

Mechanism of cytokine storm syndrome in COVID-19

Rim Harfouch¹

¹Affiliation not available

February 23, 2022

Rim M. Harfouch

Department of microbiology and biochemistry, Faculty of pharmacy, Al Sham private university, Latakia, Syria.

Correspondence Autho's E-mail: r.h.foph.lat@aspu.edu.sy

Abstract:

Cytokine storm syndrome (CSS) is a serious condition induced by the activation of cytokine cascade, characterized by systemic inflammation, haemodynamic instability, hyperferritinaemia and multiple organ failure (MOF). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan China and rapidly developed into a global pandemic at the end of 2019. This infection causes a dramatic increase of inflammatory cytokines, suggesting the development of cytokine storm in some critical COVID-19 patients. In our review, we summarize the pathogenesis, clinical manifestation of CSS, and highlight the current aspects about the recognition and diagnosis of CSS in COVID-19.

Keywords:

Cytokine storm syndrome (CSS), coronavirus SARS-CoV-2, Characteristics.

Introduction:

The coronavirus SARS-CoV-2 has infected more than 250 million people and caused death to over than 5 million, with a worldwide mortality rate of 2%. Many patients who die from COVID-19 suffer from hyperinflammation caused by cytokine storm syndrome (CSS) and associated acute respiratory distress syndrome [1]. The antiviral Remdesivir was shown to reduce the length of hospital stay for COVID-19 patients, but anti-inflammatory agents have improved survival in these patients [2]. The greatest survival rate has been found with glucocorticoids, which play as immunosuppressive agents, when given to patients with an oxygen requirement. However, patients treated with glucocorticoids may fare worse than those who receive standard care in the absence of an oxygen requirement or systemic inflammation. The selection of patients and timing of glucocorticoids administration is critical for survival benefit. Optimal treatment of targeted anti-cytokine therapy to prevent CSS is suggested earlier without increasing viral replication [3].

Cytokine storm syndrome (CSS) is characterized by secretion of large amounts of cytokines including IL-1 α , IL-1 β , IL-6, IL-18 and TNF- α , continuous activation of lymphocytes and macrophages causing immune dysregulation, and finally, overwhelming systemic inflammation and multi-organ failure (MOF) with high mortality [4].

The term CSS was first used after allogeneic stem cell transplant to describe the hypercytokinemia (increased blood cytokines) in graft. Many viral, bacterial and parasitic infections can cause CSS such as Mycobacterium tuberculosis and Epstein-Barr virus (EBV), which cause pathological immune activation characterized by elevated cytokines such as interferon- γ (IFN- γ) in patients with immune defects [5].

Levels of inflammatory cytokines especially IL-6, IL-8, MCP-1 and $\text{TNF}\alpha$ are significantly increased in COVID-19 plasma. Plasma levels of IL-8 are strongly associated with circulating vWF levels. Local and systemic circulating inflammatory markers concur with several markers revealing endothelial activation and damage in COVID-19 patients.

Pathogenesis of CSS

The pathogenesis of CSS has not been fully known. Several studies have shown that the mechanism of CSS depends on the imbalance of pro-inflammatory and anti-inflammatory process and the interaction of specific cells and cytokines, resulting in immune regulation disorder. Cytokines can be markedly increased in patients with CSS, which differ according to the heterogeneity of the disease. A previous study found that H5N1 infected patients had higher levels of interferon-gamma-induced protein-10 (IP-10), monocyte chemoattractant protein 1 (MCP-1) and IL-8 than patients with seasonal H1N1 influenza [6]. Moreover, it was confirmed that cytokines play an important role in the pathogenesis of severe CoV infection. The proinflammatory cytokines (IFN- γ , IL-1, IL-6, IL-12, transforming growth factor- β (TGF- β)) in severe SARS patients' sera were significantly higher than those with mild to moderate symptoms. Also, in severe MERS patients, serum inflammatory cytokines (IFN- α , IL-6, IL-8) were significantly increased [7].

Mechanisms of CSS in COVID-19

The cytokine storm in COVID-19 may vary from the cytokine storms in other clinical settings. It was revealed by autopsy findings, that the lymphoid tissues were destroyed in COVID-19 patients, which is rare from CSS in sepsis and CAR T-cell therapy. Spleen and lymph node atrophy are observed in patients with COVID-19, while lymphadenopathy and splenomegaly are more common in other CSS-related diseases. However, the specific mechanisms for these differences remain unclear and need to be further studied [8].

Coronaviruses (CoVs) are enveloped single-stranded RNA viruses, which have caused two marked pandemics SARS and MERS [9]. Spike (S) proteins of coronaviruses, including the SARS-CoV, facilitate entry into their target cells via the interaction with angiotensin-converting enzyme 2 (ACE2), a functional cellular receptor, which is highly expressed in vascular endothelial cells, alveolar epithelial cells, intestinal epithelial cells and renal proximal tubular cells. ACE2 suppresses angiotensin II(AngII) and activates the formation of angiotensin 1-7, a which is a vasodilator heptapeptide. 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.

Furthermore, AngII binds to the angiotensin receptor 1 (AT1R) and plays a role of proinflammatory cytokine. The AngII-AT1R axis activates NF- κ B and metalloprotease 17 (ADAM17), which stimulates the production of the epidermal growth factor receptor (EGFR) ligands and TNF- α , which activate the IL-6 amplifier (IL-6 Amp), and lead to a hyperinflammatory status, resulting in increased vascular permeability of the lungs [10].

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

Diagnosis of CSS in COVID-19

There is no standard for the diagnosis of CSS related to COVID-19, so further clinical and laboratory investigations are needed. The basic principles for consideration of CSS in COVID-19 are the following presentations:

1. A rapid or sudden regression of multiple organ functions (cardiac, liver or renal injury).
2. The elevation of systematic inflammatory biomarkers (such as CRP, erythrocyte sedimentation rate and serum ferritin).
3. A significant decrease of lymphocyte counts.
4. The elevation of cytokines, such as IL-1 β , IL-2R, IL-6, IP-10, MCP-1, TNF- α and IFN- γ .

Clinicians should keep highly alert on the possibility of CSS under these circumstances. However, that CSS is highly heterogeneous 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 studies. COVID-19 causes a decrease of lymphocyte count and an increase of C reactive protein (CRP), especially in severely ill patients. The major subtypes of 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. Other immune cells, B cell and natural killer (NK) cell, have more inconsistency in recent studies[13].

Conclusion:

The clinical, immunological, and pathologic features of COVID-19 have something in common with SARS and MERS. All the viruses can cause lymphopenia and influenza-like symptoms in the early stage. SARS and COVID-19 do not lead to the elevation of TNF- α , but the increase of IL-6 and IL-10 is more common 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.

References:

1. Harfouch RM, Moualla YM, Shahoud SM, Belal LA, Mohammad BS, Mustafa NM, Souliman OA, Elshemali YI (2021). Epidemiology of COVID-19 in the most pandemic Countries: A review article. *Acad . J. Biotechnol.* 9(1): 021-027.
2. Rim M. Harfouch, Samer Alshaikh, Mohammad Alshimaly, Amany Assaad, Jehan Ahmad, Haya Zoughaibi, Maher Hammadi, Yahya Elshimali. Therapeutic approaches for COVID 19: Challenges and successes. *Ann Clin Anal Med* 2020; DOI: 10.4328/ACAM.202
3. Cron, R.Q., Caricchio, R. & Chatham, W.W. Calming the cytokine storm in COVID-19. *Nat Med* 27, 1674–1675 (2021). <https://doi.org/10.1038/s41591-021-01500-9>.
4. Harfouch RM, Cytokine Storm Syndrome in COVID-19 Patients: Characteristics and Diagnosis. *Ann Clin Med Case Rep.* 2021; V7(18): 1-3
5. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. *Eur Respir J.* 2020;56(4):2003006. Published 2020 Oct 1. doi:10.1183/13993003.03006-2020
6. De Jong MD, Simmons CP, Thanh TT et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* 2006; 12: 1203–7.
7. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol* 2017; 39: 529– 39.
8. Yao XH, Li TY et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Chin. J. Pathol* 2020; 49: E009.
9. Alhourri A, Salloum A, Harfouch RM, Soumya G. Possible Side Effects of using Detergents during the Covid19 Pandemic in Syria. *Ann Clin Cases.* 2020;1(4):1023.
10. Murakami M, Kamimura D, Hirano T. Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. *Immunity* 2019; 50: 812–31.
11. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
12. Gao YM, Xu G, Wang B, Liu BC. 2020. Cytokine storm syndrome in coronavirus disease 2019: a narrative review. *J Intern Med* 289:147–161.
13. Tang Y, Liu J, Zhang D, Xu Z, Ji J and Wen C (2020) Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front. Immunol.* 11:1708. doi: 10.3389/fimmu.2020.01708