

# Attenuating the Effects of Novel COVID-19 (SARS-CoV-2) Infection Induced Cytokine Storm and the Implications

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## ABSTRACT

**Background:** Cytokine storm in COVID-19 is one of the leading causes of deaths among the severe to critical patients and needs to be addressed with utmost priority. Medical interventions need timely updating regarding treatment while dealing with severe inflammation.

**Summary:** Cytokine storm is the hyper inflammatory response which is generated by the body when the external pathogenic invasion is detected. But over activation can leads to severe inflammation among vital organs such as lungs and can damage the tissues resulting into multiple organ failure from which survival chances of the patients goes down. Rise in D dimer levels have found to be a common thread among the deceased patients which in turn can have the deleterious impact. Coronavirus disease 2019 or COVID-19 there is no method of curing exists that can be employed for every patient and which can have the ability to remedy the ailments since the newness of the pandemic. Therefore it becomes imperative to look for other methods instead of treatment methods and the other one is preventive measure.

**Conclusion:** Cytokine storm has established its fatal power and it is backed by the empirical evidences published across various studies. It is linked to the clinical manifestation of the COVID-19 in different types of patients. Various biomarkers can be used in order to detect the slipping of the patient's condition into severe state. More study can shed some light on effective management of the cytokine storm which can in turn save more lives losing to cytokine storm induced medical complications in COVID-19 patients.

**Key words:** COVID-19, Cytokine storm, D dimer, CRP, Interleukins, Corticosteroids

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## INTRODUCTION

Coronavirus disease 2019 or COVID-19 is the continuing pandemic that has groped the entire globe. Within the span of few weeks, it has spread through the world after its inception in December 2019 [1]. Initially it was thought that an unnamed pneumonia but later on it was found out that it was caused by the novel coronavirus, which is the latest entrant in the Coronaviridae family of viruses. In past, outbreaks such as Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS) were occurred due to the ancestors of the novel coronavirus. Since its inception in Wuhan city of the Hubei province of China, it has spread with extremely fast pace. Every person has experienced the brunt of the pandemic in one way or the other. Millions of people got infected with this virus and unfortunately some of them

met with fatal clinical outcome. Till December 1, 2021, 260,092,573 infections has been registered worldwide and 5,183,321 case fatalities happened due to COVID-19 related complications [2]. The new variant has been detected from the southern parts of African continent has already spread too far off parts creating a wave of panic all around the world [3]. The infected patients with omicron variant of the novel Coronavirus have so far reportedly have milder symptoms ranging from mild muscle aches, throat infection and cough [4]. Extreme tiredness and fatigue has been seen among 30 patients that have been admitted in last 10 days in South African health care facility. The initial observations are suggesting the milder manifestation but severe and critical manifestation cannot be denied at this early stage. Surprisingly even people who are not vaccinated are showing milder symptoms, but the guard should not be lowered as novel Coronavirus is extremely unpredictable. Cytokine storm is the leading cause behind the high death rates among severe patients. Various drugs are being used in order to curb the inflammatory response but they have their own side effects hence must be cautious while treading the medical course of treatment with them [5].

## LITERATURE REVIEW

**Pathophysiology of COVID-19:** The pathophysiology of novel Coronavirus causing Coronavirus disease 2019 or COVID-19 is extremely important to be understood as it can guide us to the best practices for controlling the spread of the disease. The emergence of the novel Coronavirus from the zoonotic source is really startling as the human animal interface needs to be rebooted for the betterment of the humanity. The Coronaviridae family of viruses has given previously two deadly members in the form of SARS-CoV-1 which happens to be the predecessor of the SARS-CoV-2 and MERS CoV, both of which caused destruction but in a limited geographical extent. The boundless existence of the novel Coronavirus made it the virus that wreaks the havoc of the unprecedented scale and the reason behind it is high transmissibility and capacity of creating medical complications among the COVID-19 patients. The structure of the virus is such that it has crown shaped spike proteins on it [6]. Hence it is named as Coronavirus in which Corona means crown. The spike protein attaches to the cell and Angiotensin Converting Enzyme 2 (ACE 2) receptors act as facilitator for the virus to enter into the cell. Cell then act as the host for the virus and virus starts to devour all the enzymes and proteins to reproduce and proliferate. The expression of ACE 2 receptors can be abundantly found on epithelium of alveolar tissues, kidney, liver, cardiovascular system etc. These organs are some of the worst affected organ and organ system during severe COVID-19 infection justifying the reason. Cell then bursts as it is no more capable of handling the viral load. The viruses are naturally design to mutate themselves every now and then and most of the times the mutation is of harmless nature. Mutation is basically change in spike proteins on the virus to innovate new ways to enter the host cell and damage it. But sometimes the mutation causes the viral behaviour to change drastically and which is cannot be predicted which is also called as instance of major mutation [7]. It can alter the functioning of the virus and more varied medical complications can arise. As the external pathogenic invasion is recognized by the white blood cells it starts to produce antibodies for them. As the novelty of the disease is concerned, there are no established courses of treatment to treat the viral infection of COVID-19. Also human body has no antibodies for the COVID-19, considering the novelty of the disease. The ad hoc treatment module is based upon the symptoms shown by the patient and also depends upon the experience of the medical officer in charge. The clinical manifestation of COVID-19 varies widely according to the clinical history of patient, age, viral load and so on. Many aspects are interlinked while assessing the impact of the COVID-19 on people of different walks. It generally spreads through the direct contact of the infected person through his or her bodily discharges like cough and sneeze. General and widespread symptoms include cough, cold and fever which can progress into diarrhoea, dyspnoea and difficulty in breathing. Higher and more severe symptoms can be shown in more vulnerable section of population which are going to

certain immunosuppressive stage [8]. These sections includes comorbid and aged patients, pregnant women, patient having daily exposure to the novel Coronavirus, for example, health care professionals and allied health care workers who are the prime contact with the infected persons. The severe and critical symptom needs high end medical care and dedicated medical attention constantly. Most of the case fatalities are contributed by these sections of population. Young adults who were thought to be in vulnerable group are the least affected group. Though the chance of getting infected is same at par with their older counterpart but the clinical manifestation of the COVID-19 is of milder nature. That is why, even without vaccination, the fatalities among the young adult section of population due to COVID-19 is extremely low [9].

**Cytokine storm:** Cytokine storm also known as hyper cytokinemia is the animal body's reaction to the external pathogenic invasion and it tries to take control over the infection through release of cytokines. Cytokines is basically a small protein that is synthesized in the body. Various types of proteins are synthesized in the body to work out the day to day functioning of the body. Protein synthesis occurs in cell. They have an important role in cell signalling. Cell signalling is the ability of the cell to communicate with itself and surrounding environment to receive, transmit and process the incoming and outgoing signals. Signals can be extracellular that is generated due to activities happened outside of the cell. Interleukins like IL-6, chemokine's and interferon are some of the cytokines. They are generally produced by B and T lymphocytes, macrophages and so on [10]. Cytokines are basically pro-inflammatory molecules used to signal when body detects the external pathogenic invasion and need to control it arises. But sometimes these cytokines are generated in huge amount flooding the system with it, creating a massive inflammation throughout the body and on various organs. This can cause cell damage and multiple organ failure can also result of the cytokine storm action. Macrophage Activation Syndrome (MAS) sometimes interchangeably used instead of cytokine storm but they have differences in there terminologies. Cytokines storm was behind the large number of case fatalities from the young adult age group in the pandemic of Spanish flu in the year 1918. Host of other infectious diseases like bird flu have been triggering the cytokine response after entering into the human body [11].

**Cytokine storm and COVID-19:** Coronavirus disease 2019 is the highly contagious disease which disturbs the healthy functioning of the body. Novel Coronavirus causing COVID-19 is infamous for increasing the oxidative stress in the body and is known for varying degree of inflammatory response inside the body. The infection may or may not produce the symptoms and it depends upon the clinical condition of the patients [12]. Although striking fact is the case fatality rate among COVID-19 patients is far less than the MERS in which it was more than 34% but the extent of the disease is large and therefore the number of case fatalities is huge and unfortunately touched and passed the five million mark.

In severe patients, pneumonia and Acute Respiratory Distress Syndrome (ARDS) has been seen frequently and is one of the leading causes of fatalities in critically ill patients. Although all three disease, SARS, MERS and COVID-19 have some similar clinical features which includes basic symptoms like cough, old and fever. The external pathogenic invasion is detected by the innate and adaptive immune system and pro-inflammatory cytokines are released to fight the pathogens. But eventually over production and activation of cytokines results into massive amount of inflammatory response which can cause organ failure and eventually fatal clinical outcome. Lymphopenia is widely seen among the patient of COVID-19 but also found to be recovering along with the improving condition of patients. In several health facilities in china, the patients are checked for lymphopenia as it is highly associated with the severe condition [13]. The systemic over inflammatory response had caused many fatalities among COVID-19 patients and it is not related to any vulnerability of the patients and can affect a healthy person as well. T lymphocytes and NK cells are one of the crucial aspects while releasing the cytokine to fight the disease infection. Various biomarkers such as C reactive proteins, D dimer, interleukin, lymphocyte count, prothrombin time, serum ferritin, PCT etc. are some of the enzymes and serums that regulate the inner function of human body. Any change from the equilibrium in case of health, these levels fluctuates from its ideal levels. Hence it can act as biomarkers for the severity of the disease. As novel Coronavirus causing COVID-19 extremely less time to decide the course of treatment to treat the patient and the case fatalities are huge in number and needs to be controlled. Also the health care infrastructure has its limitation to cater the demand of the influx of patients. Therefore it is necessary to devise the methodology to identify the patients which can slip into severe and critical condition [14]. These biomarkers are the excellent way to find out, which patient's condition is worsening. The pan body over inflammatory response can also be detected by observing these biomarkers. In many studies it is found that survived severely ill COVID-19 patients and patients who met fatal clinical outcome had elevated levels of CRP, serum ferritin, D dimer IL 2R, 6, 8, 10 etc. Also decreased levels of lymphocyte count, platelets, eosinophil and haemoglobin count are also the indicator of the deteriorating condition of the patient. When the inflammation reaches the lungs it creates unmanageable complication and case fatality rate is extremely high among such patients, ARDS is one of the common cause behind the huge case fatalities associated with the COVID-19. Monocytes and macrophages were found in the lungs and alveolar tissues of the severely ill and deceased patients which explain the blockage of air pathway through which oxygen is supplied to each and every part of the body *via* blood. Without oxygen, hypoxia is induced and severe lung infection is introduced as damaged lung tissues are not being able to repair themselves. CT scans of chest revealed the lung injury and amount of fluid that has been accumulated due to it resulting in obstruction in the

flow of oxygen. The hypothesis proposed by various studies suggests that there might be Rennin Angiotensin System (RAS) that is behind the pro-inflammatory response to overshoot which triggers the ARDS. The infiltration of neutrophil and monocytes causes apoptosis of lung cells. The biomarkers such as interleukins particularly IL 1B, 2, 7, 8, 9 etc. shots up indicating the lung injury [15].

The inflammation can be spread to important blood vessels and may induce cardiovascular damage such as myocarditis and pericarditis. Also the weakening of heart muscles along with arrhythmia that is irregular rhythm of heart beat. Comorbid patients who have underlying cardiac ailments are vulnerable to develop cardiac injury if they survived. Rise in D dimer levels have found to be a common thread among the deceased patients which in turn can have the deleterious impact.

### DISCUSSION

A therapeutic intervention is extremely necessary in case of over activation of cytokines. The case fatality rate rose due to cytokine storm can be lowered down by proper and timely intervention through various drugs. Cytokine storm has the ability to perpetuate the hyper inflammatory condition in the body hence drug intervention is extremely necessary and in severe patients it becomes inevitable. The choice of drugs is done according to the condition of the patient and its immune system response. Various drugs used for the therapy to treat the cytokine storm are all repurposed drugs which were previously being used which includes existing antivirals, antimalarial which includes chloroquine and hydroxychloroquine, anti-retroviral, immune modulatory drugs in order to suppress the immune system. Corticosteroid such as dexamethasone is among the popularly used drugs to control the hyper inflammatory response which is the leading cause behind the rising deaths among severe patients. The mild dose of corticosteroids such as dexamethasone has seen suppressing the inflammation [16]. Antioxidant such as vitamin C is famous for its anti-inflammatory properties but it needs to be administered intravenous and that too of low dosage of 500 milligram each time. Chloroquine and hydroxychloroquine made the headlines that they effectively control the inflammation all over the body, but found to be partially effective and not working in all the cases. Macrolide, Arbidol, extracorporeal therapy are some of the other therapies which are occasionally used but the empirical data backing their efficacy is absent in all of them. The side effect of continuous administration of some drugs to suppress the hyper inflammatory response has been seen and some of them are gravely serious. Hydroxychloroquine and chloroquine in large amount of dosage can induce liver injury especially among the patients having pre-existing liver ailments. Continuous administration of dexamethasone has resulted into extreme suppression of immune system response resulting in a weak immune system which cannot even resist the fungal infection such as black fungus or mucormycosis. These fungus generally is

present everywhere and body is accustomed to such infection and can easily ward off such fungal infection. The mucormycosis or the popularly known as black fungus have one of the highest fatality rate ranging from 50% to 80%. To avoid the infection reaching brain starting from the mouth and nasal passage, many patients have lost their eye in order to stop the proliferation of the fungal infection. If the infection reaches to brain, then chance of survival of the patients is slim to none. Therefore administration of corticosteroids on one hand appeared to be lifesaving later it was found out to be life threatening [17].

So it is observed that in instance of Coronavirus disease 2019 or COVID-19 there is no method of curing exists that can be employed for every patient and which can have the ability to remedy the ailments since the newness of the pandemic. Therefore it becomes imperative to look for other methods instead of treatment methods and the other one is preventive measure. Precautionary measures focuses on the facet of preventing the infection from contracting at very first instance. As we have seen that novel Coronavirus disease 2019 creates unimaginable difficulties among the affected patients which is often becomes difficult to manage the same, clinically. Moreover, the rise of new facet of COVID-19 called long COVID-19 in which affected folks feel the signs of the disease of COVID-19 even after getting relived from the hospital. Moreover, patients have to bear a lot of psychosomatic problems which arrives with COVID-19. It is observed and noted that long periods of isolation and quarantine can impact the patients psyche in a negative way. All these can be avoided and people can safeguard themselves *via* different methods which are collectively defines as precautionary methods [18]. These methods comprises donning face cover and masks of correct attribute, keeping physical distancing of at least 2 meters, not wandering outdoor if not required as it will shield one from aerial virus, vaccination, regular sanitization of palms and hands and so on are some of the methods which can one effortlessly replicate and be safeguarded from novel Coronavirus. These methods has its proven efficacy as these methods were tried and verified in presenting epidemics like SARS, MERS, Ebola, Swine flu etc. All these measures were found to be helping the cause. In case of Ebola which was initially an unknown ailment, took tolls on health care professionals treating the Ebola patients [19]. But after the practice of using the masks and proper sanitization methods started, the fatality numbers among doctors and other professionals came down radically. The theory of critical threshold in COVID-19 is extremely important as it shows the amount of the viral burden present in the body. More is the viral burden less is the possibility of the not meeting the lethal clinical outcome. Thus, one must make sure to obey all these rules at all times.

### CONCLUSION

Cytokine storm has established its fatal power and it is backed by the empirical evidences published across

various studies. It is linked to the clinical manifestation of the COVID-19 in different types of patients. The cytokine storm is creates many complications in the patients and has ability to cause multiple organ failure and further death of the concerned patient if the inflammation is not controlled in time. Certain biomarkers can indicate the inset of such severe symptoms and patients can be saved from the critical condition and fatality. By blocking interleukins which gives rise to most of the cytokine response we can achieve some success rate. Finally preventive measures are extremely essential in dealing with the patient as they can circumvent all these devastation and downfall in one person's life. The precautionary measures must be enforced with strict regulation as they still hold their significant even in the new era of Omicron which is supposed to be more infective than previous variant.

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