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REVIEW

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# SARS-CoV-2 vaccines: A double-edged sword throughout rapid evolution of COVID-19

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## Abstract

After more than 2 years of the coronavirus disease 2019 pandemic caused by severe acute respiratory syndrome coronavirus 2, several questions have remained unanswered that affected our daily lives. Although substantial vaccine development could resist this challenge, emerging new variants in different countries could be considered as potent concerns regarding the adverse effects of reinfection or postvaccination. Precisely, these concerns address some significant and probable outcomes in vaccinated or reinfected models, followed by some virus challenges, such as antibody-dependent enhancement and cytokine storm. Therefore, the importance of evaluating the effectiveness of neutralizing antibodies (nAbs) elicited by vaccination and the rise of new variants must be addressed.

**KEYWORDS**

antibody-dependent enhancement, neutralizing antibodies, SARS-CoV-2, vaccine

## 1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan (Hubei, China) in December 2019 (Bagher Pour et al., 2021; Jiang et al., 2020; Karimi & Turkamani, 2021). According to the World Health Organization (WHO), globally, there were 558,830,377 confirmed cases of COVID-19 (including 6,369,483 deaths) on July 8, 2022 (https://covid19.who.int/). Based on phylogenetic relationships and genomic structures, COVID-19 belongs to *Betacoronavirus*. A comparative analysis revealed a close similarity of the sequences of the SARS-CoV-2 with severe acute respiratory syndrome-related coronaviruses (SARSr-CoV) (Abdelrahman et al., 2020; Brant et al., 2021). Spherical or pleomorphic enveloped particles of COVID-19 cover a single-stranded (positive-sense) RNA that is linked to a nucleoprotein inside a capsid containing matrix protein and

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hemagglutinin-esterase (HE) protein, which has been observed in some coronaviruses (de Haan et al., 1998; Mousavizadeh & Ghasemi, 2020). Coronaviruses possess the largest genome (26.4e31.7 kb) of all recognized RNA viruses, with GC contents fluctuating from 32% to 43%. The SARS-CoV-2 genome structure comprises 14 open reading frames (ORFs) encoding 27 proteins (Wu et al., 2020). Two-thirds of viral RNA comprises ORF1ab translating into ORF1ab poly-proteins (pp1a and pp1ab) and 16 nonstructural proteins (Khailany et al., 2020). The rest of the genome (one-third) is located in 3′ that consists of ORF11 and ORF12 encoding four structural proteins membrane (M), nucleocapsid (N), spike (S), and envelope (E), along with other accessory proteins (Mousavizadeh & Ghasemi, 2020; Woo et al., 2010). The virus enters host cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor in most host cells (Singh et al., 2021). Once the SARS-CoV-2 spike protein binds to ACE-2, it downregulates its expression, consequently increasing capillary permeability and causing pulmonary damage (Qu et al., 2021).

The innate immune system functions as the first line of host defense against pathogens and plays a key role in combating SARS-CoV-2 (Diamond & Kanneganti, 2022). However, both arms of the immune system, the innate immune system (including granulocytes, monocytes, and macrophages, among other cells of the innate immune system) and the adaptive immune system with T and B cells perform antiviral functions to eliminate SARS-CoV-2 viruses (Schultze & Aschenbrenner, 2021). Nevertheless, uncontrolled inflammatory innate responses and impaired adaptive immune reactions can result in detrimental systemic damage and local tissue injuries (Catanzaro et al., 2020).

The acute coronavirus infectious disease is characterized by pneumonia, lymphocytopenia, exhaustion of lymphocytes, and cytokine storm syndrome in severe COVID-19 (Dhama et al., 2020). To recognize SARS-CoV-2 proteins, T-cell and B-cell responses play a pivotal role in initiating the antiviral immunity process and releasing potent and efficient antibodies in individuals with and without COVID-19, respectively (Grifoni et al., 2020; Le Bert et al., 2020). In other words, the cooperation and coordination of the stimulated B cell by $CD4^+$ T-cell activity release antigen-specific antibody and cytotoxic activity of CD8 + T-cell infected cell, as well as inflammatory response, leading to the control of viral infection (Toor et al., 2021). Moreover, the variation of specific neutralizing antibody (nAb) levels (followed by T cell response) is considerably important to immunity against SARS-CoV-2. Likewise, the effectiveness and potency of the immune response are directly related to the quality and quantity of long-lived immune memory cells; whether they can recognize and face SARS-CoV-2 variants or not needs further studies (Callaway, 2020). Thus, rational approaches must be considered to better understand the stimulation of memory T and B cells by reinfection and vaccination (Jarjour et al., 2021; Quast & Tarlinton, 2021). As of the global emergence of COVID-19, numerous studies have been conducted to achieve the most potent therapeutic approaches to cope with this serious challenge (Pandey et al., 2020). Although numerous repurposed therapeutic modalities are available, vaccination would be the most successful medical approach to disease prevention. Here, we discuss the nAbs induced by natural infection or vaccination response, as well as different types of COVID-19 vaccine strategies.

## 2 | A BRIEF DESCRIPTION OF THE SPIKE (S) GLYCOPROTEIN

Understanding the mechanism of SARS-CoV-2 pathogenicity (followed by choosing a potent and effective strategy in terms of treatment and vaccine approaches) is closely related to a deep conception of the structural biology of such a virus (Hu et al., 2021). The spike protein comprises three regions: an intracellular tail, a single-pass transmembrane, and an ectodomain (Li, 2016). Throughout infection, the ectodomain region of the spike protein is divided into S1 and S2 subunits, consisting of the receptor-binding domain (RBD) and responsible for membrane fusion in terms of viral entry, respectively (Li, 2016; Papageorgiou & Mohsin, 2020). The cryo-electron microscopy structure of the SARS-CoV-2 trimeric spike (S) glycoprotein indicates that the S2 subunit of the spike protein, which comprises heptad repeat (HR1), central helix (CH), and connector domain (CD), follows a low variable pattern compared to the RBD domain of the S1 subunit that could be targeted for drug development (Kalathiya et al., 2020). Conformational changes occur in HR1 and HR2 of the S2 subunit after binding of the RBD of the S1 subunit to prepare a close situation for the host cell and spike protein to accomplish virus infection and fusion mission (Xia et al., 2020). The SARS-CoV-2 spike protein is considered a significant factor in binding and entering the cell via the ACE2 receptor, the same receptor of SARS-CoV, while the dipeptidyl peptidase-4 (DPP-4) is believed to act as a receptor for MERS-CoV (Alnaeem et al., 2020). According to the specific analysis of receptor affinity, a mutation in genomic sequencing of the spike protein RBD domain may improve the SARS-CoV-2 binding ability and pathogenicity compared to SARS-CoV (Wan et al., 2020). However, the higher binding ability of the SARS-CoV-2 protein to its receptor, which may cause serious lung conditions, is not completely understood (Pandey et al., 2020; Zhu et al., 2020).

SARS-CoV-2 continuously evolves through mutations during the replication of its genome. Numerous mutations have been identified by viral sequencing during the pandemic, which is used for SARS-CoV-2 variant classifications and genetic lineages (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/). Now, Delta (B.1.617.2 and AY lineages) and Omicron (B.1.1.529 and BA lineages), which have amino acid changes in spike, are variants of concern (VOC) based on SARS-CoV-2 Interagency Group (SIG) and WHO weekly epidemiological updates (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/; https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html). Most of the VOC contain mutations in RBD, which are responsible for increased viral infectivity. Of note, relevant amino acid changes may be present in other regions of the SARS-CoV-2 genome. The main features of VOC are related to their virulence, rate of transmission over the

population, declined neutralization capability of antibodies within vaccination or reinfection, detection difficulties, and reduction in therapeutic measurements effectiveness (Sanyaolu et al., 2021).

Substitutions and deletions in the spike gene could affect the physicochemical property and structure of the spike protein, which subsequently alters the affinity of SARS-CoV-2 spike RBD for the human ACE2 receptor and may lead to changes in the antigenicity of the SARS-CoV-2 spike protein and producing nAbs (Ding et al., 2021; Harvey et al., 2021). There is emerging evidence of variants exhibiting resistance to antibody-mediated immunity elicited by vaccines (Harvey et al., 2021). Regarding all considerations for the potency and safety of COVID-19 vaccines, concerns for all individuals immunized by COVID-19 vaccines have been raised. These concerns address some significant and probable outcomes in vaccinated models, followed by some virus challenges, such as antibody-dependent enhancement (ADE) and cytokine storm.

## 3 | ADE AND CYTOKINE STORM

ADE in a viral infection is a circumstance where virus-specific antibodies augment the virus admittance into and occasionally the viral replication inside monocytes/macrophages and granulocytes. ADE is triggered via contacting the Fc and/or complement receptors to monocytes/macrophages (Halstead & O'Rourke, 1977; Halstead, 1981; Mady et al., 1991; Maemura et al., 2021). ADE was first stated by Hawkes and Lafferty (1967) in dengue virus (DENV) infection (Hawkes & Lafferty, 1967). Through in vitro and in vivo experiments on several viruses, including DENV, HIV, influenza, respiratory syncytial virus (RSV), Ebola, SARS-CoV, and chikungunya virus (CHIKV), the existence of ADE has been shown (Kam et al., 2007a; Kulkarni, 2020). Importantly, ADE is not the main feature of such viral infections and usually occurs by the interaction between non-nAbs that are produced against infectious viruses and Fcγ receptors of the host cells (FcγRs can augment the virus uptake) (Halstead & O'Rourke, 1977; Hotez et al., 2020; Smatti et al., 2018). The basic process of ADE comprises the internalization of the combination of virus and antibody attaching to the host cell by interacting with the cellular Fc receptors (Cardosa et al., 1983; Hawkes & Lafferty, 1967). Furthermore, studies have revealed that in HIV-1 patients, IgM, IgA, and IgG antibodies in different concentrations improve the diffusion of HIV into mononuclear cells, such as monocytes, dendritic cells, and particular types of granulocytes by their Fc receptor throughout phagocytosis (Janoff et al., 1995; Kozlowski et al., 1995).

*In vivo* and in vitro vaccine experiments on SARS-CoV indicate that despite the presence of protective and neutralizing IgGs against full-length spike protein, B cell lineages are infected via FcγRII and ACE2 receptors instead of the endosomal/lysosomal pathways (Kam et al., 2007b). Moreover, not only a certain concentration of the antibodies against the spike protein neutralized SARS-CoV severe infection, but also ACE2 receptors and the FcγRII as an alternate cell entry promoted the ADE mechanism into immature monocyte cell lineage (Wang et al., 2014). It has been indicated by relevant studies on feline infectious peritonitis virus (FIPV) and other related coronaviruses that the majority of monoclonal antibodies that promote the ADE mechanism are of the immunoglobulin G2a subclass and against the spike protein. Hence, early feline deaths from the ADE phenomenon are likely exerted by a combination of high levels of IgG and the spike protein (Corapi et al., 1992; Vennema et al., 1990). Du et al.'s experiment on animal models provided varied information about adequate, protective, long-term nAbs against the SARS-CoV RBD epitope. However, most of the animal models did not cause immunopathological damage throughout this vaccination experience (Du et al., 2007). Protection due to encountering viral infections is strongly influenced by nAbs, which has been considered as a significant strategy in immune vaccine production due to the abrogation of virus infectivity (Zinkernagel, 2003). Viral diseases and infections could be obstructed through the neutralization by specified antibodies produced via both infection and vaccination. Several experimental vaccine studies on influenza and polio/smallpox viruses have claimed that in investigations of vaccine efficiency, both the quality and quantity of nAbs should be considered as gold standards (Huang et al., 2020; Zinkernagel, 2003). According to neutralization kinetics, this process nullifies the viral infection by preventing cell entry through several complex mechanisms. Studies on the stoichiometry of antibody neutralization have hypothesized two models in this regard. The single-hit model claims that the antibody attachment to specific virus epitopes in a precise position is adequate to implement the neutralization. On the other hand, because of some limitations of the single-hit model, an alternative model called the "multiple hit" has been suggested, in which the neutralization is accomplished by the occupation of viral epitopes with several antibody molecules. Thus, complete neutralization directly depends on the number of antibodies and virion size (Klasse & Sattentau, 2002; VanBlargan et al., 2016). Although convalescent plasma therapy in severe COVID-19 patients has been suggested in recent clinical trials based on the fact that particular and optimal dosages of nAbs have promising outcomes, the observation of pulmonary lesions has been a concern in 2 patients in this trial. It should be noted that due to the prevention of such effects of nAbs, more investigations and larger clinical studies must be conducted in this respect (Duan et al., 2020). In addition, according to an in vitro study conducted on SARS-CoV-2 infected primary B cells, monocytes, and macrophages, there was some ADE effect similar to dengue that can provide some valuable understanding of the possibility of such a phenomenon in COVID-19 patients (Shen et al., 2021).

According to molecular studies, based on the ADE phenomenon in coronaviruses, ADE occurs when the binding of nAb to the RBD spike protein is proved, followed by conformational alterations and the facilitation of viral entry through the IgG's Fc receptor. Moreover, the antibody concentration must be considered as a significant element that can affect viral entrance via the receptor of the virus and the Fc receptor (Huang et al., 2020). Studies on COVID-19 outcomes have demonstrated a significant correlation between the severity of the disease and antibody titers, as well as increased cytokines (Vabret et al., 2020). In SARS-CoV-2, constantly infected

macrophages have not been detected. Nonetheless, the ADE mechanism in SARS CoV-2 is thought to be an immunological complex formed after lung tissue damage caused by antibody–antigen contact (Lee et al., 2020). In the lung tissues of severe COVID-19 patients, researchers discovered increased pro-inflammatory macrophages and the occurrence of gasdermin D (GSDMD) driven pyroptosis, which results in a fast release of pro-inflammatory cytokines and cytokine storms (Zhang et al., 2021). Zhang et al. also represented a direct relation between high levels of IgG/IgM and elevated pro-inflammatory cytokines such as interleukin 2 (IL-2), IL-6, IL-8, and IL-10 in severe COVID-19 patients compared with nonsevere patients (Zhang et al., 2020).

Moreover, regardless of the absence of viral load monitoring in recovered patients in this experiment, augmented innate and acquired immune system responses to SARS-CoV-2 substantially correlated with the severity of the illness (Wu et al., 2020). However, the precise immunopathological mechanisms of antiserum, such as IgG, have remained unclear (Yang, 2020). Conversely, the evidence showed that by blocking FcγR on the cell surface, detrimental consequences of the mentioned antibody could be mitigated (Liu et al., 2019). High levels of pro-inflammatory cytokines (including IL-1β, IL-2, IL-6, IL-7, IL-8, and IL-17) and aggressive production of cytokines (including IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α) were detected in intensive care unit (ICU) patients during their acute SARS-CoV-2 infection. However, through a seroconversion analysis, the relationship between the adverse outcome of cytokine release syndrome and elevated nAbs against SARS-CoV-2 (especially the spike protein) must be assessed (Huang et al., 2020; Shi et al., 2020). Cytokine storm has a catastrophic effect not only on lung tissues but also on the kidney, liver, and heart because of extremely elevated pro-inflammatory factors. Such massive cytokine production induces immense neutrophils, macrophage infiltration, and extended alveolar lesions, which are formed as hyaline membrane and thickened alveolar epithelium. In addition to organ failure and immune system dysregulation, the biopsy assessments of deceased cases demonstrated atrophic and necrotic spleen and lymph node, respectively (Cao, 2020; Prete et al., 2020). Previously, a comparative animal model study based on host immune response to SARS-CoV structural proteins (comprising N, S, M, and E epitopes) revealed that acute pneumonia could be induced by an extreme immune reaction against the N protein of SARS-CoV. Therefore, the N protein promotes a more specific Th1-Th2 response compared with other structural proteins (Yasui et al., 2008). Additionally, gaining comprehensive information about nAb epitopes from several data banks is significantly important in terms of rational design and development of efficient therapy and vaccine (Edwards et al., 2021). In the case of HIV-1, nAbs block virus entrance by targeting some distinct or discontinuous structural proteins on the viral envelope. In addition, envelope antigens are valuable sites in nAb investigations in terms of breadth and potency (Kumar et al., 2018).

Site direct mutagenesis and crystal structure analysis have recognized 2 amino acid residues of the RBD domain of the spike protein (Ile-489-Tyr-491), which are significantly conserved. Likewise, mAb (m396) is likely to have the most affinity to these hot spot residues, and this high binding energy might be the possible answer for its cross-reactivity to all known isolated SARS-CoV except bat-derived viruses (Tay et al., 2020; Wong et al., 2004; Xiao et al., 2003; Zhu et al., 2007). Some pieces of evidence on ADE were revealed by a study on nonhuman primates immunized by peptide vaccine based on a spike protein (S597-603 epitope) analysis of SARS-CoV. Hence epitope sequence-dependent (ESD) could be a reliable strategy to prevent such detrimental effects in vaccine development (Wang et al., 2016). While at least 17 substitutions in the 1255-amino acid sequence of the SARS-CoV spike protein have been identified by molecular analyses, possible related differences in function and characteristics such as nAb resistance or ADE-like evidence were observed in humans and animals, respectively (Yang et al., 2005). Moreover, despite vast antigenic differences between both SARS-CoV and SARS-CoV-2, a recent molecular analysis of the amino acid composition of both viral strains revealed no substantial differences in their structures (Kumar et al., 2020).

The possible roles of ADE in viral infections of different types of viruses and those monoclonal antibodies that neutralize the receptor RBD epitope of the spike protein of MERS and promote viral entry should be considered significant concerns in the immunopathological effects of the ADE within reinfection, vaccine design, and sera therapy (Smatti et al., 2018). Nonetheless, due to the information about three messenger RNA (mRNA)-based vaccines and other approved products that induced B-cell-mediated antibody response against the spike protein, it is recommended to consider T-cell-based vaccines and those target mutant-specific spike proteins, ORF1ab, and nucleocapsid protein, which could be more adaptive in the induction of CD8 + memory T cell and high concentration of nAbs to simulate natural infection in the emergence of new variants (Hasan et al., 2021a). Depending on the vaccination method used, SARS-CoV immunization experiments in animal models have yielded outcomes that vary substantially in terms of protective effectiveness, immunopathology, and probable ADE. Despite this, vaccines that elicited nAbs against the S protein reliably protect animals against SARS-CoV infection and illness (Lee et al., 2020; Yang et al., 2004). These findings show that human SARS-CoV-2 vaccination techniques that evoke high nAbs titers have a high likelihood of success while posing a low risk of adverse events ADE. Therefore, virus escape mechanisms, followed by genetic diversity and rapid evolution in structural proteins (especially spike protein as one of the most important targets for potent and safe vaccine development), must be considered to prevent possible phenomena such as ADE.

## 4 | SARS-COV-2 IMMUNE EVASION STRATEGIES AT A GLANCE

Undoubtedly, constant variations in viruses such as HIV-1, hepatitis C virus (HCV), and influenza virus, which have the ability to tolerate structural mutations, are the most significant features related to escape from the host immune system (Carlson et al., 2012). Although

the alterations in the surface antigens of the virus envelope are among the major causes of this phenomenon, the effects of the immune system on such pathogens and their replication and transmission in the host should not be underestimated (Burton et al., 2012; VanBlargan et al., 2016). As a result, one of the most variable regions in viral glycoprotein antigens is the receptor binding site, where the diversification following the mutations cannot mitigate virus functions (Yi et al., 2020). Hence, the genetic diversification of strategic regions in viruses is completely related to their immunogenicity and can be used as a virus serotype definition (Corti & Lanzavecchia, 2013). Furthermore, innate immune escape mechanisms of viruses, such as interfering with the interferon (INF) production system, natural killer cell cytotoxicity, and cytokine storm induction, must be considered (Bouayad, 2020). Mutations in viruses' genomes are influenced by polymerase misprinting, impaired nucleotide, and base-pair mechanisms, as well as other mechanisms such as replication and recombination, which could be defined as point mutations, deletions, or insertions (Hadfield et al., 2018). The levels of these alterations determined by experimental assessments in considerable variations over 25 viruses are $10^{-8}$ to $10^{-6}$ substitutions per nucleotide per cell infection (s/n/c) for DNA viruses and $10^{-6}$ to $10^{-4}$ s/n/c for RNA viruses (Peck & Lauring, 2018). It must be noted that because of the type of polymerase involved in the replication process, mutations occur faster in RNA viruses than in retroviruses and DNA viruses, respectively (Duffy et al., 2008). These alterations facilitate the virus evasion from humoral and cellular immune systems, which results in host environmental adaptation and could lead to the emergence of a wide range of variants with different pathogenesis when the mutation is in the spike protein (Saha et al., 2020). The diversity of the SARS-CoV-2 virus S-protein antigenic determinants may result in ADE of infection. ADE is more likely to occur when a person is vaccinated with a virus or genetic construct expressing an S-protein with a predominant open form of RBD, as well as infected with a virus with a predominantly closed conformation of this protein (Nechipurenko et al., 2020). Nevertheless, virus evasion mechanisms in hot spots and structural regions of SARS-CoV-2, such as spike glycoprotein, must be fully evaluated in vaccine design to cope with the rapid involvement of COVID-19.

## 5 | ADE CONCERNS IN SARS-COV-2 VACCINES

Since SARS-COV-2 emerged, with the benefit of whole-genome sequencing, it has been characterized by several mutations, resulting in the diagnosis of VOC that covered the globe dominantly and those variants of interest that were found sporadically in certain countries (Cantón et al., 2021). Epidemiological assessments have revealed at least 5 VOC throughout the SARS-CoV-2 pandemic, encompassing the Alpha variant (B.1.1.7; the first VOC reported in the UK in late December 2020), Beta variant (B.1.351; first reported in South Africa in December 2020), Gamma variant (P.1; first reported in Brazil in early January 2021), Delta variant (B.1.617.2; first reported in India in December 2020), and Omicron variant (B.1.1.529; first reported in South Africa in November 2021) (Choi & Smith, 2021; Thakur & Ratho, 2022). Since SARS-CoV-2 has been nominated as a highly mutational rate in the genome, the emergence of new variants must be addressed in the advancement of all different types of vaccine platforms, either boosting control/spread of infection and hospitalization or preventing adverse effects such as ADE.

After a long season of challenges with the SARS-CoV-2 outbreak, all concerns go to the safety and potency of those available types of COVID 19 vaccines (Sanyal et al., 2021). Due to the lack of understanding about cross-reactivity between coronaviruses (including SARS-CoV, MERS-CoV, and SARS-CoV-2), the suboptimal level of neutralization of the pre-existing antibodies against coronaviruses and SARS-CoV-2 vaccine could potentially result in ADE or a more severe illness. However, recent research on the currently available vaccine excludes the possibility of such a phenomenon (From the American Association of Neurological Surgeons AANS et al., 2018). Individuals who have not been vaccinated could be considered as a source of VOC, which might be more detrimental rather than the occurrence of ADE (Ajmeriya et al., 2022).

Regardless of a broad variation in effectiveness, potency, and risk of ADE in animal immunization studies, vaccines based on S protein were more reliable and could protect animals without immunopathological effects. However, there is no evidence that DNA vaccines, vectored mucosal vaccine, and attenuated virus based on encoding the SARS-CoV spike (S) glycoprotein (in which nAbs are elicited) may improve infection (Bisht et al., 2004; Bukreyev et al., 2004; Yang et al., 2004).

Nevertheless, anti-S-IgG antibodies induced by those spike protein-based vaccines (which are unable to neutralize SARS-COV-2 completely as a result of alteration in spike sequence) are more likely to cause severe disease and ADE (Seow et al., 2020). Hence, it is suggested that along with all consideration of long-lasting immunity in vaccine development, non-S-epitopes (such as ORF/N/M epitopes that are unlikely included for remarkable mutations) could be added to vaccine platforms (Hasan et al., 2021b).

## 6 | CONCLUDING REMARKS

Although among at least 200 vaccine candidates, just a few of them have won the race, global concerns have been raised about the safety and potency of those COVID-19 vaccines with emerging new strains in different countries. Regarding the rapid evolution of SARS-CoV-2, unexpected human immune system responses (such as ADE) must be considered to prevent adverse outcomes. Although there is no evidence for ADE in SARS-CoV-2 pathological investigations, more immunotherapies must be conducted to elicit a higher titer of potent and nAbs instead of non or sub-nAbs with low concentrations to avoid ADE in vaccinated individuals.

### AUTHOR CONTRIBUTIONS

**Mohammad Ali Zolfaghari**: Writing—original draft. **Farzaneh Ghadiri Moghaddam**: Writing—review & editing. **Shabnam Rajput**: Validation.

**Abbas Karimi**: Conceptualization; funding acquisition. **Mohadeseh Naghi Vishteh**: Writing—review & editing. **Ata Mahmoodpoor**: Investigation. **Sanam Dolati**: Software. **Mehdi Yousefi**: Supervision.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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