Healthcare Research and Public Safety Journal

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Mini Review *Volume 4 Issue 1*

Multiple Organs Failure in COVID-19 Patients

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Received Date: August 17, 2022; **Published Date:** September 20, 2022

Abstract

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in December 2019 form Wuhan, China leads to coronavirus disease 2019 (COVID-19) pandemic. COVID-19 is accompanied by multi-organ failure in severe patients. The involvement of different organs in severe patients results in lengthening the hospitalization duration and increasing the mortality rate. The multi-organ dysfunction is characterized by acute lung failure, acute liver failure, acute kidney injury, cardiovascular disease, and as well as a wide spectrum of hematological abnormalities and neurological disorders. The most important mechanisms are related to the direct and indirect pathogenic features of SARS-CoV2. Although the presence of angiotensin-converting enzyme 2, a receptor of SARS-CoV2 in the lung, heart, kidney, testis, liver, lymphocytes, and nervous system was confirmed, there are controversial findings to about the observation of SARS-CoV2 RNA in these organs. Moreover, the organ failure may be induced by the cytokine storm, a result of increased levels of inflammatory mediators, endothelial dysfunction, coagulation abnormalities, and infiltration of inflammatory cells into the organs. Therefore, further investigations are needed to detect the exact mechanisms of pathogenesis. Since the involvement of several organs in COVID-19 patients is important for clinicians, increasing their knowledge may help to improve the outcomes and decrease the rate of mortality and morbidity.

Keywords: Multi-Organ Failure; Coronavirus SARS-CoV-2; Characteristics

Abbreviations: SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; CSS: Cytokine Storm Syndrome; EBV: Epstein-Barr virus; ALF: Acute Liver Failure; AST: Aspartate Aminotransferase; TB: Total Bilirubin; ACE2: Angiotensin-Converting Enzyme 2.

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 hyper-inflammation caused by cytokine storm syndrome (CSS) and associated acute respiratory distress syndrome [1,2]. 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 [3]. 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 [4].

Definition of Cytokine Storm Syndrome (CSS)

Cytokine storm syndrome (CSS) is characterized by secretion of large amounts of cytokines including IL-1α, IL-1β, 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 [5]. 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 [6].

It has been found that SARS-CoV2 is related to the dysfunction or damage of liver tissue, and after the lung, it seems to be the second organ. Acute liver failure (ALF) in COVID-19 patients may result from the virus invasion, which directly infects liver cells. Some infections of the upper respiratory tract can influence the liver. The function of the liver can be considered as a marker of disease progression, as the high frequency of serious COVID-19 cases showed of liver injury than mild cases. Several studies on COVID-19 patients primarily have demonstrated various degrees of raised serum biochemistries of the liver, such as irregular aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TB) levels. In another study, the elevated level of AST was identified in ICU admitted patients (62%) more frequently than other hospitalized patients (25%). Therefore, the ALF was predominant in critically ill cases than mild cases. Elevated GGT, a diagnostic factor of cholangiocyte injury, and ALP levels were reported in 30/56 (54%) and 1/56 (1.8%), respectively among COVID-19 patients during hospitalization. The higher levels of ALF indicators, especially AST, are strongly attributed to the higher mortality risk [7,8].

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 [9].

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-κB 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:

- A rapid or sudden regression of multiple organ functions (cardiac, liver or renal injury).
- The elevation of systematic inflammatory biomarkers (such as CRP, erythrocyte sedimentation rate and serum ferritin).
- A significant decrease of lymphocyte counts.
- The elevation of cytokines, such as IL-1β, 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 [13,14].

Conclusion

COVID-19 mainly in severe cases in addition to lung involves different organs such as heart, liver, and kidney, as well as hematological and nervous system, and induces multi-organ failure. SARS-COV2 may directly invade the host cells of different organs through the ACE2 receptor due to the presence of this receptor in these organs. On the other hand, activation of the complement system, cytokine storm, dysregulated immune responses, coagulation dysfunction, and infiltration of inflammatory cells in SARS-CoV2 infection can induce the multi-organ failure in these patients. Consequently, increasing the knowledge on the pathophysiology of SARS-COV2-induced multi-organ failure may ultimately result in better ways to treat COVID-19 patients and decrease the associated morbidity and mortality.

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