

## Cytokine Storm Syndrome in Covid-19 Patients: Characteristics and Diagnosis

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### ABSTRACT

Cytokine storm syndrome (CSS) is a critical condition induced by a cascade of cytokine activation, characterized by overwhelming systemic inflammation, hyperferritinaemia, haemodynamic instability and multiple organ failure. At the end of 2019, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and rapidly developed into a global pandemic. There is a dramatic increase of inflammatory cytokines in patients with COVID-19, suggesting the existence of cytokine storm in some critical illness patients. Here, we summarize the pathogenesis, clinical manifestation of CSS, and highlight the current understanding about the recognition and diagnosis of CSS in COVID-19.

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### Introduction

The coronavirus SARS-CoV-2 has infected more than 200 million people and killed over 4 million, with a mortality rate of approximately 2% worldwide. Many who die from COVID-19 suffer hyper-inflammation with features of cytokine storm syndrome (CSS) and associated acute respiratory distress syndrome [1]. Although the antiviral Remdesivir was shown to reduce the length of hospital stay for those with COVID-19, only anti-inflammatory approaches have improved survival in these patients [2]. The greatest survival benefit has been demonstrated with broadly immunosuppressive glucocorticoids when given to those with an oxygen requirement. However, in the absence of an oxygen requirement or substantial systemic inflammation (as measured by C-reactive protein (CRP)), patients treated with glucocorticoids may fare worse than those who receive standard care. Thus, the selection of patients and timing of the administration of glucocorticoids is critical for survival benefit. Ideally, earlier use of more-targeted anti-cytokine therapy to prevent CSS, without increasing viral replication, is needed [3].

### Definition of Cytokine storm syndrome (CSS)

Cytokine storm syndrome (CSS) is characterized by the following clinical features: Immune dysregulation due to perpetuated activation of lymphocytes and macrophages, secretion of large quantities of cytokines including including IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-18 and TNF- $\alpha$  and overwhelming systemic inflammation and multi-organ failure with high mortality[4].

The term CSS was first coined to describe the hypercytokinemia

in graft versus host disease after allogeneic stem cell transplant. Many viral, bacterial and parasitic infections can cause CSS. Infectious pathogens such as Epstein-Barr virus (EBV) and Mycobacterium tuberculosis cause pathological immune activation characterized by markedly elevated cytokines such as interferon- $\gamma$  (IFN- $\gamma$ ) and soluble interleukin-2 receptor (sIL-2r) in patients with immune defects, leading to the clinical syndrome of hemophagocytic lymphohistiocytosis (HLH) [5].

Levels of inflammatory cytokines IL-6, IL-8, MCP-1 and TNF $\alpha$  are significantly increased in COVID-19 plasma. Detailed correlation analysis revealed strong associations between some of the endothelial derived markers but only weak associations with age or general inflammatory parameters such as CRP. Fibrinogen levels correlate with increased P-selectin. In addition, plasma levels of IL-8 were strongly associated with circulating vWF levels. Local as well as systemic, circulating inflammatory markers coincide with various markers revealing endothelial activation and damage in COVID-19 patients.

### Pathogenesis of CSS

To date, the pathogenesis of CSS has not been fully elucidated. Previous studies have shown that the development of CSS involves the imbalance of pro-inflammatory and anti-inflammatory mechanisms and the interaction of a variety of cells and cytokines, resulting in immune regulation disorder, causing a series of clinical manifestations. Previous studies have shown that a variety of cytokines can be markedly increased in patients with CSS, which may vary according to the heterogeneity of the disease background. In the setting of influenza virus-related CSS, a previous study found that patients infected with H5N1 had higher levels of monocyte

chemoattractant protein 1 (MCP-1), monokine induced by IFN-gamma (MIG), interferon-gamma-induced protein-10 (IP-10) and IL-8 than patients infected with seasonal H1N1 common influenza [6]. Moreover, previous studies also confirmed that cytokines played an important role in the pathogenesis of severe CoV infection. The serum proinflammatory cytokines (IFN- $\gamma$ , transforming growth factor- $\beta$  (TGF- $\beta$ ), IL-1, IL-6, IL-12) in severe SARS patients were significantly higher than those with mild to moderate symptoms, and serum proinflammatory cytokines (IFN- $\alpha$ , IL-6, IL-8) in severe MERS patients were significantly increased as well [7].

### Mechanisms of CSS in COVID-19

The cytokine storm in COVID-19 may have some differences from the cytokine storms in other clinical settings. Remarkably, the autopsy findings revealed that the lymphoid tissues and organs had been destroyed in COVID-19 patients, which is very unusual from CSS in sepsis and CAR T-cell therapy. Spleen atrophy and lymph node atrophy are observed in patients with COVID-19, whilst in other CSS-related diseases, lymphadenopathy and splenomegaly are more common. However, the specific mechanisms for these differences remain unclear and need to be further clarified [8].

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses, which have caused two large-scale pandemics in the last two decades, SARS and MERS [9]. Spike (S) proteins of coronaviruses, including the SARS-CoV, facilitate viral entry into their target cells via the interaction with functional cellular receptor identified as angiotensin-converting enzyme 2 (ACE2), which is highly expressed in alveolar epithelial cells, vascular endothelial cells, intestinal epithelial cells and renal proximal tubular cells. Functionally, ACE2, belonging to the ACE family, inactivates angiotensin II (AngII) and generates angiotensin 1-7, a biologically active heptapeptide characterized by a potent vasodilator function. It has been demonstrated that the binding of the coronavirus spike protein to ACE2 leads to the down-regulation of ACE2, which in turn results in excessive production of vasoconstrictor AngII and reduced production of vasodilator angiotensin [1-7].

AngII also plays the role as a proinflammatory cytokine via angiotensin receptor 1 (AT1R). The AngII-AT1R axis further activates NF- $\kappa$ B and metalloprotease 17 (ADAM17), which stimulates the production of the mature form of epidermal growth factor receptor (EGFR) ligands and TNF- $\alpha$ . The activation of both NF- $\kappa$ B and STAT3, which in turn activate the IL-6 amplifier (IL-6 Amp), a mechanism for the hyperactivation of NF- $\kappa$ B by STAT3, will lead to a hyperinflammatory state, resulting in increased pulmonary vascular permeability [10].

A retrospective study also found higher plasma concentrations of IL-2, IL-7, IL-10, IP-10, MCP-1, MIP-1a and TNF- $\alpha$  in intensive care unit (ICU) patients compared with nonsevere patients, suggesting there might be a cytokine storm in the body of severe patients [11].

### Diagnosis of CSS in COVID-19

There is no standard for the diagnosis of COVID-19 associated with CSS, and further clinical and laboratory investigations are needed. Here is a basic principle for consideration of CSS in COVID-19:

- A sudden or rapid progression with multiple organ involvement (such as liver, cardiac or renal injury)
- A significant decline of peripheral blood lymphocyte counts

- The significant elevation of systematic inflammatory indicators (such as CRP, serum ferritin, erythrocyte sedimentation rate)
- The elevation of multiple cytokines, such as IL-1 $\beta$ , IL-2R, IL-6, IFN- $\gamma$ , IP-10, MCP-1 and TNF- $\alpha$ .

Clinicians should keep highly alert on the possibility of CSS under these circumstances. However, given that CSS is a highly heterogeneous disease and may present with unspecific syndromes, the diagnosis of CSS in COVID-19 is very challenging and the development of a specific diagnostic test that helps to make the diagnosis of CSS earlier is a high priority for future research [12].

The inflammatory disorders in COVID-19 have been reported in many clinical studies. The COVID-19 is inclined to cause a decrease of lymphocyte count and an increase of C reactive protein (CRP), especially in severely ill patients. The major subsets of the T lymphocytes (T cell) (CD3+ CD4+ T cell and CD3+ CD8+ T cells) are reduced in the COVID-19 and are significantly lower in the severe cases. The results of the other immune cells, the B cell and natural killer (NK) cell, have more inconsistency in recent researches. IL-6 was observed increased [13].

### Conclusion

The clinical, immunological, and pathologic features of COVID-19 have something in common with SARS and MERS. For example, all the viruses can cause lymphopenia and influenza-like symptoms in the early stage. SARS and COVID-19 do not lead to the upgrade of TNF- $\alpha$ , but the increase of IL-6 and IL-10 is more prevalent in COVID-19. The IL-6 plays a crucial role in the pathologic of COVID-19, including the chemotaxis of neutrophils and lymphocyte necrosis. Importantly, COVID-19 is more able to cause cytotoxic lymphocytes exhaustion.

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