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# ROLE OF CYTOKINE STORM IN COVID-19 SEVERITY AND ITS TREATMENT MANAGEMENT

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## ABSTRACT

The human body has defense systems called the innate and adaptive immune systems. These systems include cells that produce substances called cytokines, like interleukins and interferons, to help the body respond to infections and other challenges. Normally, there's a mild stability among the body's inflammatory and anti-inflammatory responses, regulated by complex mechanisms. When this balance is disrupted, it can trigger a cascade of reactions leading to a massive release of cytokines. This can cause a self-amplifying cycle, leading to severe damage, organ failure, or even death. Disturbances can be triggered not only by infections but also by genetic conditions or certain medical treatments that affect the immune system. Understanding and treating these situations are challenging because of the intricate interactions within the immune systems. There's still much to learn, and effective treatments are limited at the moment.

**KEYWORDS:** Cytokine storm, COVID-19, *IL-6, IL-1.*

## INTRODUCTION

In 2019, an emerging pathogen SARS-CoV-2 originated in Wuhan, China (1). It became a major health concern as it rapidly spread around the world (2). This virus causes COVID-19 lung infection and poses a major risk to public health. An immune system that is overactive because to COVID-19 might lead to a "cytokine storm" in the lungs. This happens when the immune system becomes too active and releases a lot of signalling molecules called cytokines. This uncontrolled release of cytokines can harm the lungs and make the illness more severe. The term "cytokine storm" describes a situation where the body's immune system goes into overdrive, leading to various problems that can even be life-threatening (3). This overactive immune response can cause a serious condition called ARDS, which affects the lungs. It's important to note that ARDS is more about the body's immune response than the amount of virus present (4). Researchers are discovering more and more data that suggests specific signalling molecules, referred to as cytokines, may be significant in evolving COVID-19 and the difficulties it might bring (5).

### 1. Historical perspective of cytokine storms

The historical perspective of cytokine storms traces back to various instances where an overwhelming immune response led to significant health challenges. The term "cytokine storm" describes a scenario where the immune system releases an excessive amount of signaling molecules, or cytokines, which can result in severe inflammation and damage to the body.

- **Influenza-Like Syndrome:** Historical accounts often referred to cytokine storms as an influenza-like syndrome. It highlights the notion that infections and treatments can trigger uncontrolled immune responses (6).
- **Plague (Yersinia pestis Infection):** The devastating pandemics caused by Yersinia pestis, the bacterium responsible for the plague (e.g., the Black Death), showcased the association between this infection and cytokine storms. Alveolar macrophages in the lungs produce excessive cytokines, causative to the severity of disease (7).
- **Influenza Disease:** This disease exposed that exaggerated immune response played a role in the high mortality rate. Studies on the virus responsible for the pandemic showed that it induced marked pulmonary inflammation in mice, underscoring the involvement of cytokine dysregulation (8).

| Cytokine | Part in Respiratory Diseases | Reference(s) |
|---|---|---|
| **Interleukin-1β (*IL-1*β)** | contributes to inflammation and tissue injury | (63) |
| **TNF-α** | Promotes airway inflammation, contributes to lung tissue damage | (64) |
| ***IL-6*** | Elevated levels related with the severity of respiratory infections and chronic lung diseases | (65) |
| **Interleukin-8 (*IL-8*)** | Role in recruiting neutrophils to the airways, contributing to inflammation | (66) |
| **Interferon-γ (*IFN-γ*)** | Involved in antiviral responses and modulation of inflammation in respiratory infections | (67) |

***Table 1: Proinflammatory Cytokines and their role in Respiratory Diseases***

## 2. COVID-19 and Cytokine storm

Many severely ill, dying individuals do not exhibit adverse symptoms in the initial phases of yhe COVID-19. Some people experienced minor symptoms including fever, coughing, or muscle aches. However, their circumstances rapidly deteriorated later on or during the rehabilitation process. This fast deterioration resulted in ARDS and failure of multiple organs (9). The cytokine stprm is a substantial contributor to ARDS and multi-organ failure (10). This hyperactive immune response is critical in disease progression (11). Clinical investigations have reported a cytokine storm in serious COVID-19 infected individuals (12). As a result, efficiently regulating the cytokine storm is critical for preventing COVID-19 patient deterioration and preserving lives (13). A study found that individuals with COVID-19 had increased concentrations of various proinflammtory cytokines in their blood (14). More precisely, individuals in the ICU had elevation of proinflammatory cytokines in comparison to those who were not in the ICU (14). A further study found that those not survive COVID-19 had higher levels of IL6 compared to those did survive. This suggests that the death frequency of COVID-19 may be associated with a cytokine storm caused by the virus (15). Many experts experience that certain people are predisposed to a cytokine storm in the context of COVID-19, while conclusive data is still missing. This belief supports the well-documented hereditary tendency to cytokine storms in primary hemophagocytic lymphohistiocytosis (HLH). Primary HLH is linked to genetic defects in the perforin and granzyme-dependent pathways, affecting the function of natural killer (NK) cells and cytotoxic T lymphocytes (16). One study, for example, discovered that certain individuals with systemic SJIA had perforin gene alterations associated with decreased perforin activity (17). One more research found that perforin manifestation was low in SJIA patients, but it might be restored after clinical enhancement after stem cell relocation (18) (Figure. 1).

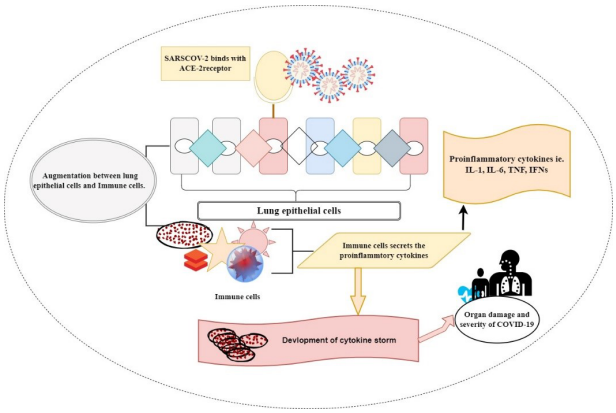


***Fig. 1: Development of Cytokine Storm in SARSCOV-2 Infected Patients.***

## 3. Proinflammatory cytokines and cytokine storm

Cytokines are crucial in regulating the body's response to various stimuli, including infections, immune responses, inflammation, and trauma. Among them, some cytokines are pro-inflammatory, contributing to disease progression, while others are anti-inflammatory, aiding in reducing inflammation and promoting healing. When cytokines i.e. IL-1, TNF are introduced to individuals, they can potentially do inflammation, tissue damage, & in severe cases, shock and death. Several strategies are employed to mitigate the effects of IL-1 and TNF on biological processes, including the use of neutralizing antibodies, soluble receptors, receptor antagonists, and protease inhibitors, which are enzymes that activate inactive precursors. Inhibiting IL-1 or TNF has proven beneficial for individuals with conditions i.e. Inflammatory bowel disease, Rheumatoid arthritis however, this approach has not been as successful for

those with sepsis. Activated macrophages, which are a primary source of pro-inflammatory cytokines, also significantly contribute to amplifying inflammatory responses. Research has demonstrated that certain cytokines are tangled in the development of pathological pain (19) (Table 2).

| Cytokine | Function | Reference(s) |
|---|---|---|
| **TNF-α** | Induces inflammation, apoptosis, and immune cell activation | (68) |
| **IL-1β** | Mediates inflammation, induces fever, and activates immune responses | (69) |
| **IL-6** | Regulates immune response, induces acute-phase protein synthesis | (70) |
| **IL-8** | Attracts neutrophils to sites of inflammation | (71) |
| **IFN-γ** | Activates macrophages and enhances immune responses | (72) |

***Table 2: Proinflammatory Cytokines and their Functions***

### 4.1 Interleukin-6

The IL-6 gene in humans is located on chromosome 7. The initial size of this protein is approximately 20 kDa, but glycosylation can alter its natural size to range between 21 and 26 kDa (25). IL-6 is crucial for the immune system, primarily regulating antiviral immune responses. As a versatile pro-inflammatory cytokine, IL-6 influences inflammation through various mechanisms and is considered pleiotropic because it can modulate the function of multiple cell types. IL-6 displays both anti-inflammatory and pro-inflammatory properties and is among the cytokines released by muscle cells during physical activity. This glycoprotein is present in various cell types, including T and B lymphocytes. The levels of *IL-6* in the bloodstream increase in response to trauma, septic shock, and burns (20).

IL-6 has multiple roles, such as promoting platelet production and in the differentiation of B-lymphocytes. It stimulates hepatocytes to produce inflammatory proteins like fibrinogen and C-reactive protein (CRP) (21). Due to its ability to regulate inflammation, hematopoiesis, and e immune system, it is a critical factor in the development of cytokine release syndrome. In infected patients, plasma levels of IL-6 exceed normal limits, correlating with the severity of the disease, as indicated by oxygen saturation (SpO2) levels (22). Multiple investigations have established a correlation between increased levels of IL-6 and the seriousness of COVID-19 (23-24).

### 4.2 Interleukin-1

IL-1 cytokine gene family, is recognized for its part in inflammation (26). The IL-1α and IL-1β cytokine genes are situated adjacent on chromosome 2 at the q14.1 arm (2q14.1), and they encode the respective proteins (27). In response to inflammatory stimuli, innate immune cells produce pro-IL-1α (271 amino acids) and IL-1β (269 amino acids), which are the precursors of IL-1α and IL-1β, respectively (27,28). Mature forms of pro-IL-1α and pro-IL-1β are produced through processing, resulting in proteins consisting of 158 and 152 amino acids, respectively (27). Unlike pro-IL-1β, both the unprocessed and processed forms of IL-1α, as well as pro-IL-1α, are biologically active. However, the mature form of IL-1α shows significantly enhanced biological activity and binding affinity compared to its precursor, pro-IL-1α. Various proteases facilitate the conversion of these precursor proteins into their mature forms. Pro-IL-1β is primarily processed by caspase-1, with additional support from cathepsin G, chymase, neutrophil elastase, and proteinase-3.

IL-1α is secreted in response to epithelial injury caused by COVID-19, attracting monocytes, neutrophils to the infection place. Additionally, in response to infection, monocytes and macrophages produce IL-1β (29). Studies have shown that peripheral blood and bronchoalveolar lavage fluid (BALF) from peopless with COVID-19 pneumonia contain both IL-1β and IL-1Ra (30,31).

### 4.3 TNF-α

The TNF-α receptors, including TNFR1, TNFR2, had a vital function in facilitating cellular systems affected by this cytokine (32). These receptors may also be relevant to the severity and death rate of COVID-19. Significantly, the levels of soluble TNFR1 (sTNFR1) in the blood are notably higher in patients in the ICU who have COVID-19 associated to individuals who do not need ICU treatment (33). Our research group recently discovered a connection between elevated levels of sTNFR1 and ADAM17 and the seriousness and death rate of COVID-19. In addition, patients exhibited elevated points of both TNFR1 and sTNFR2 compared to healthy controls (34). Extensive research has examined genetic variations in TNF-α and its receptors, uncovering links to autoimmune (34, 35),

chronic (36, 37), and infectious disorders (35, 38), as well as cancer (39). They can influence the transcription of cytokine genes (40). Severe sepsis has been connected to the former (41), whereas vulnerability to influenza A (H1N1) has recently been linked to the latter (42).

## 1. Management of Cytokine Storm

PRRs are vital constituents of the immune system that are responsible for detecting and identifying antigens derived from invading pathogens, including viruses. Damage/death-associated molecular patterns (DAMPs) are chemicals that are secreted by cells of the host organism in reaction to threats or injury. These molecules consist of HMGB1 and heat shock proteins (HSPs). PRRs has the capacity to detect Damage-Associated Molecular Patterns (DAMPs) and response to cellular death. This aids in the prevention of excessive activation following antigenic stimulation. In COVID-CS, insufficient cytolytic activity results in increased inflammation, which can potentially lead to illnesses such as ARDS and failure of organs, and in some cases, death. The management of COVID-19 involves the use of antiviral medications to hinder the replication of SARS-CoV-2 and the use of immunosuppressive drugs to manage widespread inflammation, thereby preventing consequences such as cytokine storms. COVID-CS exhibits resemblances to hyperinflammatory disorders as cytokine storms in hemophagocytic lymphohistiocytosis (HLH) or CRS after CAR-T. However, available treatment choices may differ (43-49).

### 5.1 Corticosteroid therapies

Anti-inflammatory properties are attributed to the class of steroid hormones known as corticosteroids, which are frequently employed to decrease inflammation. The primary strategy employed to regulate the immune system throughout the 2003 SARS pandemic was corticosteroids. The prompt and effective administration of corticosteroids often results in immediate benefits, including reductions in fever, alleviation of lung radiation infiltration, and enhancements in oxygenation (50-52). A retrospective study was undertaken to examine 401 individuals who had been diagnosed with severe SARS. The findings indicated that the prudent use of glucocorticoids substantially decreased mortality rates and shortened hospital stays among patients with severe SARS (53). Glucocorticoid-treated patients also experienced a decreased incidence of complications, including secondary infections. However, some studies indicate that using corticosteroid medication for treating human SARS-CoV infection can lead to negative outcomes. In non-intensive care unit (ICU) patients with SARS, early initiation of corticosteroid therapy was associated with an increase in viral load in the bloodstream, worsening the condition (50).

### 5.2 Inhibition of IL-6/IL-6R

Tocilizumab, initially prescribed for treating rheumatic disorders, has demonstrated efficacy in mitigating cytokine storms triggered by CAR-T treatment in individuals with haematological malignancies (54,55). A meta-analysis revealed that the levels of IL-6 in individuals with severe instances of COVID-19 were 2.9 times greater compared to those with less severe cases (56). A further meta-analysis has reaffirmed the association between increased levels of IL-6 and the severity of the disease, underscoring IL-6 as a dependable marker for predicting a negative outcome in COVID-19. At present, IL-6/IL-6R blockers are undergoing first clinical trials for COVID-19, and there are ongoing multi-center trials as well. According to reports, giving siltuximab, a monoclonal antibody that targets IL-6, to COVID-19 patients who have severe respiratory failure and need ventilatory support can lower the risk of death and minimise excessive inflammation caused by cytokines (56,57).

### 5.3 Utilization of stem cells for medical treatment

Mesenchymal stem cells (MSCs) are crucial stem cells recognized for their capacity to regenerate themselves and transform into different types of cells. They have notable anti-inflammatory and immunoregulatory characteristics. In addition, they can suppress the release of pro-inflammatory cytokines, thus decreasing the likelihood of cytokine storms (58,59). In their first investigation, Leng et al. examined the application of stem cell treatment in the context of COVID-19. The researchers noted that the intravenous administration of clinical-grade MSCs led to improved functional outcomes and accelerated recovery in a group of seven patients (60). This study carried out at Beijing YouAn Hospital in China, had a total of seven COVID-19 patients, consisting of one patient in critical condition, four patients in severe condition, and two patients with intermediate sickness.

## DISCUSSION

Severe symptoms of SARS-CoV-2 infection might result in impaired function in various organs. Currently, vaccines play a central and powerful role in combating the infection. Nevertheless, the appearance of the novel omicron variant (B.1.1.529) elicits apprehension regarding possible diminutions in the effectiveness of current vaccinations and specific monoclonal antibody therapies. Corticosteroids and

tocilizumab, both immunomodulators, have been thoroughly investigated for their efficacy in treating severe forms of the condition. However, the utilization of these medications in outpatient environments may be restricted due to the occurrence of unfavorable consequences such as secondary severe infections and hyperglycemia, which raises worries about safety. No significant safety concerns were identified in clinical trials evaluating the use of anakinra for the therapy of sepsis. Secondary infections were reported in cases when anakinra was used for an extended period of time along with tumor necrosis factor-alpha blockers, as opposed to cases where it was administered for a short duration. The concurrent administration of corticosteroids and anakinra appears to augment clinical results in comparison to the exclusive utilization of anakinra. For COVID-19 patients who are experiencing hemodynamic instability, intravenous (IV) injection of anakinra may be more favorable in terms of the mode of delivery. Moreover, anakinra is typically reserved for COVID-19 individuals who specifically suffer from pericarditis and MIS-C, since it has shown enhanced efficacy in these cases (61,62). While medications may eliminate and deter the virus, they could potentially harm the lungs, leading to long-term consequences. Stem cell therapy, in contrast, cannot only efficiently repair injured lungs but also enable the transplanting of new lungs, thus completely restoring respiratory function.

## CONCLUSION

This review emphasizes differentiating between beneficial inflammatory responses and harmful cytokine storms to assist researchers in formulating appropriate treatment approaches. While both inflammation and cytokine storms encompass host responses, regardless of the presence of infectious stimuli, our focus is specifically on cytokine storms triggered by infectious diseases. At this time, numerous infectious diseases present substantial risks to worldwide health, such as bacterial peritonitis, influenza, and others that frequently result in severe illness and death. Cytokine storms are a common occurrence during the course of numerous infectious diseases and are typically managed by directing attacks at both the host and the pathogen. Nonetheless, continuous investigation is critical to enhance the efficacy of treatments. Effective treatment strategies must be taken into consideration not only for chemokine cyclones but also for cytokine storms. Moreover, to effectively combat pathogen infection while avoiding the induction of severe cytokine storms, novel therapies should target and mitigate inflammatory cascade reactions, alleviate pathological damage caused by cytokine storms, and restore immune system equilibrium. Furthermore, it is crucial to identify discrepancies in immune function and immune system attributes among populations that are prone to or resistant to cytokine release syndrome (CRS) in order to develop treatment strategies that are suitable for a wide range of individuals. Although the main focus of this paper is CRS in relation to infectious microorganisms, it is crucial to not rule out the possibility of individual susceptibility to CRS, which is frequently associated with particular haplotypes or other conditions.

## ABBREVIATIONS

| | |
|---|---|
| SARS-CoV-2: | Severe acute respiratory syndrome coronavirus 2 |
| COVID-19: | Coronavirus disease 2019 |
| ARDS: | Acute respiratory distress syndrome |
| TNF-α: | Tumor Necrosis Factor-α |
| SJIA: | Systemic juvenile idiopathic arthritis |
| TNFR: | 1 Tissue Necrosis Factor receptor-1 |
| PRRs: | Pattern recognition receptors |
| PAMPs: | Pathogen-associated molecular patterns |
| MAPK: | Mitogen-activated protein kinase |
| CAR-T: | Chimeric antigen receptor T-cell treatment |
| HMGB1: | High mobility group box 1 |
| MIS-C: | Multisystem inflammatory syndrome in children |

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