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# INNATE IMMUNE RESPONSE: A CAUSE OF DEATH IN COVID-19 !!

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## ABSTRACT

**The main function of the immune system is to provide defence against different types of pathogens and protect the body. Out of the two arms of the immune system (innate and adaptive immunity), innate immunity provides the first line of defence. But several research studies have shown that body's innate immune response can be fatal for someone infected with Covid-19. An elevated levels of cytokines (chemicals secreted by a group of immune cells), called 'cytokine storm' has been observed in a number of patients of Covid-19. Cytokine storm may be one of the major causes of ARDS and multiple organ failure in critical patients, with COVID-19 and may lead to death. Timely control and management of the cytokine storm, in its early stage, may be helpful in prevention of many deaths in Covid-19.**

**KEYWORDS:** Covid-19, Cytokine Storm, SARS-CoV-2, ARDS, Innate Immune Response

Covid-19 has developed into an unprecedented global pandemic, affecting many countries globally. Covid-19 has become greatest threat to the survival of mankind. Covid-19, caused by a noval virus SARS-CoV-2, has caused several lacs of deaths all over the world within a few months. On March 11, 2020, WHO declared Covid-19 as a pandemic. Coronavirus are a group of related RNA viruses that have long been recognized as important pathogens to cause respiratory infections, ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). So far, seven human corona viruses (HCoVs) that can invade humans have been identified. Different types of coronoviruses differ in their pathogenicity. According to their pathogenicity, HCoVs are divided into *mildly pathogenic* HCoVs (including HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU) and *highly pathogenic* coronoviruses (including SARS-CoV, MERS-CoV and SARS-CoV-2) (Qing *et al.*, 2020). Covid-19 virus, a new member of the betacoronavirus genus, is closely related to severe acute respiratory syndrome–coronavirus (SARS-CoV) and several bat coronaviruses (Zhou *et al.*, 2020). Compared with SARS-CoV and MERS-CoV, Covid-19 virus (SARS-CoV-2) exhibits faster human-to-human transmission (Chan *et al.*, 2020)

## STRUCTURE OF SARS-CoV-2

Coronaviruses (CoVs) are enveloped positive sense, single-stranded RNA viruses that belong to the subfamily Coronavirinae, family Coronavirdiae, order Nidovirales. There are four genera of Coronaviruses i.e. alpha coronaviruses (αCoV), beta coronaviruses (βCoV), delta coronaviruses (δCoV), and gama coronaviruses (γCoV). SARS-CoV-2, most recently discovered member of corona family is a betacoronavirus. SARS-CoV-2 has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm (Cascella *et al.*, 2020). Like other members of its family, SARS-CoV-2 is a positive-stranded RNA virus with a crown-like appearance under an electron microscope. It is due to the crown-like appearance, that the virus is called Corona virus. The crown like appearance is because of the presence of spike glycoproteins on the envelope. There are four structural proteins, namely envelope (E), spike (S), membrane (M), and nucleocapsid (N), present on SARS-CoV-2. (Mousavizadeh and Ghasemi, 2020) (Figure 1).

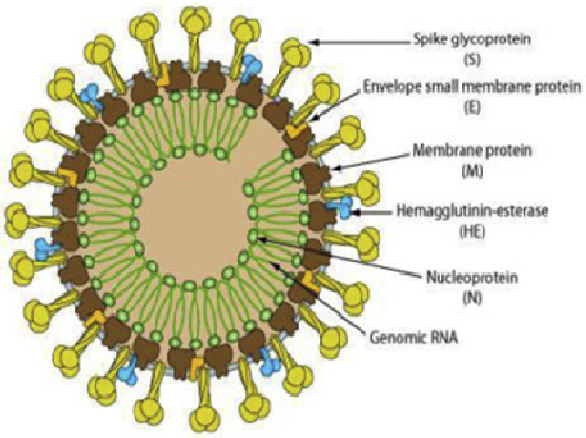


**Figure 1: Structure of SARS-CoV-2**

## TRANSMISSION OF THE COVID-19

Covid-19 spreads through small droplets, expelled by a person with Covid-19 during coughing, sneezing, or speaking. People of any age group may be infected by the disease, though elderly people and people with pre-existing medical conditions such as cardiovascular disease, diabetes, chronic respiratory illness, high blood pressure and cancer appear to be more susceptible to Covid-19 (Zimmer, 2020).

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## PROGRESSION OF THE DISEASE

SARS-CoV2 virus infects the lower respiratory tract and causes pneumonia in humans but ultimately becomes a lethal disease of hyperinflammation and respiratory dysfunction (Chen *et al.*, 2020). There are three phases of the disease. First is an asymptomatic phase with or without detectable virus. The second is again a non-severe but symptomatic phase with upper airway involvement. Third is the severe stage leading to acute respiratory distress syndrome (ARDS) and multi organ failures. ARDS and multi organ dysfunction are among the leading causes of death in critically ill patients with COVID-19 (Lewis *et al.*, 2020) (Ruan, 2020) (Huang *et al.*, 2020).

In most of the patients of Covid-19, severe clinical manifestations do not develop in the early stages of the disease and the patients show just mild symptoms like mild fever, cough, or muscle soreness. But in some patients the conditions deteriorate suddenly in the later stages of the disease or in the process of recovery. Acute respiratory distress syndrome (ARDS) and multiple organ failure occurs rapidly, resulting in death within a short time. A virus-induced hyperinflammatory response or "cytokine storm" has been hypothesized to be a major pathogenic mechanism of ARDS in these patients through modulation of pulmonary macrophages, dendritic cells and/or neutrophils (Wong *et al.*, 2004) (Channappanavar *et al.*, 2016). ARDS leads to inflammatory injury to the alveolo–capillary membrane, which results in increased lung permeability and the exudation of protein-rich pulmonary edema fluid into the airspaces, leading in the end to respiratory insufficiency (Bhatia *et al.*, 2012)

## IMMUNE RESPONSE IN THE BODY

The main function of the immune system is to protect the body from any type of infection. There are two types of immune responses: a nonspecific defence response, known as *innate immune response* and a highly specific second line of defence response, called *adaptive immune response*. There are several components of innate immunity, through which it provides the first line of defence. One of those components is a group of low molecular weight proteins or glycoprotein molecules, called cytokines. Cytokines are the chemical molecules, released by a group of immune cells, which can modulate the functions of the same cell (by which they are produced) or other cells. They are secreted by leukocytes, activated endothelial cells, activated epithelial cells, some connective tissue cells and some other cells during pathological conditions in the body. Different types of cytokines include: Interferons (IF), Interleukins (IL), Colony stimulating factors (CSF), Chemokines, Tumor Necrosis Factor (TNFα) and Transforming growth factors (TGF-β).

Cytokines have important role in immune and inflammatory responses. A cytokine may act on different cell types and can have different biological roles on different cells. Cytokines exert their effects in tissues locally or circulate in the blood and lymph. But in many bacterial infections and in many cardiovascular diseases, elevated levels of cytokines have been observed. This excessive secretion of cytokines is called cytokine storm or cytokine storm syndrome. Several evidences suggest that a subset of patients with Covid-19 develops a cytokine storm syndrome (CSS) that is associated with elevation of proinflammatory cytokines, including IL-6, IL-2R, IL-8, TNF-α, and G-CSF (Ruan *et al.*, 2020) (Mehta *et al.*, 2020) (McGonagle *et al.*,2020). Elevated levels of cytokines were earlier observed in patients of SARS-CoV and MERS-CoV (Wong *et al.*, 2004) (Zhang *et al.*, 2004) (Chien *et al.*, 2006) (Kim *et al.*, 2016). Wong *et al.*, 2004 investigated changes in plasma T helper (Th) cell cytokines, inflammatory cytokines and chemokines in SARS patients and demonstrated marked elevation of Th1 cytokine IFN γ, inflammatory cytokines IL-1, IL-6 and IL-12 for at least 2 weeks after disease onset. Significantly elevated concentration of IL-6 was measured in severe SARS patients by Zhang *et al.*, 2004. Kim *et al.*, 2016 observed significantly elevated levels of IL-6 and CXCL-10 in MERS-CoV patients who developed severe diseases.

Proinflammatory cytokines (IL-6, IL-8, IL-1 β, granulocyte macrophage colony-stimulating factor, and reactive oxygen species) and chemokines (such as CCL2, CCL-5, IFN γ -induced protein 10 (IP-10), and CCL3) are known to enhance the occurrence of ARDS (Jiang *et al.*, 2005) (Cameron *et al.*, 2008). The serum levels of cytokines are significantly increased in patients with ARDS, and the degree of increase is positively correlated with mortality rate. The serum levels of IL-2R and IL-6 in patients with Covid-19 are positively correlated with the severity of the disease (Chen *et al.*, 2020). Cardinal features of Cytokine storm includes include unremitting fever, cytopenia, massive increases in ferritin, high erythrocyte sedimentation rate (ESR) and ARDS (Shakir, 2020).

In case of SARS-CoV-2 infection, cytokine storm appears to be one of the most dangerous and life threatening event (Coperchini *et al.*, 2020). Cytokine storms can be severe in young patients who have more efficient immune systems and responses than older patients.

Wang and Ma, 2008 reviewed the role of cytokine storm in severity of organ dysfunction in Multiple Organ Dysfunction Syndrome and concluded that cytokine storm is a key factor in determining the clinical course of extrapulmonary multiple-organ failure. In case of Covid-19 also, cytokine storm is an important cause of damage to extrapulmonary tissues and organs (Qing *et al.*, 2020).

## MANAGING CYTOKINE STORM

Since cytokine storm is considered as one of the major causes of ARDS and multiple organ failure in critical patients, with covid-19, leading to death, preventing the cytokine storm can be an approach in the treatment of Covid-19. There can be several strategies to prevent cytokine storm. Anticytokine therapies or immunomodulators are being investigated for preventing cytokine storm.

One of the ways is by using *antibodies* to block the primary mediators of the storm, like IL-6, or its receptor, which is present on all cells of the body. This can be done by drug Tocilizumab, an IL-6 antagonist that suppresses the function of the immune system (Qing *et al.*, 2020). In addition to IL-6 antagonist, Qing *et al.*, (2020) have mentioned several other drugs that could be a hopeful candidate in the treatment Covid -19.

TNFs are key inflammatory factors that trigger a cytokine storm. Studies have shown that in mice, neutralization of TNF activity or loss of TNF receptor provides protection against SARS-CoV-induced morbidity and mortality (Channappanavar *et al.*, 2016) (McDermott *et al.*, 2016). Though there is no report of any study with TNF blockers in case of Covid-19 but there may be some chances with TNF blockers.

Ulinastatin, known to reduce the levels of proinflammatory factors such as TNF-α, IL-6, and IFN-γ, and to increase the level of anti-inflammatory factor IL-10, has great application prospects in the treatment of Covid-19 (Qing *et al.*, 2020). Chloroquine ,an old drug for treatment of malaria, is shown to have apparent efficacy and acceptable safety against Covid-19. It inhibits the production and release of TNF and IL-6, which indicates that chloroquine may suppress the cytokine storm in patients infected with Covid-19 (Gao *et al.*, 2020).

Mesenchymal stem cells (MSC) can also inhibit the secretion of pro-inflammatory cytokines, such as, IL-1, TNF-α, IL-6, IL-12, and IFN-γ, thereby reducing the occurrence of cytokine storms (Uccelli *et al.*, 2020). It can also be expected to make it an effective method for the treatment of Covid-19.

A team of Howard Hughes Medical Institute, led by Vogelstein are making trials with a drug called alpha blockers on Covid-19 patients of ages 45 to 85 who are not on a ventilator or in the ICU. In 2018, Vogelstein *et al.*, had reported that alpha blocker can lessen cytokine storms in bacterial infected mice.

The hyperinflammatory immune response as seen in COVID-19, shares many biological characteristics with macrophage activation syndrome (Bracaglia *et al.*, 2017) and thus it appears to be driven by macrophage activation even in Covid -19. A recent study has shown that acalabrutinib, a drug approved for the treatment of several types of B cell cancers, improved the oxygenation levels and decreased molecular markers of inflammation in a majority of patients hospitalized for the treatment of severe COVID-19 (Roschewski *et al.*, 2020). The drug acalabrutinib inhibits the Bruton tyrosine kinase (BTK) that regulates macrophage signaling and activation.

## CONCLUSION

In Covid-19, cytokine storm is one of the causes for mortality in some patients. Increased levels of cytokines like IL-6, IL-2R, IL-8, TNF-α and G-CSF have been detected in such patients, especially at their critical stages. The increased levels of these cytokines lead to acute respiratory distress syndrome (ARDS) and multi organ failures which cause mortality. Control of cytokine storm, at early stages by using immunospressive drugs and anticytokine therapy, may help to avoid a large number of deaths of patients with Covid-19 but a balanced level of cytokines is also required that could be helpful in the elimination of the virus.

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