Antibody-Dependent Enhancement and the Critical Pattern of COVID-19: Possibilities and Considerations

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Highlights of the Study

- The pathogenicity of several viral infections is mediated by effector mechanisms of the immune system.
- Antibodies produced during the previous exposure to seasonal coronaviruses or possibly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are proposed to trigger antibody-dependent enhancement.
- Antibody-dependent enhancement might lead to more severe and lethal illness upon infection with SARS-CoV-2, results in cytokine storm and tissue damage, and can modulate immune responses toward an inflammatory profile.

Abstract

Coronavirus disease 2019 (COVID-19), a pandemic infection with profound effects on human society, has challenged our ability to control viral infections. Although at the beginning of the COVID-19 outbreak, the epidemic seemed controllable in Southern Iran, the disease presented a critical pattern as of May 2020. After a few months of the emergence of CO-VID-19, its severity and mortality increased dramatically. It has been proposed that antibodies produced during previous exposure to local circulating human coronaviruses or possibly severe acute respiratory syndrome coronavirus 2 might contribute to the development of more severe and lethal presentations of COVID-19 possibly by triggering antibody-dependent enhancement. The binding of virions complexed with antibodies to Fcγ receptors on the target cells initiates receptor-mediated signaling events, leading to enhanced expression of inflammatory cytokines and suppression of intracellular antiviral responses at the transcriptome level, followed by endocytosis of the virus and subsequent activation of immune cells. The activated immune cells might accumulate in the lung and promote cytokine storm and lymphopenia. Furthermore, the formation of immune complexes can promote complement activation and subsequent tissue damage. Although there are currently no clinical data to support this hypothesis, a better understanding of these immunopathologic phenomena and their rela-

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tion to the disease course and severity might give insights into the development of the most efficient prophylactic and therapeutic approaches. This review demonstrates the critical pattern of COVID-19 in Southern Iran and highlights the possible interplay of factors leading to this condition.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), an unprecedented pandemic that is currently the greatest concern of global health [1–4]. This pandemic has affected every corner of the world, with 134,957,021 confirmed cases and 2,918,752 deaths globally as of 11 April 2021 [5]. COVID-19 is characterized by an asymptomatic, mild, or severe course; while most patients have asymptomatic or mild to moderate clinical symptoms of viral pneumonia, some patients experience life-threatening clinical illness due to acute respiratory distress syndrome, kidney injury, multiple organ dysfunction, and lung failure, eventually leading to death [6–8].

SARS-CoV-2 is a novel *Betacoronavirus* in the family *Coronaviridae*, with a positive single-stranded RNA genome and enveloped icosahedral capsid [9–11]. This virus shares 96.2% sequence identity to a bat coronavirus, suggesting interspecies transmissions [12, 13]. The viral genome encodes spike (S), nucleocapsid (N), membrane (M), and envelope (E) structural proteins and 16 nonstructural proteins [8, 14–16]. The S gene, encoding the most immunogenic viral protein, encounters the highest frequency of mutation and recombination, resulting in the evolution of different strains of SARS-CoV-2 [17, 18]. The S protein has 2 subunits: subunit 1 that contains a receptor-binding domain (RBD) and subunit 2. The RBD of spike protein binds with high affinity to angiotensin-converting enzyme 2 (ACE2) receptor, the main host cell receptor for SARS-CoV-2, and facilitates the entry of the virus into target cells, predominantly resulting in viral spreading into the heart, lungs, and gastrointestinal tract, that is, tissues that express high levels of ACE2 [8, 19–21]. Antibodies targeting the RBD of S protein are neutralizing antibodies, while antibodies against other parts of S protein tend not to neutralize the virus but to induce more severe disease upon secondary infection [22]. Non-neutralizing antibodies are produced commonly during the course of human coronavirus infection, such as MERS-CoV and SARS-CoV. Moreover, seasonal human coronaviruses may cause repeated infection with short-lived immunity [23–25].

Neutralizing antibody responses against coronaviruses wane rapidly over time; therefore, the chance of reinfection is high [26]. However, despite short-lived neutralizing antibody responses in most cases of SARS and MERS, the probability of a secondary infection is extremely low due to the low prevalence of SARS-CoV and MERS-CoV in the community [25, 26]. On the contrary, the risk of reinfection in the case of SARS-CoV-2 seems to be more real [26]. SARS-CoV-2 infects a significant proportion of the general population due to the high circulation of the virus in the community. Furthermore, various SARS-CoV-2 strains have been isolated from infected persons. The RBD domain of the SARS-CoV-2 spike protein encounters critical mutations that might increase RBD-binding affinities of some of the mutated strains [18]. Pre-existing anti-RBD antibodies obtained from primary SARS-CoV-2 infection bind with reduced affinity to the RBD-mutated strain. The development of such mutated strains might exacerbate the COVID-19 pandemic with higher severity and mortality due to the reinfection of convalescent patients with the mutated strains [27]. Furthermore, protective neutralizing antibodies are serotype-specific and are therefore cross-reactive against other serotypes but cannot neutralize them [24].

The Critical Pattern of COVID-19 in Southern Iran

Since the emergence of the SARS-CoV-2 pandemic, Iran became one of the world's worst-affected countries. As of 11 April 2021, more than 2,049,078 confirmed cases of COVID-19 with 64,232 deaths have been documented in Iran [5]. Nevertheless, the number of infected cases is presumably much higher, resulting from asymptomatic cases of SARS-CoV-2 infection, symptomatic cases with undetectable viral load in the nasal and pharyngeal swabs, or lack of analysis due to limited resources. Moreover, part of symptomatic cases might not be detected due to low viral load. The high incidence of false-negative results is the greatest limitation of COVID-19 diagnostic tests, which is influenced by viral mutations, sampling time, improper sample types, inadequate handling, and improper transportation of samples [28, 29]. In addition to the transmissibility of COVID-19, high viral load is reported to correlate with worse disease outcomes, thus fatal symptomatic cases have higher viral loads than asymptomatic cases [30–32].

Southern Iran has been particularly heavily affected by COVID-19 and had a critical disease pattern as of May 2020, despite having a controllable epidemic pattern with very low severity and mortality in the first few months of COVID-19 emergence. At the beginning of the outbreak, severe course of SARS-CoV-2 infection and hospitalization were reported mostly among aged patients in Southern Iran. Children and young people were less likely to have symptomatic SARS-CoV-2 infection as than adults and the elderly [33]. Therefore, young infected subjects mainly remained undiagnosed, despite having a risk of infection similar to adults. Being deceived by mild or absent clinical symptoms, young people became drivers of SARS-CoV-2 transmission in society. After a few months of COVID-19 emergence, the severity and mortality of COVID-19 increased dramatically, and symptomatic cases and cases with severe clinical illness were increasingly reported among young people. The age distribution of the pandemic changed, and severe forms of COVID-19 and subsequently mortality were observed in all age-groups. Furthermore, the incidence of SARS-CoV-2 infection has been progressively increasing even in the hot humid weather of Southern Iran, while the transmissibility and stability of respiratory viral infections decrease with hot and humid weather conditions [34, 35].

Underlying Factors Responsible for the Critical Pattern of COVID-19

Multiple interplaying factors could have contributed to increasing the incidence of COVID-19 in Southern Iran. The use of face masks was initially thought to be ineffective in protecting against SARS-CoV-2 infection [36]. In the traditional society of Southern Iran, most young people live with their parents. This multigenerational cohabitation was believed to increase the risk of SARS-CoV-2 transmission among family members. Moreover, the positive cases were mostly in clusters of family members and relatives, indicating transmission of SARS-CoV-2 at family gatherings by asymptomatic or irresponsible infected persons. The government initially underestimated the threat of COVID-19 and perceived it as some sort of flu with cold-like symptoms. On the other hand, the general population did not take the disease seriously, and people were generally reluctant to adhere to the social restrictions enforced by the government. Furthermore, a full lockdown was not enforced due to economic reasons. Southern Iran is vital to the economy of the entire country, where business activities are essential.

The repeated cycles of circulation of the virus within healthcare settings have been proposed as a significant contributor to enhancing the risk of COVID-19 in the community. Hospital-associated transmission has been suggested since a considerable proportion of the infected population is healthcare staff. Considering the role of the abovementioned factors in increasing the incidence of COVID-19 in Southern Iran, it can be presumed that SARS-CoV-2 has probably been circulating in the community for weeks before the first cases were detected. The virus had enough time to circulate and infect a significant proportion of the population, most of whom had asymptomatic infections and remained undiagnosed. Exclusively, hospitalized COVID-19 patients with severe presentations of COVID-19, of note older patients and those with major underlying diseases or comorbidities, were identified. Due to limited resources, there was no possibility of public screening and only those severely ill patients, their close contacts, and healthcare workers were tested for SARS-CoV-2 infection.

We hypothesize that individuals with prior exposure to local circulating human coronaviruses experience more severe and lethal forms of the disease when they become infected with SARS-CoV-2. Moreover, most individuals naive to SARS-CoV-2 experience an asymptomatic or mild infection. However, these SARS-CoV-2 convalescent individuals might experience a severe and lethal illness upon reinfection with different strains of SARS-CoV-2 [27, 37]. According to this hypothesis, we speculate that the antibodies obtained from primary infections with circulating seasonal human coronaviruses or SARS-CoV-2 lead to more severe and lethal illness in secondary infection with SARS-CoV-2 possibly by triggering Fcγ receptor-mediated uptake of the virus. Also, our hypothesis for disease severity and fatality in older people is the repeated exposure to coronavirus infections in lifetime, which increases with age [35, 38–40]. Immunologic memory to closely related coronaviruses may induce antibody-dependent enhancement of infection and immune complex deposition [39, 41–43].

Secondary infection by related virus strains might lead to an exacerbated illness due to the presence of pre-existing cross-reactive nonneutralizing antibodies. The phenomenon in which nonneutralizing or sub-neutralizing antibodies facilitate viral cell entry by intermediation of Fcγ receptors (FcγRs) and/or complement receptors (CR) and lead to enhanced infection is termed antibody-dependent enhancement (ADE) (Fig. 1) [8, 27, 44–47]. Binding of virions complexed with antibodies and/or complement fragments to FcγRII and/or CR on target
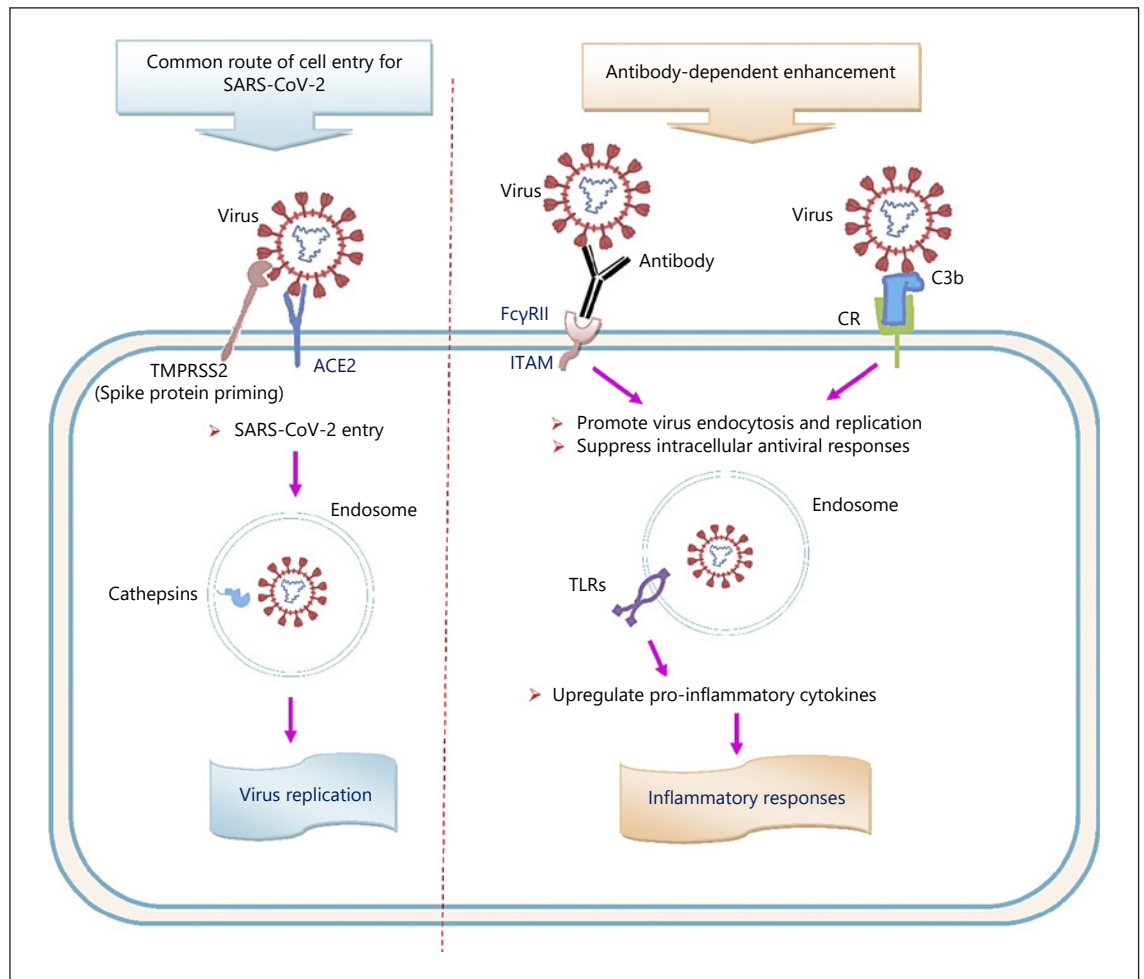
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Fig. 1. Potential routes of cell entry for SARS-CoV-2. TMPRSS2, transmembrane protease serine 2; ACE2, angiotensin-converting enzyme 2; FcγRII, Fcγ receptor II; CR, complement receptor; ITAM, immunoreceptor tyrosine-based activation motif; TLRs, toll-like receptors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

cells initiates receptor-mediated signaling events, leading to enhanced expression of inflammatory cytokines and suppression of intracellular antiviral responses at the transcriptome level, followed by endocytosis of the virus and subsequent activation of immune cells. The activated immune cells might accumulate in the lung and promote cytokine storm and lymphopenia [22, 41, 48–50]. Furthermore, the formation of immune complexes can promote complement activation and subsequent tissue damage (Fig. 2) [41, 51, 52].

ADE acts mainly through 2 pathways: FcγR-mediated ADE and complement-mediated ADE. In FcγR-mediated ADE, virus-antibody complexes bind to FcγRII on immune cells. The FcγRII activates signaling pathways by an immunoreceptor tyrosine-based activation motif to pro-

mote virus endocytosis and replication and to suppress the intracellular antiviral responses by decreasing antiviral transcription factors by inhibition of the STAT pathway. Besides, viral particles in the endosomes signal through Toll-like receptors to upregulate the production of pro-inflammatory cytokines and to activate immune cells [22, 53]. In complement-mediated ADE, following the activation of the complement cascade by virus-antibody complexes, complement-coated virions form and bind to CR on cells. Complement receptors activate signaling pathways to increase viral replication by suppressing intracellular antiviral responses [48, 54].

Hyperactivation of immune cells, notably inflammatory macrophages, triggers the excessive and prolonged inflammatory response known as cytokine storm [38].

Fig. 2. Potential pathways of antibody-dependent enhancement of SARS-CoV-2 infection. SARS-CoV-2 is recognized by cross-reactive nonneutralizing antibodies obtained from previous infections with circulating human coronaviruses. Virus-antibody complexes bind to immune cells and initiate receptor-mediated signaling events, followed by endocytosis of the virus and subsequent activation of immune cells. The activated immune cells, notably inflammatory macrophages, accumulate in various organs and promote cytokine storm, tissue damage, and lymphopenia, which contribute to the development of more severe presentations of COVID-19. On the other hand, IL-6 and GM-CSF induce monocyte activation and differentiation to inflammatory macrophages. Furthermore, the formation and deposition of immune complexes in various organs can promote complement activation and subsequent tissue damage. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.
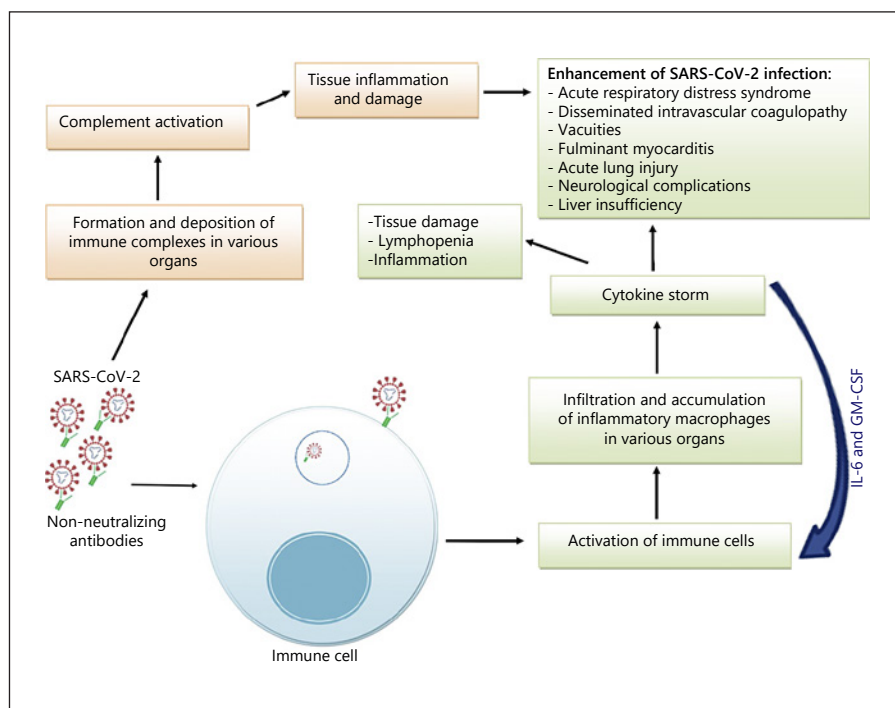
Cytokine storm is mediated by increased levels of inflammatory mediators and cytokines, such as tumor necrosis factor-alpha, interferon-γ inducible protein 10, IL-1, IL-2, IL-6, IL-7, IL-8, IL-10, IL-18, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, CCL2/monocyte chemotactic protein, CXCL10, and CCL3/macrophage inflammatory protein 1 alpha, which may promote acute lung injury, respiratory distress syndrome, disseminated intravascular coagulopathy, fulminant myocarditis, vacuities, multiple organ dysfunction, and many others [2, 3, 8, 38, 41, 55].

Lymphopenia is a predictor of disease severity and requirement for intensive care in COVID-19 patients. Lymphocyte apoptosis in response to high levels of inflammatory cytokines, lymphocyte lysis following the entry of SARS-CoV-2 into cells, inhibition of lymphocyte proliferation due to the interference by COVID-19 infection, and impairment of the cytotoxic activity of CD8+ T cells followed by the exhaustion of T cells have been proposed as the possible causes of lymphopenia. Nevertheless, the exact etiology remains unknown [56, 57].

There are currently no clinical data to support this hypothesis. The possibility of the development of more severe presentations of COVID-19 sustained by ADE, cytokine storm, and immune complex deposition, if confirmed, would have relevant implications for the management of the COVID-19 pandemic. A better understanding of these immunopathologic phenomena and their relation to disease course and severity might give us insights into the development of the most efficient prophylactic and therapeutic approaches. In addition to the immune-mediated pathogenesis, the severity of COVID-19 could be related to host genetic factors, such as mutations in the ACE2 protein, which are related to enhancing replication of the virus, as well as nonbiological factors [58, 59]. Notably, single-nucleotide polymorphisms in the genes related to immune responses, including cytokine genes and FcγR genes, can affect the severity and susceptibility of infectious diseases [49]. For example, FcγRIIa-R131 polymorphism is associated with SARS severity [27, 44]. The GCC haplotype in the IL10 promoter region is associated with the highest expression level of IL10 [49]. Inborn errors of Toll-like receptor 3- and interferon regulatory factor 7-dependent type I IFNs immunity are reported to correlate with life-threatening COVID-19, and patients with neutralizing autoantibodies against type I IFNs are at risk of developing critical COVID-19 [60, 61].

Given the rapid speed of SARS-CoV-2 transmission and life-threatening consequences of COVID-19 being observed over time, the global administration of efficient prophylactic vaccines seems to be the most affordable so-

lution for controlling this pandemic. Moreover, pandemic management relies on prevention both at the individual and community levels [62]. Effective prevention can be achieved through promoting public health interventions, including face masks, handwashing, social distancing, public education, stay-at-home orders, workplace restrictions, and school closures, and establishing comprehensive screening programs for prompt identification and quarantining of infected subjects with the aim of breaking the cycle of SARS-CoV-2 transmission in the society [25]. Although prevention is a promising strategy to mitigate SARS-CoV-2 transmission, it may not suffice to eliminate this pandemic. In fact, offering regular SARS-CoV-2 testing to the general populations is impossible in resource-limited settings. Therefore, the specific focus should be on high-risk populations with the aim of protecting the vulnerable [63, 64]. Nevertheless, asymptomatic cases and those with undetectable viral load can be potentially considered as mobile infectious sources, contributing to SARS-CoV-2 spread [8]. Moreover, the socioeconomic impacts of social isolation and full lockdown and the afterward economic crisis are some other obstacles to manage this pandemic [65]. In these conditions, the development of potent prophylactic and therapeutic tools against COVID-19 is essential to drive away the rising wave of SARS-CoV-2 infection in Southern Iran.

Conclusion

Given previous data on the role of ADE in the pathogenicity of several viral infections, it is advisable to hypothesize a similar risk for COVID-19. Risk of ADE may be due to antibodies obtained from primary infections with circulating seasonal human coronaviruses or SARS-CoV-2. In addition, our hypothesis for disease severity and fatality in older people is the repeated exposure to coronavirus infections in the lifetime, which increases with age. Further thoughtful and rigorous research is needed to understand whether there is an association between ADE and rates of severity and mortality attributable to COVID-19.

Statement of Ethics

The author confirms that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Conflict of Interest Statement

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to the manuscript.

Author Contributions

Farshadpour F. and Taherkhani R. designed the study and drafted the manuscript; Taherkhani R. performed the literature review and edited the manuscript. All authors approved the final draft of the manuscript.

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