthar *et al.*, 2020; Trinité *et al.*, 2021). The neutralizing antibodies can persist for up to 1 year in recovered COVID-19 patients (Figueiredo-Campos *et al.*, 2020; Xiang *et al.*, 2021), although some reports showed that neutralizing antibody levels decreased from 4 or 7 months after the initial infection (Chen *et al.*, 2021a; Feng *et al.*, 2021b; Legros *et al.*, 2021). The correlation between COVID-19 severity and antibody durability has not yet been defined, due to the lack of long-term studies to demonstrate differences between groups. However, several studies have indicated that the longevity of the neutralizing antibody response correlates with COVID-19 severity (Masiá *et al.*, 2021; Trinité *et al.*, 2021).

In addition, accumulating somatic hypermutation was observed in temporal analysis of the antibody sequences in convalescent patients. This suggests that the maturation of antibodies occurred during the convalescent phase (Wong and Perlman, 2022). Asymptomatic or mildly symptomatic patients may not be able to generate virus-specific germinal center (GC) B cells, prohibiting them from developing vigorous and sustained antibody responses during the acute and convalescent phases (Gao *et al.*, 2021). Long-term follow-up research is needed to confirm this relationship.

Differential B Cell Immunity Associated with COVID-19 Severity

Higher and more rapid humoral immune responses in severe COVID-19 cases can currently be explained by the following hypothesis: severe COVID-19 patients exhibit hallmarks of extrafollicular B cell activation and shared B cell repertoire features previously described in autoimmune settings (Woodruff *et al.*, 2020). Extrafollicular activation correlates strongly with large antibody-secreting cell expansion and the early production of high concentrations of SARS-CoV-2-specific neutralizing antibodies (Woodruff *et al.*, 2020). The higher quantity and more sustained antibodies against SARS-CoV-2 antigens in severe cases may also result from the more efficient generation of viral antigen-specific B cell responses driven by Th2-skewed immunity (Kim *et al.*, 2021c). In addition, the delayed clearance of viral antigens may support longer antigen-specific GC reactions in secondary lymphoid organs. Yang *et al.* (2021b) reported that asymptomatic subjects exhibited lymphopenia, a significant decrease in the B-cell population, a low frequency of antibody-secreting cells, and a low cytokine response. By contrast, patients with severe pneumonia exhibited increased B cell counts (including memory B cells and plasmablasts) despite having more severe

lymphopenia during the acute phase of infection (Marcos-Jimenez *et al.*, 2021; Vigón *et al.*, 2021). In other studies, however, the number or frequency of total memory B cells in severe COVID-19 patients declined as a result of accumulating the “disease-relating” B cells. These include “atypical” memory (CD27⁺) B cells and antibody secreting cells which are specific to SARS-CoV-2. This decline in B cells was followed by dysregulated humoral immune responses (De Biasi *et al.*, 2020; Kaneko *et al.*, 2020; Oliviero *et al.*, 2020; Sosa-Hernandez *et al.*, 2020). Koutsakos *et al.* (2021) indicated that C-X-C motif chemokine receptor 3 (CXCR3)⁺ circulating follicular helper T (cT_{FH}) cell activation correlates to antibody levels, neutralization activity, and inflammatory cytokine (interleukin [IL]-6, soluble IL-6 receptor [sIL-6R], and IL-18) levels. However, the upregulated frequency of a cytotoxic T_{FH} response that can eliminate B cells negatively correlates with antibody levels (Meckiff *et al.*, 2020). Overall, these studies indicate that there is a complex dysregulation of B cell responses depending on the disease severity, and these could be one of the driving factors for disease progression in COVID-19. Further studies are needed to analyze the specific mechanism responsible for the aberrant B cell differentiation.

The Pathogenic Effects of Antibody Responses in COVID-19 Patients

Virus-specific antibody responses are mainly thought to be protective. However, dysregulated antibody responses can contribute to disease progression in COVID-19 patients through worsening cytokine storms, coagulopathy, vasculopathy, and thrombosis, thereby causing pulmonary damage. Antigen-specific antibodies can form immune complexes with viral antigens and generate an exaggerated immune response through interaction with FcγR-expressing immune cells (Platzer *et al.*, 2014). Recently, we reported consistent detection of IgG-positive immune complex deposition in the vascular walls and interstitial region of the lungs in six fatal cases (Kim *et al.*, 2021c). This indicated that the pathogenic IgG-related immune complex is associated with ARDS in fatal COVID-19 cases. This observation is consistent with other studies showing immune complex deposition inside vascular walls or increased soluble immune complex in serum samples from critical COVID-19 patients (Roncati *et al.*, 2020; Ankerhold *et al.*, 2021; Chakraborty *et al.*, 2021b).

Several studies have found an aberrant glycosylation, afucosylation, in the Fc glycan region of S-specific IgG in critical COVID-19 patients (Ankerhold *et al.*, 2021; Bye *et al.*, 2021; Chakraborty *et al.*, 2021b). Increased afucosylated IgG in immune complexes may facilitate the interaction with FcγRIIIa or FcγRIIa expressed on macrophages, enhancing their activation (Nazy *et al.*, 2020; Chakraborty *et al.*, 2021b). The enhanced inflammatory immune complex is thought to induce cytokine storms and contribute to COVID-19 pathogenesis by causing the secretion of proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF) from phagocytic cells (Roncati *et al.*, 2020; Chakraborty *et al.*, 2021b; Jarlhelt *et al.*, 2021). In addition, the immune complex with only an afucosylated IgG is reported to cause platelet-mediated thrombosis in COVID-19 patients (Nazy *et al.*, 2020;

Bye *et al.*, 2021). Rapid reduction of the viral release from infected host cells was observed in COVID-19 patients (Kim *et al.*, 2021c). This facilitates binding of the rising antibodies with cells presenting viral antigens on the surface, suggesting that infected pulmonary cells of the acute COVID-19 patients could be the major targets for the antigen-antibody immune complexes (Kim *et al.*, 2021c). On the other hand, deficient B cell tolerance induced by prolonged extrafollicular B cell activation may induce autoreactive antibody responses (Woodruff *et al.*, 2020). This could potentially play a role in severe COVID-19 pathogenesis by further enhancing the formation of immune complexes. Bastard *et al.* (2020) demonstrated that about 10% of patients in their study cohort with critical COVID-19 pneumonia exhibited autoantibodies against type I interferons (IFNs), suggesting that preexisting autoimmunity underlies severe disease in some patients. Wang *et al.* (2021) identified autoantibodies against type I IFNs in 5.2% of patients who were hospitalized with COVID-19. They also found that patients with COVID-19 had high levels of autoantibodies against immunomodulatory proteins (including cytokines, chemokines, complement components, and cell-surface proteins) and that these autoantibodies perturb immune function and impair virological control by inhibiting immunoreceptor signaling and altering peripheral immune cell composition (Wang *et al.*, 2021). Even though a variety of such autoantibodies are detected when some patients are hospitalized with severe COVID-19, there is still work to be done to determine whether these antibodies are important contributors to severe disease or an epiphenomenon of severe inflammation (Knight *et al.*, 2021). Nevertheless, the deposition of immune complexes containing IgG bound to activated FcγR could induce the excessive inflammatory responses that cause lung damage in critically ill patients with COVID-19.

The complement activation pathway is a conserved innate humoral response against viral infection. SARS-CoV-2 infection can induce overt complement activation directly or indirectly via multiple pathways: the classical pathway, the lectin pathway, and the alternative pathway. Overt complement activation results in pathogenic progression in severe cases (Java *et al.*, 2020; Afzali *et al.*, 2022). In plasma from severe COVID-19 patients, we and others found higher levels of IgG1 and IgG3, as well as increased levels of activated complement components, including C3a, C3b, C4b, and C5a; IgG1 and IgG3 are IgG subclasses primarily associated with the classical complement activation pathway (Carvelli *et al.*, 2020; Cugno *et al.*, 2020; Shen *et al.*, 2020; Jarlhelt *et al.*, 2021; Kim *et al.*, 2021c). In addition, the concentration of the complement pathway components was correlated with the levels of the IgG subclasses, as well as the disease severity (Howell *et al.*, 2021; Jarlhelt *et al.*, 2021; Kim *et al.*, 2021c). In critical COVID-19 patients, the deposition of complement components, such as membrane attack complexes (MAC), was also found in multiple tissues, including lungs, kidneys, liver, and hearts (Noris *et al.*, 2020; Pfister *et al.*, 2020; Kim *et al.*, 2021c; Macor *et al.*, 2021; Pellegrini *et al.*, 2021). IgG immune complexes with complement components have been consistently observed in lung biopsies from fatal cases. This evidence further supports the hypothesis that immune complexes may be involved in complement-mediated pathogenesis in critical

COVID-19 patients by promoting the classical complement pathway (Kim *et al.*, 2021c; Macor *et al.*, 2021). Systemic and local complement activation may induce multiple pulmonary pathologies, such as endothelialitis, hyperinflammation, and thrombotic microangiopathy (Java *et al.*, 2020; Afzali *et al.*, 2022). Activated complement components, including C3a, C5a, and MAC, play a major role in the pathogenic processes by triggering the recruitment of inflammatory neutrophils, monocytes, and macrophages (Drosos *et al.*, 2021). The activated complement components also initiate coagulation cascades by promoting platelet and endothelial activation (Foreman *et al.*, 1994; Kilgore *et al.*, 1998; Skeie *et al.*, 2010). Collectively, complement activation driven by the immune complex-mediated classical pathway can lead to lung damage and systemic cytokine storms in critical COVID-19 patients. Although antibody responses induced by the current vaccines and prior infection are considered to provide beneficial protection against future infections, the potential pathogenic role of continuously waning antibodies should be carefully monitored, especially in high-risk individuals.

Antibody Responses as Immune Pressure for Selecting Antibody-Escaping Variants

The continuous emergence and spread of new SARS-CoV-2 variants have made it difficult to control the COVID-19 pandemic. SARS-CoV-2 variants can be designated as a variant of interest (VOI) or a variant of concern (VOC) by the WHO based on its transmissibility, disease severity, or susceptibility to available vaccines and therapies (Chakraborty *et al.*, 2021a). Currently, the delta (B.1.617.2) and omicron (B.1.1.529) variants are classified as VOCs (<https://www.who.int>). These variants have evolved to increase their binding affinity to the host receptor to enhance infectivity and/or transmissibility. In addition, they are capable of escaping pre-formed host antibodies induced by previous infections and vaccines. The SARS-CoV-2 variants contain amino acid substitutions in regions of the spike protein, which is involved in virus entry by binding to the host receptor ACE2. Although the roles of each substitution in the variants are not clearly defined, most conserved mutations in the spike protein may be associated with increased transmissibility and/or binding affinity to the ACE2 receptor, as well as decreased susceptibility to pre-existing neutralizing antibodies (Weisblum *et al.*, 2020; Yang *et al.*, 2021a). The B.1.617 variants, including the kappa and delta variants, had higher infectivity and greater resistance to neutralizing antibodies compared to the ancestral SARS-CoV-2 D614G mutant (Hu *et al.*, 2021). The omicron variant is rapidly spreading worldwide and also shows lower neutralizing sensitivity against immune sera from convalescent patients or vaccinated individuals (Ai *et al.*, 2022; Wang *et al.*, 2022). In particular, the K417N/T, E484K/Q, and N501Y substitutions, which are common in the spike protein of SARS-CoV-2 variants such as alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta, and omicron variants that were once or are currently designated as VOCs, are likely to be highly resistant to neutralizing antibodies (Chen *et al.*, 2021b; Garcia-Beltran *et al.*, 2021; Lubin *et al.*, 2021; Liu *et al.*, 2022). The L452R substitution in the omicron variant spike protein may reduce

the antibody binding affinity, which indicated an antibody escaping mutation (Yang *et al.*, 2021a). Therefore, SARS-CoV-2-specific antibodies acquired by prior infection or vaccination continuously confer selective pressure on SARS-CoV-2, resulting in ongoing antibody-escaping mutations. Establishing stable host adaptation is a common strategy of coronavirus evolution. Moreover, as observed in other human coronaviruses, it's now clear that the decreased neutralization of "future" SARS-CoV-2 will be ongoing due to the antigenic evolution of the viral spike, especially in the RBD (Eguia *et al.*, 2021). Therefore, SARS-CoV-2 vaccines may need to be periodically updated before there is a universal vaccine platform (Morens *et al.*, 2022).

Conclusion

This review summarized and discussed the beneficial and pathogenic characteristics of antibody responses in COVID-19 patients based on rapidly accumulating evidence since the start of the COVID-19 pandemic. There have been conflicting data on several critical issues, and there are still unresolved questions regarding the critical drivers of severe COVID-19. However, it is becoming clear that dysregulation of specific immunity, including humoral responses, and overt inflammatory reactions, may be one of the primary culprits that could serve as a specific target for better therapeutic interventions. In addition, antibody-escaping SARS-CoV-2 variants are continuously emerging, driven by the selective pressure of pre-existing antibodies. This calls for carefully monitoring the potential adverse effect of continuously waning antibodies, particularly in high-risk individuals. Furthermore, the limitations of the current SARS-CoV-2 vaccines suggest that they will need to be replaced by more efficient vaccines that induce more broadly protective and durable immunity.

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Conflict of Interest

The authors have no conflict of interest to report.

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