

Review

The Cytokine Storm in COVID-19: The Strongest Link to Morbidity and Mortality in the Current Epidemic

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Abstract: COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. The clinical presentations of the SARS-CoV-2 infection are widely variable and treatment strategies for COVID-19 are dependent on the infection phase. Timing the right treatment for the right phase of this disease is paramount, with correlations detected between the phase of the infection and the type of drug used to treat. The immune system activation following COVID-19 infection can further develop to a fulminant cytokine storm which can progress to acute respiratory distress syndrome. The inflammatory phase, or the hyperinflammation phase, is a later stage when patients develop acute respiratory distress syndrome (ARDS), sepsis, and kidney and other organ failure. In this stage, the virus is probably not necessary and all the damage is due to the immune system's cytokine storm. Immunosuppressive or immunomodulatory agent administration is the major strategy in treating COVID-19 patients at this stage. On the other hand, immunodeficient patients who are treated with immunomodulator agents have attenuated immune systems that do not produce enough cytokines. Current data do not show an increased risk of severe COVID-19 in patients taking biologic therapies or targeted disease-modifying antirheumatic drugs. However, more comprehensive studies are needed to assess the effect of these medications, and whether they may actually be protective of the severe type of disease. Although medications for COVID-19 and for the cytokine storm are important, the main breakthrough in slowing down the pandemic was developing effective vaccines. These vaccines showed a dramatic result in reducing morbidity and mortality up to the Delta variant's spread. However, the emergence of the new variant, Omicron, influenced the successful results we had before. This variant is more contagious but less dangerous than Delta. The aim now is to develop vaccines based on the Omicron and Delta immunogens in the future for broad protection against different variants.

Keywords: Cytokine Storm; Delta variant; Omicron variant; severity; COVID-19; mortality



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1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. The presentation of the SARS-CoV-2 infection ranges in clinical severity, from asymptomatic to a mild upper respiratory tract illness, to a diffuse viral pneumonia causing acute respiratory failure, with sequelae including acute lung injury, multiorgan dysfunction syndrome, and death [1–3]. Most people infected with the virus will be asymptomatic or experience mild to moderate respiratory illnesses and recover without requiring special treatment. However, some will become seriously ill and require medical attention [4,5]. Older people and those with underlying medical conditions, such as cardiovascular diseases, diabetes, chronic respiratory diseases, or cancer, are more likely to develop a serious illness [3–5].

The viral infection is divided into three stages [2,3]. The first stage is the early infection or viral response phase, during which symptoms of upper respiratory tract infection dominate. The second stage is the pulmonary phase, when patients develop viral pneumonia,

probably bilateral, with all its associated symptoms [2]. This pulmonary phase is divided into two distinct parts [1–3]. Stage IIA is pneumonia without hypoxia and stage IIB is pneumonia with hypoxia. Patients at stage IIB will likely require hospitalization and oxygen supplementation [1–3]. The third stage is the inflammatory phase or the hyperinflammation phase, when patients develop acute respiratory distress syndrome, sepsis, and kidney and other organ failures. In the third stage, otherwise known as the cytokine storm, the virus is probably not directly involved, and all the damage is caused by an overreactive immune system [1–3]. There is a direct correlation between the cytokine storm and morbidity and mortality [1–3].

Treatment strategies in COVID-19 depend on the infection phase [5–12]. In the early viral phases, the treatments of choice are antiviral agents such as Remdesivir, which is an RNA-dependent polymerase inhibitor [6], and convalescent plasma, i.e., plasma from patients that have been cured from COVID-19 infection [9]. Other treatments include hydroxychloroquine, a well-known drug used for several decades for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and malaria prophylaxis [10,11], and lopinavir-ritonavir [8], which is an HIV protease inhibitor and is indicated in combination with other antiretroviral products for the treatment of human immunodeficiency virus [8]. However, recently, the NIH Panel for COVID-19 Treatment Guidelines recommends against the use of lopinavir/ritonavir or other HIV protease inhibitors in COVID-19 infections [8]. This is due to unfavorable pharmacodynamic data and mainly due to the lack of clinical benefit in patients with COVID-19 [8]. A new confirmed antiviral agent is the Regen-COV-2 antibody cocktail, which consists of two monoclonal antibodies, casirivimab and imdevimab. This cocktail has successfully helped patient immune systems eradicate the virus [12].

The main risk factor in this SARS-CoV-2 infection is the development of a fulminant cytokine storm [4]. This storm happens when the immune system's reaction due to the SARS-CoV-2 virus becomes hyperactive, resulting in an excessive inflammatory reaction with the release of large amounts of pro-inflammatory cytokines. The cytokine storm in COVID-19 can mimic hemophagocytic lymphohistiocytosis or macrophage activation syndrome, which can progress to acute respiratory distress syndrome (ARDS) and multiorgan failure [5], with a serious risk of death to the patient [5]. The purpose of this review is to emphasize the importance of the cytokine storm situation and the dangers behind it, especially in critically ill and immunodeficient patients.

Vaccination of the population against the coronavirus disease has reduced both the mortality and severity of the disease [5,13]. This development cycle of the vaccine against SARS-CoV-2 was the turning point. The current main challenge is the emergence of new variants that have developed in non-vaccinated countries that can infect vaccinated people [5]. This is due to a restricted immune memory [5,13], which is about six months in twice-dosed vaccinated people [5,13]. Beyond six months, the data show a similar increase in the rate of infections [5]. The rate of severe cases also increases as a function of time from vaccination. Serological studies show a correlated time-dependent reduction in neutralization titers [5,13].

The efficacy of a fourth dose of the COVID-19 mRNA vaccine against Omicron was studied [13]. The study confirmed that the fourth dose of the mRNA vaccine is immunogenic, safe, and somewhat efficacious against symptomatic disease. A comparison of the initial response to the fourth dose with the peak response to a third dose did not show substantial differences in humoral response or in levels of Omicron-specific neutralizing antibodies. This confirms the superiority of a third dose relative to the second dose, whereby the maximal immunogenicity of mRNA vaccines is achieved after three doses, and that antibody levels can be restored by a fourth dose [13].

2. COVID-19: Clinical Presentations and Laboratory Findings

The disease presentation has a wide spectrum [14–16]. Asymptomatic or pre-symptomatic individuals test positive for SARS-CoV-2 using a molecular diagnostic tool such as PCR

but have no symptoms. Mild illness or mildly symptomatic patients are those who have any of the various signs and symptoms of COVID-19 (such as fever, cough, sore throat, malaise, headache, and muscle pain) without dyspnea or pneumonia. Moderately ill patients have evidence of pneumonia or lower respiratory disease by clinical assessment or imaging, but the saturation is preserved above 93% in room air. Severely ill patients are those who have a respiratory rate above 30 breaths per minute, $\text{Spo}_2 < 94\%$ in room air, or $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. Finally, critically ill patients have respiratory failure, septic shock, and multiple organ dysfunctions and failures.

Mildly clinical patients may not initially require hospitalization. This decision depends on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the patient's ability to self-isolate at home [14]. Available data suggest that the majority of SARS-CoV-2 infections are asymptomatic or have mild to moderate symptoms [14–16]. Some studies show that about 75% of those who have a positive PCR test have no symptoms and will remain asymptomatic [15]. Those with severe presentations such as pneumonia, hypoxemic respiratory failure, ARDS, sepsis and septic shock, and acute kidney injury should be hospitalized, as they are at a high risk of dying [16].

Laboratory findings and clinical parameters are both essential for effective patient management and treatment. Many studies have shown the typical laboratory findings of COVID-19 patients [13,17–20]. Common laboratory findings among hospitalized patients with COVID-19 include lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, elevated inflammatory markers (e.g., ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate), and abnormalities in coagulation tests [18]. Some studies show that the most common laboratory findings include increased CRP, ESR, IL-6, and increased LDH [17]. Basheer et al. showed clinical and laboratory findings that affect the mortality in COVID-19 patients [19]. They show that male gender, elderly, overweight, hypertension, diabetes mellitus type 2, lung disease, hemodialysis, and past use of aspirin are predictors of mortality in COVID-19 patients. Laboratory predictor factors that were found to be associated with increased disease severity and/or mortality are NLR and BUN. They also show that the cytokine levels of CXCL-10, G-CSF, IL-2, and IL-6 are high upon admission of severe patients and significantly reduced upon discharge in these COVID-19 patients. Other studies show that high D-dimer levels and severe lymphopenia are associated with critical illness or mortality [20].

3. Cytokine Storm in COVID-19: The Correlation between the Cytokine Storm, Morbidity, and Mortality

Globally, humans have suffered from many viral pandemics in the last century [21], with recent ones being severe acute respiratory syndrome (SARS) [22], the influenza virus pandemic [23], and the H1N1 swine influenza [23]. These viral infections pose risks to our health in that some of them are zoonotic infections with the threat of human-to-human transmission and excessively high mortality rates [24]. At the end of 2019, another strain of SARS-CoV was identified, SARS-CoV-2, which has caused the COVID-19 pandemic.

The main effects of SARS-CoV-2 on the immune system are in the distribution and apoptosis of lymphocytes. There is a decrease in the total number of lymphocytes, cytotoxic and helper T cells, B, and NK cells, and almost all their subsets, especially in patients with a severe course of COVID-19 [4]. Development of fulminant cytokine storm due to the SARS-CoV-2 virus infection results in an excessive inflammatory reaction with the release of large amounts of pro-inflammatory cytokines (Figure 1). This condition mimics a dangerous situation called hemophagocytic lymphohistiocytosis, or macrophage activation syndrome, with a serious risk of death [5]. Cytokine storms are strongly correlated with severe disease and death [12,19,24].

The inflammatory third phase of the SARS-CoV-2 infection is the dangerous one. It is not related to the viral load but to an uncontrolled immune activation [24–30]. Elevation in inflammatory mediators, including cytokines and chemokines such as interleukin (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte colony-stimulating factor (G-CSF),

monocyte chemoattractant protein-1, and other inflammatory cytokines, such as C-reactive protein, ferritin, and D-dimers, significantly correlate with disease severity [25–33]. Some of these cytokines predict mortality in COVID-19 patients [9,19,20,34,35]. These cytokines mediate lung capillary permeability and penetration. This mediated, diffuse, bilateral ground glass infiltrate can develop into hypoxemia. Endothelial injury mediated coagulation disorders and fibrotic damage to the lungs (Figure 1).

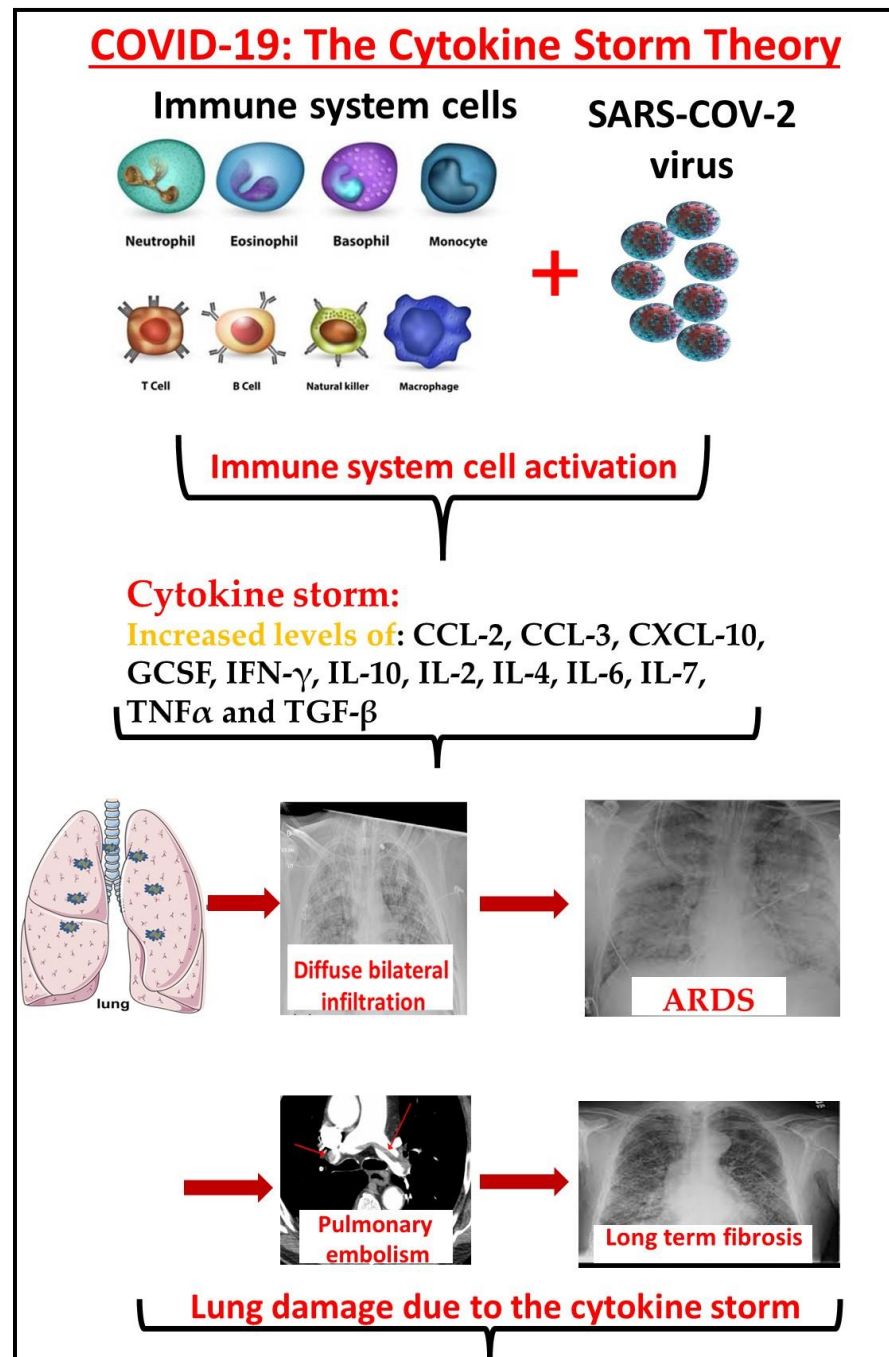


Figure 1. The effect of the cytokine storm on COVID-19 patients. The SARS-CoV-2 virus infection activates the immune system, which releases large concentrations of cytokines such as CCL-2, CCL-3, CXCL-10, GCSF, IFN- γ , IL-10, IL-2, IL-4, IL-6, IL-7, TNF α , and TGF- β . These cytokines mediate lung capillary permeability and penetration. Diffuse bilateral ground glass infiltrate develops and the patient becomes hypoxemic. Endothelial injury mediated coagulation disorders, and pulmonary embolism could develop in these patients. The fibrotic damage to the lungs is probably long term.

Serum pro-inflammatory cytokine levels were measured upon admission and again upon discharge in severely ill patients [19]. CXCL-10, GCSF, IL-2, and IL-6 serum concentrations were significantly reduced upon discharge [19]. A comparison of these cytokines between severely ill patients who died during their hospitalization period and mildly ill patients who were discharged two days later show significant elevation in the non-surviving group [19,36].

4. Cytokine Storm in Immunodeficient Patients

The uncontrolled production of cytokines, i.e., the cytokine storm, has the strongest link between morbidity and mortality in COVID-19 patients [35–38]. The cytokine storm is usually a warning sign of COVID-19 escalation and severity, characterized by rapid releases of inflammatory cytokines and chemokines [38–44].

Treating immunocompromised patients is unique in this epidemic [40–43]. This subgroup of immunocompromised patients is treated with a wide range of immunomodulator agents, such as rituximab, anti-TNF-alpha, and others [40–43]. These drugs could be harmful in the initial phase of COVID-19 in that the host's immune response is necessary to inhibit viral replication [40–42]. However, these drugs which are used in situations of immunocompromised conditions, including primary immune deficiency and secondary immune suppression issues, could be beneficial. Attenuation of the immune system could avoid cytokine release and inhibit the dangerous cytokine storm in COVID-19 patients. Attenuation of the inflammatory response by immunosuppressant drugs could affect the disease severity by suppressing some of the immune system's cellular or humoral responses and inhibit the host's immune response against the virus [44]. A decrease in cytokines which are related to patient mortality could preserve the patient and avoid death [19,20,34,35].

Many studies show the effect of immunosuppressant drugs on mortality in COVID-19 patients [45–49]. Patients treated with anti-tumor necrosis factor, vedolizumab, or ustekinumab (IBD treatments) are typical for COVID-19, and the incidence and mortality is similar to that in the community [45–49]. In addition, research has shown that the use of an anti-TNF- α agent is not associated with an increased risk of COVID-19 infection [45–51]. The Global Rheumatology Alliance recently released its report on COVID-19 patients with an underlying rheumatologic disease. Less than half of the patients were hospitalized. Monotherapy with a biologic or a JAK inhibitor is associated with a lower odd's ratio of hospitalization [51].

In dermatology, research on patients treated with biological treatments such as dupilumab for atopic dermatitis, ixekizumab for psoriasis, guselkumab, or ustekinumab showed that they presented as mild patients [52–58].

Rituximab, an anti-CD20 monoclonal antibody, is one of the main treatments for B-cell malignancies and autoimmune diseases [59,60]. It acts by depleting normal cells and pathogenic B cells [60,61]. This medication prolongs B-cell depletion, which impairs the adaptive immune response and the ability to produce neutralizing antibodies. Patients treated with rituximab are at a higher risk for prolonged severe forms of COVID-19 [62–65]. The effect of rituximab on the severity of COVID-19 patients is controversial. Some reports show that patients taking rituximab for granulomatosis with polyangiitis were mild patients, but there are also reports of severe, but recovered, infections in patients with granulomatosis or polyangiitis and other rheumatologic diseases [62–65].

COVID-19 is also prevalent in patients with autoimmune systemic diseases. This issue verifies the possible interactions between SARS-CoV-2 infection and impaired immune systems of patients with autoimmune systemic diseases. This is due to patients' increased susceptibility to infections and favored by the high exposure to the virus at medical facilities [66,67].

The existing data do not show an increased risk of severe COVID-19 in patients taking biologic therapies or targeted disease-modifying antirheumatic drugs. More comprehensive studies are needed to reveal the direct effect of these medications in modulating the response to COVID-19, and whether they may actually be protective in the severe disease.

5. The Cytokine Storm as a Target Choice in the Treatment of COVID-19

The cytokine storm plays an essential role in the pathogenesis and clinical outcome of virus infections [24]. Blocking the cytokine storm provides greater protection than does antiviral therapy in the influenza virus [24].

The cytokine storm in fatal COVID-19 is represented by several pathological features, such as ARDS, coagulation, and multiorgan dysfunctions [12,19,24]. Patients with serious COVID-19 infections may suffer from a release of cytokines which can damage the lung tissues [12,19,24]. A severe COVID-19 cytokine storm is characterized by the release of proinflammatory mediators [12,19,24,67], and the amplified pulmonary inflammatory response results in enlarged alveolar–capillary gas exchange, making oxygenation difficult [67].

Elevated IL-6 and IL-1 concentrations correlate with intrapulmonary macrophage activation and pulmonary vascular disease [67]. These cytokines significantly contribute to fever, lymphopenia, coagulation, lung injury, and multiorgan failure [67,68]. IL-1 β is a mediator of lung inflammation, fever, and fibrosis. Suppression of IL-1 family members and IL-6 has been shown to have a therapeutic effect in many inflammatory diseases, including viral infections such as SARS-CoV-2 [67–69]. Therefore, many drugs which target cytokines in COVID-19 were tested for their effect on mortality and morbidity [70–80].

IL-6 levels are highly correlated with the lethal complications of COVID-19, and are associated with poor prognosis and progression, as well as disease augmentation [35,69–76]. Agents which mediate IL-6 inhibition may improve the patients' conditions. Tocilizumab is a recombinant, humanized, monoclonal anti-interleukin IL-6 antibody that targets the human IL-6 receptor (IL-6R). However, results using tocilizumab are mixed [69–80]. While some studies show that tocilizumab is not efficacious in improving hospitalized patients infected with severe acute respiratory syndrome coronavirus [75], other studies show that decreasing IL-6 levels by tocilizumab correlates with a decrease of the risk of mortality caused by COVID-19 [69,76]. Furthermore, many studies confirm that the use of tocilizumab decreases the need for mechanical ventilation [77–89].

Anti-IL-1 molecules were also tested for their efficacy on reducing morbidity and mortality in COVID-19 patients [90,91]. Anakinra is the main treatment in this group. Anakinra treatment, compared to the standard of care, shows a decrease in twenty-eight-day mortality and in hospital stay [91].

Anti-TNF agents are commonly used for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. While serum TNF- α levels are moderately elevated in patients with SARS [92,93], much higher serum levels are observed in COVID-19 patients, positively correlating with disease severity [92,93]. Although anti-TNF treatment was suggested as a potential treatment for COVID-19, there is insufficient data [92]. Some studies have demonstrated that there is a correlation between anti-TNF- α therapy with an increase in the risk of intracellular infection of SARS-CoV-2 infection via induction of the Notch-1 signaling pathway [93].

The efficacy of corticosteroids (CS) on inflammatory organ injury in viral pneumonia remains controversial [72,74,94]. Immunosuppressive glucocorticoids when administered to severely ill patients who need oxygen show the greatest benefit in preventing deterioration of these patients [36,37]. Steroids are not recommended to non-hypoxic patients [35–37]. In the absence of an oxygen requirement, patients on glucocorticoids may fare worse than those who receive standard care [35–37]. Since there is no positive evidence coming from randomized clinical trials, the WHO guidelines do not recommend routinely using systemic CS treatment for patients with COVID-19 [94]. Thus, the selection of patients and timing of the administration of glucocorticoids is critical for survival benefits [35]. Timing is paramount in this epidemic. Suppressing the host response too early during rapid viral replication is probably deleterious, whereas waiting for the requirement for respiratory support may be the appropriate time to intervene with these medications [35].

In clinical practice, intravenous immunoglobulin (IVIG) is used in patients with immune deficiencies for treating infectious diseases, as well as for treatment-resistant pa-

tients with autoimmune diseases as an immunomodulatory agent [95,96]. IVIG polyclonal immunoglobulin G (IgG) was also studied for its effect on morbidity and mortality in COVID-19 patients [95]. Previous favorable experiences from patients with SARS and MERS suggest the efficacy of a high dose of IVIG (0.3–0.5 g/kg) in patients with a serious COVID-19 infection in the early phase of the disease [95,96]. IVIG has demonstrated clinical efficacy in critically ill patients with COVID-19 [95]. There may be a relationship between the efficacy of IVIG and the COVID-19 disease severity [95,96].

Convalescent plasma is plasma from patients that were cured of a COVID-19 infection. Convalescent plasma may offer various beneficial actions in COVID-19 disease. In non-critical hospitalized patients, convalescent plasma therapy reduces the morbidity and mortality in moderately ill COVID-19 patients and shortens the hospitalization length [19]. The proposed mechanism of how convalescent plasma helps COVID-19 patients in the first stage of infection is not completely known [19]. Some studies show that antibodies from convalescent plasma can suppress viremia [59]. Administering convalescent plasma at the early stage of the disease was found to be more effective [19,59].

Mast cells may be another therapeutic target point in SARS-CoV-2 infection. This virus could activate mast cells. These cells mediate allergic and pulmonary diseases by secreting cytokines and material such as histamine, leukotrienes, and proteases [97]. Inhibition of mast cells could attenuate the effect of these cells on the organs, especially the lungs. The flavone luteolin could bind to the surface spike protein of SARS-CoV-2 and inhibit entry of the virus into host cells. This material also inhibits serine proteases, which is required for viral infectivity. Luteolin also inhibits mast cells and has anti-inflammatory properties, inhibiting secretion of the pro-inflammatory cytokines from human mast cells [97]. This drug could be effective in targeting the cytokine storm mediated by SARS-CoV-2 infection.

In summary, the cytokine storm is the most dangerous factor in this disease. This stage causes permanent or long-lasting damage to the body most of the time. Some of these damages are still unknown and unclear. Targeting some of the players in the cytokine storm can possibly attenuate the storm and prove to be beneficial. More evidence is currently being accumulated about the effect of this “storm” and on possible treatment modalities.

6. Omicron versus the Delta Variant

Genome changing and the production of new variants are features of the SARS-CoV-2 virus. So far, we have been exposed to many SARS-CoV-2 variants. The development of vaccines was quite effective against the Delta variant, and mortality and morbidity rates were reduced [98–101]. However, the new variant, Omicron, has shown various features especially in relation to its high infectivity, even to people who have once been infected with other variants or people who have administered the vaccines. Omicron shows different clinical severity [98,99].

The Omicron variation includes 30 mutations in the spike protein, compared to the 16 mutations in the Delta version [98,99]. These mutations affect the ability to connect to the ACE2 receptor. Kumar et al. studied the effect of the numerous mutations in the spike protein's receptor-binding region in Omicron compared to the Delta variant [100]. The results suggest that the Omicron variant may be immunologically resistant to antibody-mediated protection. Their study showed large changes in the RBD region of the Omicron variant that might contribute to the high binding specificity with ACE2, which may result in a higher transmission rate and considerable impact on pathogenesis when compared to the Delta variant [100].

While individuals infected with Delta are at risk of developing severe lung disease, Omicron infection causes less severe disease, mostly upper respiratory symptoms [101]. Rahul et al. showed that infection with Delta, but not Omicron, induces broad immunity in an *in vivo* experiment. While Omicron-infected mice serum could neutralize the Omicron variant, serum of Delta-infected mice shows effective ability against Delta and Omicron variants [101]. Omicron decreases the cytokine release and pulmonary viral replication [101].

In a human study, serum from Omicron and Delta patients reveals effective cross-variant neutralization induced by both viruses in vaccinated individuals [101]. Omicron infection enhances preexisting immunity elicited by vaccines, but not in unvaccinated individuals [101]. Omicron infection did not show effective cross-neutralizing antibodies against other variants in unvaccinated individuals [101]. In vaccinated individuals, Omicron infection effectively induces immunity against itself and enhances protection against other variants [101]. This explains the situation in the current epidemic, where vaccinated patients had relatively mild symptoms of upper respiratory tract and musculoskeletal involvement, and the unvaccinated patients showed a wide range of symptoms [98–101].

7. Discussion

People infected with SARS-CoV-2 may develop COVID-19 in a wide range of clinical severity, from a mild upper respiratory tract inflammation to a diffuse bilateral viral pneumonia [1,2]. According to the NIH management guidelines, the majority of the COVID-19 patients worldwide were classified as asymptomatic or mild, and only about less than twenty percent were classified as severe [16]. Three stages of SARS-CoV-2 infection are recognized [14,16]. The early infection or viral response phase, the second stage or the pulmonary phase [16], and the third stage or the inflammatory phase, when patients develop acute respiratory distress syndrome, sepsis, and kidney and other organ failures [2,3]. Treatment strategies in COVID-19 are dependent on the phase of the infection [6–12]. Some patients showed continuous post-corona syndrome. One possible theory is to do with the spike protein, which could damage the endothelium in an animal model and disrupt the blood–brain barrier, resulting in perivascular inflammation [102]. Moreover, the spike protein appears to share antigenic epitopes with human molecular chaperons, resulting in autoimmunity, and can activate toll-like receptors, leading to continuous release of inflammatory cytokines [102]. This releasing material mediated the prolonged effect on the CNS.

The dangerous phase of the infection is the third one, when the cytokine storm develops. Antiviral agents do not affect mortality and morbidity in this phase of the infection [6–12,95,103], where the damage is not caused by the virus itself but by a dys-regulated immune response. The cytokine storm develops as a massive non-responsive activation of the immune system. During this inflammatory phase, anti-inflammatory agents are the treatments of choice. The main purpose of these agents is to prevent and subdue the developing cytokine storm. Steroids [92,93], interleukin-6 and 1 (IL-6 and IL-1) receptor antagonists, and others were studied [80–92]. Some of these agents have been shown to be beneficial, as described above.

One of the accepted treatments throughout this pandemic is the use of vitamin D, which could sensitize the immune system against allergens and reduce the risk of unresponsive activation of the immune system [104]. On the other hand, vitamin D deficiency is associated with microbiome dysbiosis, which is linked to both the onset of intestinal inflammatory processes and extra-intestinal conditions associated with chronic inflammation and metabolic dysfunction. Both the microbiome and vitamin D deeply influence each other and the immune system in many different ways. They could help in preventing the development of infections and regulate the immune response by preventing the development of allergies [104].

One possible key in containing the coronavirus disease 2019 (COVID-19) pandemic is mass vaccination of the population [5]. The maximum rescue came from vaccinating the population [105–107], which reduced both the mortality and severity of the disease [5,105].

These vaccines showed a dramatic result in reducing morbidity and mortality up to the Delta variant's spread. However, the emergence of the new variant, Omicron, influenced the success we had before. This variant is more contagious but less severe than Delta. Apparently, the immunity we have accumulated so far against other variants partially helped against this variant. This is due to a restricted immune memory [105]. Therefore,

we should develop vaccines based on the Omicron and Delta immunogens, in the future, for broad protection against a wide range of variants.

One of the main purposes of vaccination is to prevent the dangerous phase, the cytokine storm phase. The mechanism of the vaccine in preventing cytokine storm is mediated by reducing the initial inflammatory reaction and protecting against severe disease [108,109]. COVID-19 vaccines could produce sufficient therapeutic antibodies. It appears that such immunity might not be present in all individuals [108,109]. Therefore, the effect of these vaccines on preventing the cytokine storm could vary from one person to another. To date, there are not enough studies concerning the actual effects of COVID-19 vaccines on preventing the cytokine storm. Further studies are needed in order to emphasize the relationship between the new vaccines and the inflammatory response and to verify if the vaccination program is an effective strategy to prevent the cytokine storm.

8. Conclusions

People infected with SARS-CoV-2 may develop COVID-19, which has a wide range of clinical severity. Fulminant cytokine storm is still the major risk factor in this epidemic. The treatment strategy is dependent on the phase of the infection, and some treatments for treating the cytokine storm show survival benefits.

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