REVIEW

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The cytokine storm and COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19), which began in Wuhan, China, in December 2019, has caused a large global pandemic and poses a serious threat to public health. More than 4 million cases of COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been confirmed as of 11 May 2020. SARS-CoV-2 is a highly pathogenic and transmissible coronavirus that primarily spreads through respiratory droplets and close contact. A growing body of clinical data suggests that a cytokine storm is associated with COVID-19 severity and is also a crucial cause of death from COVID-19. In the absence of antivirals and vaccines for COVID-19, there is an urgent need to understand the cytokine storm in COVID-19. Here, we have reviewed the current understanding of the features of SARS-CoV-2 and the pathological features, pathophysiological mechanisms, and treatments of the cytokine storm induced by COVID-19. In addition, we suggest that the identification and treatment of the cytokine storm are important components for rescuing patients with severe COVID-19.

KEYWORDS
COVID-19, cytokine storm, literature review, SARS-CoV-2

1 | INTRODUCTION

An outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world.[1] The initial symptoms of COVID-19 mainly include fever, cough, myalgia, fatigue, or dyspnea. In the later stages of the disease, dyspnea may occur and gradually develop into acute respiratory distress syndrome (ARDS) or multiple organ failure.[2] It has been reported that a cytokine storm is associated with the deterioration of many infectious diseases, including SARS (severe acute respiratory syndrome)[3] and Middle East respiratory syndrome (MERS).[4] The cytokine storm caused by COVID-19 has been suggested to be associated with COVID-19 severity.[2,5] However, there is currently a limited understanding of the cytokine storm in severe COVID-19. Therefore, here, we have discussed the current findings and treatment strategies for the cytokine storm in severe COVID-19.

2 | FEATURES OF SARS-CoV-2

SARS-CoV-2 is the newest coronavirus known to infect humans. SARS-CoV, MERS-CoV, and SARS-CoV-2 cause severe pneumonia, while other human coronaviruses, including 229E, OC43, HKU1, and NL63, cause only the common cold.[6] SARS-CoV-2 belongs to the genus *Betacoronavirus*, which also includes SARS-CoV and MERS-CoV, both of which have caused SARS and MERS, respectively.[7] SARS-CoV-2, SARS-CoV, and MERS-CoV have similarities and differences. Genetic sequence analysis has revealed that SARS-CoV-2 shares 79% sequence identity with SARS-CoV and 50% identity with MERS-CoV.[8] The genomes of SARS-CoV-2 and the bat coronavirus RaTG13 are 96.2% homologous.[9] As of 11 May 2020, COVID-19 has resulted in 278 892 deaths and 4 006 257 cases, with an approximate case fatality rate of 7.0%.[10] SARS-CoV and MERS-CoV had a case fatality rate of 9.6% (774/8096) and 34.4% (858/2494), respectively.[11] The reproduction number (R_0) of COVID-19 is thought to be between 2 and 2.5,[12] which is slightly higher than of SARS (1.7.1.9) and MERS (<1).[13] COVID-19 appears to be more infectious than SARS and MERS, but maybe less severe. The origins of SARS-CoV, MERS-CoV, and SARS-CoV-2 are considered to be zoonotic. Both SARS-CoV and MERS-CoV originated in bats and spread directly to humans from marked palm civets and dromedary camels, respectively.[14] However, the origin of SARS-CoV-2 remains unclear. SARS-CoV-2 has been reported to be transmitted between humans through direct contact, aerosol droplets, the fecal-oral route, and

intermediate viruses from symptomatic and asymptomatic patients.[15] SARS-CoV and MERS-CoV are also thought to spread from infected to noninfected individuals through direct or indirect contact.[15] The clinical symptoms of SARS, MERS, and COVID-19 range from mild respiratory diseases to severe acute respiratory diseases.[2,16] Patients with mild cases of SARS, MERS, and COVID-19 primarily exhibit fever, cough, and dyspnea. ARDS is a common severe complication of SARS and MERS.[17] Among 1099 inpatients with COVID-19, 15.6% of the patients with severe pneumonia were reported to have ARDS.[18] Feng et al[19] proposed that SARS-CoV-2 infection triggers an excessive immune response known as a cytokine storm in cases of severe COVID-19. A cytokine storm is a potentially fatal immune disease characterized by the high-level activation of immune cells and excessive production of massive inflammatory cytokines and chemical mediators.[20] It is considered to be the main cause of disease severity and death in patients with COVID-19,[5] and is related to high levels of circulating cytokines, severe lymphopenia, thrombosis, and massive mononuclear cell infiltration in multiple organs.[21]

It has been found that SARS-CoV-2 genomes from different parts of the world have evolved in different clusters.[22,23] Forster et al[23] reported there to be at least three central variants of SARS-CoV-2 globally, named A, B, and C. The A type is the most similar to the bat coronavirus and is mainly found in the United States and Australia. The B type is more common in East Asia and has evolved through several mutations. The C type is primarily found in Europe. Different viral isolates exhibit significant differences in pathogenicity and viral load.[24] Notably, given the diverse clinical symptoms of patients, it will be challenging to establish a genotype-phenotype relationship. With new sequences being uploaded to the global initiative on sharing all influenza data every day, new results may be produced as more data become available. The emergence of variants may add to the challenges of vaccine development.

3 | LUNG PATHOLOGY OF COVID-19

Pathological alterations in patients with COVID-19 include pulmonary edema, diffuse alveolar injury with the formation of hyaline membranes, the presence of reactive type II pneumocyte hyperplasia, proteinaceous aggregates, fibrinous exudates, monocytes and macrophages within alveolar spaces, and inflammatory infiltration of interstitial mononuclear cells.[25-28] Electron microscopy has revealed the presence of SARS-CoV-2 virus particles in bronchial and alveolar type II epithelial cells, but not in other tissues.[26,27] Therefore, although a polymerase chain reaction test may be negative from blood or throat swabs, SARS-CoV-2 viral inclusions may be detected in the lungs. Immunohistochemical staining indicated that CD68$^+$ macrophages, CD20$^+$B cells, and CD8$^+$T cells infiltrated the alveolar cavity and alveoli.[26] The levels of CD8$^+$T cells may be slightly higher than that of CD4$^+$T cells within the alveolar septa.[29] These pathological features are very similar to those of SARS-CoV and MERS-CoV infections,[30,31] indicating that effective treatments for SARS and MERS may be suitable for COVID-19. Excessive local release of cytokines is considered to be the determinant of pathological alterations and the clinical manifestation of ARDS.[32] Overall, the primary pathological manifestations in the lung tissue are viral cytopathic-like changes, infiltration of inflammatory cells, and the presence of viral particles. Thus, severe lung injury in patients with COVID-19 is considered as the result of both direct viral infection and immune overactivation.

4 | MECHANISMS OF THE CYTOKINE STORM IN COVID-19

Cellular entry of SARS-CoV-2 depends on the binding of S proteins covering the surface of the virion to the cellular ACE2 receptor[9,33] and on S protein priming by TMPRSS2, a host membrane serine protease.[33] After entering respiratory epithelial cells, SARS-CoV-2 provokes an immune response with inflammatory cytokine production accompanied by a weak interferon (IFN) response. The proinflammatory immune responses of pathogenic Th1 cells and intermediate CD14$^+$CD16$^+$monocytes are mediated by membrane-bound immune receptors and downstream signaling pathways. This is followed by the infiltration of macrophages and neutrophils into the lung tissue, which results in a cytokine storm.[34]

Particularly, SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete proinflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6). GM-CSF further activates CD14$^+$CD16$^+$ inflammatory monocytes to produce large quantities of IL-6, tumor necrosis factor-α (TNF-α), and other cytokines.[35] Membrane-bound immune receptors (eg, Fc and Toll-like receptors) may contribute to an imbalanced inflammatory response, and weak IFN-γ induction may be an important amplifier of cytokine production.[34] Neutrophil extracellular traps, the extracellular nets released by neutrophils, may contribute to cytokine release.[36] The cytokine storm in COVID-19 is characterized by a high expression of IL-6 and TNF-α. Hirano and Murakami[37] proposed a potential mechanism of the cytokine storm caused by the angiotensin 2 (AngII) pathway. SARS-CoV-2 activates nuclear factor-κB (NF-κB) via pattern-recognition receptors. It occupies ACE2 on the cell surface, resulting in a reduction in ACE2 expression, followed by an increase in AngII. In addition to activating NF-κB, the AngII-angiotensin receptor type 1 axis can also induce TNF-α and the soluble form of IL-6Ra (sIL-6Ra) via disintegrin and metalloprotease 17 (ADAM17).[38] IL-6 binds to sIL-6R through gp130 to form the IL-6-sIL-6R complex, which can activate signal transducer and activator of transcription 3 (STAT3) in nonimmune cells. Both NF-κB and STAT3 are capable of activating the IL-6 amplifier to induce various proinflammatory cytokines and chemokines, including vascular endothelial growth factor, monocyte chemoattractant protein 1 (MCP-1), IL-8, and IL-6.[39] IL-6 not only binds to sIL-6R to act in cis-signaling but can also bind to the membrane-bound IL-6 receptor (mIL-6R) through gp130 to act in trans-signaling. The latter can lead to pleiotropic effects on acquired and innate immune cells, resulting in cytokine storms.[40] Collectively, the impaired acquired immune responses and uncontrolled inflammatory innate responses to SARS-CoV-2 may cause cytokine storms.

5 | ASSOCIATIONS WITH COVID-19 SEVERITY

Earlier studies have indicated that the levels of IL-1β, IL-6, IL-8, IL-12, inducible protein 10 (IP-10), MCP-1, and IFN-γ are increased during SARS-CoV infection.[41] Low levels of the Th2 cytokine IL-4 were also observed in patients with SARS. MERS-CoV infection was also reported to induce increased concentrations of IL-15, IL-17, IFN-γ, and TNF-α.[42] Some studies have found that patients with severe COVID-19 exhibit higher levels of IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1, TNF-α, macrophage inflammatory protein 1 alpha, and granulocyte-CSF than patients with mild and moderate infections.[2,43,44] The fluctuations of these cytokines (eg, IL-6, IL-10, and TNF-α) are small or within the normal range.[43] In addition, increased levels of proinflammatory cytokines (eg, IL-4 and IFN-γ) are also observed in patients with COVID-19. Liu et al[44] found significant and sustained decreases in lymphocyte counts (CD4+cells and CD8+ cells), especially CD8+ T cells, but increases in neutrophil counts in the patients with severe COVID-19 compared to the mild patients. T cell loss may lead to increased inflammatory responses, while T cell restoration may reduce inflammatory responses during SARS-CoV-2 infection. Thus, the neutrophil-to-lymphocyte ratio (NLR) may be predictive of COVID-19 outcome. Interestingly, Ong et al[45] revealed that the levels of most cytokines, except IL-1, peaked after respiratory function nadir, indicating that cytokine expression might not be the primary cause of impaired respiratory function in patients with COVID-19. Dynamic cytokine storms and T cell lymphopenia are associated with COVID-19 severity. These findings indicate that clinicians should be able to identify patients at risk of developing severe COVID-19 as early as possible by monitoring dynamic cytokine storms and NLR. Changes in the major cytokines induced by the three coronaviruses discussed here are shown in Table 1, and cytokine secretion patterns based on COVID-19 severity are shown in Table 2.

6 | THERAPIES FOR THE CYTOKINE STORM IN COVID-19

Prevention and mitigation of the cytokine storm may be the crux to save patients with severe COVID-19. Currently, many therapies are being evaluated in clinical trials due to the lack of high-quality evidence.

6.1 | Corticosteroids

Corticosteroids inhibit the host inflammatory response and suppress the immune response and pathogen clearance.[46] In a retrospective study of 401 patients infected with SARS-CoV, the rational use of corticosteroids shortened hospital stays and reduced the mortality of seriously ill patients without complications.[47] Given the urgent clinical demand, some experts have recommended the rational use of corticosteroids in individuals with severe COVID-19.[48,49] However, the outcomes of corticosteroid use in patients with MERS, SARS, and influenza indicated an impaired clearance of viral RNA and complications (eg, secondary infection, psychosis, diabetes, and avascular necrosis).[50] A recent meta-analysis of 15 studies found that corticosteroids were associated with significantly higher mortality rates in patients with COVID-19.[51] Overall, although evidence indicates a potential role for the use of corticosteroids in patients with severe COVID-19, caution should be exercised given the possibilities of viral rebound and adverse events.

6.2 | Hydroxychloroquine and chloroquine

Given their in vitro antiviral effects and anti-inflammatory properties, chloroquine (CQ) and its analog hydroxychloroquine (HCQ) are considered to be potential therapies for COVID-19. Considering the

TABLE 1 The major cytokines related to cytokine storms during coronaviruses infection

cytokines	SARS-CoV[41]	MERS-CoV[42]	SARS-CoV-2[2,43,44]
	↑IL-1β	↑IL-15	↑IL-2
	↑IL-6	↑IL-17	↑IL-4
	↑IL-8	↑IFN-γ	↑IL-6
	↑IL-12	↑TNF-α	↑IL-7
	↑IP-10		↑IL-10
	↑MCP-1		↑G- CSF
	↑IFN-γ		↑IP-10
	↓IL-4		↑MCP-1
			↑MIP1A
			↑TNF-α
			↑IFN-γ

Note: ↑ = increased. ↓ = decreased.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; IFN-γ , interferon γ; IL, interleukin; IP-10, inducible protein 10; MCP-1, monocyte chemoattractant protein 1; MERS-CoV, Middle East respiratory syndrome coronavirus; MIP1A, macrophage inflammatory protein 1 alpha; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor α.

TABLE 2 Patterns of symptoms, cytokine secretion, and T cell lymphopenia related to the severity of COVID-19[2,43,44]

State of COVID-19	Uninfected individual	Mild and moderate COVID-19	Severe COVID-19
Symptoms	No symptoms	Fever, myalgia, fatigue, or dyspnea	Fever, myalgia, fatigue, dyspnea, ARDS, or MOF
Cytokine patterns	No cytokines	↑IL-6, IL-10, and TNF-α	↑↑IL-6, IL-10, TNF-α, IL-2, and MCP-1
T cell lymphopenia	No changes	↓Lymphocytes (CD4$^+$T and CD8$^+$T cells)	↓↓Lymphocytes (CD4$^+$T cells, especially CD8$^+$T cells)

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MOF, multiple organ failure; TNF-α, tumor necrosis factor-α.

severe side effects of CQ, HCQ may be a better therapeutic option. CQ and HCQ are able to reduce CD154 expression in T cells[52] and suppress the release of IL-6 and TNF.[53] A test of the pharmacological activities of CQ and HCQ in SARS-CoV-2-infected Vero cells revealed that low doses of HCQ might mitigate cytokine storm in patients with severe COVID-19.[54] A small French trial showed significant reductions in viral load and the duration of viral infection for COVID-19 patients who received 600 mg/day HCQ for 10 days, and these effects could be enhanced by cotreatment with azithromycin.[55] However, a meta-analysis of clinical trials indicated no clinical benefits of HCQ treatment in patients with COVID-19.[56] In fact, HCQ might actually do more harm than good given its side effects, which include retinopathy, cardiomyopathy, neuromyopathy, and myopathy.[57] Some clinical trials have suggested that taking high doses of HCQ or CQ may cause arrhythmia.[58,59] The role and risks of HCQ and CQ in the treatment of COVID-19 still need more data to further verify.

6.3 | Tocilizumab

Tocilizumab (TCZ), an IL-6 receptor (IL-6R) antagonist, can inhibit cytokine storms by blocking the IL-6 signal transduction pathway.[60] Currently, a small-sample clinical trial in China (clinical trial registration ID: ChiCTR2000029765) has found TCZ to be effective in critically ill patients with COVID-19.[61] Xu et al[62] found that out of 21 patients with severe COVID-19, 90% recovered after a few days of treatment with TCZ. A retrospective case-control study of COVID-19 patients with ARDS revealed that TCZ might improve survival outcomes.[63] However, the risks associated with TCZ (eg, severe infections, thrombocytopenia, neutropenia, and liver damage) should also be noted.[64] It is unclear whether there are different effects between IL-6 antagonists (siltuximab) and IL-6R antagonists (TCZ). Siltuximab binds to sIL-6 and inhibits only cis- and trans-signaling. TCZ binds to both mIL-6R and sIL-6R and inhibits both cis- and trans-signaling and trans-presentation.[40,65] Of note, IL-6 inhibitors are not able to bind to IL-6 produced by viruses such as HIV and human herpesvirus-8.[65] Currently, the application of TCZ for COVID-19 treatment is under study. The three drugs mentioned above (corticosteroids, HCQ, and TCZ) are immunosuppressants. Owing to the overall damage to the immune system caused by autoimmune diseases and the iatrogenic effects of immunosuppressants, the risk of infection in patients with autoimmune diseases will be increased compared to the general population. Currently, rheumatology societies[66-69] recommend the use of immunosuppressive drugs (except glucocorticoids) to be suspended in patients with COVID-19.

6.4 | Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have a wide range of immune regulatory functions and can inhibit the abnormal activation of T lymphocytes and macrophages and the secretion of proinflammatory cytokines.[70] MSC therapy was found to significantly reduce the mortality of patients with H7N9-induced ARDS and had no harmful side effects.[71] A clinical trial of MSC therapy revealed that MSCs were able to rapidly and significantly improve the clinical symptoms of COVID-19 without any observed adverse effects.[72] Although the side effects of MSC treatment are rarely reported, the safety and effectiveness of this treatment require further investigation.

6.5 | Other therapies

Anakinra, an IL-1 receptor antagonist that blocks the activity of proinflammatory cytokines IL-1α and IL-1β, has been reported to improve the respiratory function and increase the survival rate of patients with COVID-19.[73] IL-1 receptor antagonists increase the risk of bacterial infections, but this is extremely rare for anakinra.[65] Janus kinase (JAK) inhibitors can inhibit inflammatory cytokines and reduce the ability of viruses to infect cells.[74] A small nonrandomized study reported that patients treated with JAK inhibitors exhibited improved clinical symptoms and respiratory parameters.[75] However, JAK inhibitors can also inhibit IFN-α production, which helps us to fight viruses.[76] Intravenous immunoglobulin (IVIG) can exert various immunomodulatory effects by blocking Fc receptors, which are related to the severity of the inflammatory state.[77] IVIG has been reportedly used to treat patients with COVID-19.[78] Given its uncertain effectiveness and the risk of severe lung injury and thrombosis,[79] IVIG treatment requires further investigation. Furthermore, convalescent plasma therapy containing coronavirus-specific antibodies from recovered patients can be directly used to obtain artificial passive immunity. This approach has demonstrated promising results in the treatment of SARS and influenza.[80,81] However, a Cochrane systematic review revealed weak evidence on the effectiveness and safety of this therapy for patients with COVID-19.[82] Some individuals experienced moderate fever or anaphylactic shock after receiving

TABLE 3 Summary of the treatments for COVID-19 patients with cytokine storm

Treatments	Mechanisms	Advantages	Disadvantages
Corticosteroids	1. Inhibiting the inflammatory response[46] 2. Suppressing the immune response[46]	1.Reducing hospital stay[47] 2. Reducing mortality[47]	1. Impaired clearance of viral RNA[50] 2. Adverse events (secondary infection, psychosis, diabetes, and avascular necrosis)[50]
HCQ and CQ	1. Reducing CD154 expression in T cells[52] 2. Suppressing the release of IL-6 and TNF[53]	1. Reducing viral load[55] 2. Reducing the duration of viral infection[55]	1. Damage to the heart (arrhythmias)[58,59] 2. Other side effects (retinopathy, cardiomyopathy, neuromyopathy, and myopathy)[57]
TCZ	1. Blocking the IL-6 signal transduction pathway[60]	1. Improving survival outcome[63]	1. Adverse events (severe infections, thrombocytopenia, neutropenia, and liver damage)[64]
MSCs	1. Inhibiting the activation of T lymphocytes and macrophages[70] 2. Inhibiting the secretion of proinflammatory cytokines[70]	1. Reducing mortality[71] 2. Improving clinical symptoms[72]	1. Unclear
IL-1 receptor antagonist	1. Blocking the activity of proinflammatory cytokines IL-1α and IL-1β[73]	1. Improving respiratory function[73] 2. Increasing survival rate[73]	1. Increasing the risk of bacterial infections[65]
JAK inhibitors	1. Inhibiting inflammatory cytokines[74] 2. Reducing the ability of infected lung cells of the virus[74]	1. Improving clinical symptoms[75] 2. Improving respiratory parameters[75]	1. Blocking the production of beneficial cytokine (IFN-α)[76]
IVIG	1. Blocking Fc receptors[78]	1. Exerting various immunomodulatory effects[77]	1. Severe lung injury[79] 2. Thrombosis[79]
Convalescent plasma therapy	1.Transfusion of plasma with antibodies specific [80,81]	1. Obtain artificial passive immunity[80,81]	1. Moderate fever[82] 2. Anaphylactic shock[82]

Abbreviations: COVID-19, coronavirus disease 2019; CQ , chloroquine; HCQ, hydroxychloroquine; IFN-α, interferon α; IL-1, interleukin-1; IVIG, intravenous immunoglobulin; JAK, Janus kinase; MSCs, mesenchymal stem cells; TCZ, tocilizumab; TNF, tumor necrosis factor.

convalescent plasma. Currently, many effective treatments, such as IFNs, TNF blockers, S1P1 receptor agonists, and continuous renal replacement therapy, remain open to further study. A summary of the treatments available for COVID-19 patients with cytokine storm is shown in Table 3.

7 | CONCLUSION

The cytokine storm leads to deleterious clinical manifestations or even acute mortality in critically ill patients with COVD-19. Impaired acquired immune responses and uncontrolled inflammatory innate responses may be associated with the mechanism of the cytokine storm in COVID-19. Early control of the cytokine storm through therapies, such as immunomodulators and cytokine antagonists, is essential to improve the survival rate of patients with COVID-19.

Although many research articles are published each month, the majority of the existing literature about COVID-19 comes from descriptive works. In addition, high-quality evidence will be necessary to understand and treat the cytokine storm of COVID-19.

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