

## Thromboembolic Disorders in Covid-19 Patient

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### ABSTRACT

*Background: Thrombotic events can be seen among patients having cardiovascular illness. Along with COVID-19 the disease severity has found to be increasing. Thromboembolism has been widely seen among severely ill patients. The autopsies of the ceased patients due to complications created by COVID-19 indicated the role of deep vein thrombosis, endothelium dysfunction and so on. 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 where living chances of the patients plunges. Several enzymes and vital proteins inside the patient's body was found to be out of their tolerance level and showing huge fluctuations in their readings. These are termed as biomarkers as they can be used as indicators for the worsening condition of the patient.*

*COVID-19 must be dealt with utmost precaution as it is still considered as understudied pathogenic disease. Various biomarkers can be used in order to detect the deterioration of the patient's condition into critical condition. Empirical study highlighting facts about bidirectional relationship between COVID-19 severity and impact of cardiovascular function of non-Comorbid patient must be done in order to understand the viral behavior.*

**Key words:** Covid-19, Cytokine Storm, D Dimer, CRP, Endothelial Dysfunctional, Thrombosis`

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### INTRODUCTION

Coronavirus disease 2019 or COVID-19 is the lethal disease that has been ravaging through globe since past more than one and half years. On March 11th 2020 World Health Organization (WHO) declared the outbreak turned public health emergency of international concern (PHEIC) as pandemic, one of the most unfortunate declaration in recent years. Novel Coronavirus also known as SARS-COV-2 is the successor of SARS-COV-1 which caused the previous outbreak of severe acute respiratory syndrome (SARS) in early 2000's. Both of these virus strains belongs to the same family known as coronaviridae family. Another outbreak by MERS-COV caused havoc through the infection known as Middle Eastern respiratory syndrome. 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 10, 2021, 268,343,207 infection has been registered worldwide and 5,285,485 case fatalities happened due to COVID-19 related complications [1].

The new variant has been detected from the southern parts of African continent has already spread towards far off parts creating a wave of panic all around the world [2]. 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. Extreme tiredness and fatigue has been seen among 30 patients that has 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 [3]. 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 [4].

### Pathophysiology of the Covid-19

The world has been witnessing medical emergency of

huge scale in the form of COVID-19 for more than one and half years. Still effects of the COVID-19 are at all waning and in fact creating new challenges day by day. Humanity as a whole was caught by pandemic unguarded and this has made a huge difference as more than five million people lost their lives and millions of people bore the brunt of the pandemic of COVID-19 in one way or the other. Not only medical but socioeconomic emergencies were created alongside as pandemic had wide spectrum of effects. This was all because of the peculiar pathophysiology of the novel coronavirus. It is the latest member of the coronaviridae family and is a beta type coronavirus. Initially it was identified as normal harmless cough and cold causing virus mainly in European countries in mid-1960 [5]. Then for four decades no major catastrophe or outbreak happened due to human coronaviruses. But at the start of the twenty first century, an unidentified viral pneumonia outbreak was identified as Severe acute respiratory syndrome (SARS) which was caused by the coronavirus mainly severe acute respiratory syndrome coronavirus 1 (SARS-COV-1) [6]. This event made ripples around the research world and more and more research was done on the virus's behavior. Again it went inactive till 2012 when Middle Eastern respiratory syndrome (MERS) outbreak happened which rapidly infected many people but eventually limited to certain geographic limits. This was later known to be caused by Middle Eastern respiratory syndrome coronavirus (MERS-COV). Then by studying behavioural pattern of the coronavirus, scientists suggested that it will continue and the virus will cause more such outbreaks in future. As the viruses are notorious for their mutation which keeps them sturdy and strong. But they can mutate only when inside the host as they are categorized as half living organism which only activates when host is there otherwise they are inactive [7].

Therefore, it is important to keep the virus away from the host in order to curb the spread as one entered it starts its action rapidly and if the patient's immune response is not sufficient enough then the body will not be able to fight the virus and debilitating impact can be seen on the body. The virus has wide ranging clinical impact on the anatomy of the humans. The patients are classified according to the symptoms they produced post infection by novel coronavirus.

New strain of coronavirus holds the capacity to remain in atmosphere as suspended particle and it can reintroduce the aforementioned in ventilation settings. The novel coronavirus can enter in to the human body through bodily discharges and through openings such as mouth, nose and eyes. Then via respiratory tract it goes down further increasing its viral load. The angiotensin converting enzyme 2 (ACE 2) RECEPTORS are present on almost every viral organs and organs systems which includes alveolar tissues that is lungs, heart and blood vessels, liver, kidney, brain and so on. The ACE 2 receptors is the entry point for the virus and which facilitate the same [8]. The virus gestates

for 3 to 10 dates post entry and amid around 4th day the signs of the COVID-19 starts to play a part. Varied array of symptoms can be seen amongst sufferers of COVID-19 and it is basically relies on the clinical past of the concerned and the quantitative load of the virus that patient is beholding [9]. Minor symptoms which are primarily seen among the patients are cough, cold and fever accompanied by fatigue. The intensity of fever and fatigue can change amongst the kind of patients as high grade fever and weakness is primarily linked to huge viral load and can take more days to be relieved from the disease. There are categories among the types of COVID-19 patients. Patients can be grouped into mildly ill, moderately ill, severely ill and critically ill. Males are more vulnerable than female possibly due to the lifestyle differences among the two sexes. Comorbidities such as diabetes mellitus, lung injuries such as bronchitis and asthma, cardiovascular diseases, old age are some of the circumstances which are worse to have in COVID-19 infection. As these can result into more complications to arise. As the health care infrastructure had totally failed to cater the demand of the incoming infected patients, health care professionals tried treating the former two categories of the patients at their home as there was no bed left to lodge all of the patents inside the hospital care facility [10].

#### **Comorbidities and Covid-19**

Novel coronavirus causing COVID-19 is one of its kind disease and presenting new challenges in front of the health care professionals on daily basis. Be it in the form of new variant or changed viral behavior that causes the scientific and health care professionals to rethink and re strategize the efforts against the COVID-19. The crucial aspect of the novel coronavirus causing COVID-19 is how it pans out in the patient's body. It is now seen from various studies which has established that certain group among the general populace is more prone to get sicker due to COVID-19 than others. They experience severe and critical symptoms and can meet fatal clinical outcome if not managed in time. The disease manifests itself in such patients in different way making it more difficult to manage the patient in the hospital care facility. The treatment of the patient becomes difficult and often it is seen that they are not saved due to severe symptoms and irreparable damage. These group of people must be medically protect at any cost to reduce the mortalities [11]. The section of patient which can come up with severe symptoms includes elderlies, pregnant women and persons having underlying medical illness or comorbidities. All these people have one thing in common that they are in their immunosuppressive phase of their life, therefore the immune system of body is busy dealing with the already existing ailments and thus novel coronavirus exploits this loophole making the patient sicker. Especially comorbid patient is bigger cause of concern as they are huge in numbers as various illnesses has been grappling the world which are chronic in nature long before the arrival of COVID-19. Various comorbidities which were grappling the whole

world prior to the COVID-19 for long time includes cardiovascular ailments, liver ailments like cirrhosis and fatty liver, obesity and diabetes mellitus, renal ailments and disease, various types of cancers etc. All these ailments and disease along with other disorders takes huge toll on the body of the affected person as these are chronic ailments [12]. These ailments are the result of changing lifestyle which includes eating unhealthy food with high sugar and high fat content, sedentary lifestyle, consumption of intoxicants in large quantity and for long time, genetic inheritance and so on. It takes years to form such diseases and if one is detected with any of them then generally he or she has to live with it for the rest of the life as the damage done to the body is quite grave. They have their own medications which is used to curb the spread and keep the patient in the manageable condition. The playout of the COVID-19 in such patient is quite complex and can take any turn during the course of treatment. The clash of medications along with over administration has been already proven fatal in many cases. Therefore, it is important to have a research backed by the empirical data to show the efficacy of each drug in patients so that administration of that particular drug does not cause any harm to the patient.

Certain comorbidities such as diabetes mellitus, cardiovascular diseases have much more debilitating impact and have the capacity to create severe unmanageable complications along with COVID-19. The world is already suffering from various cardiovascular illnesses. High blood pressure, hypertension, various congenital disorders affects the functioning of the whole body as blood is one of the most important connective tissue which carries oxygen all over the body along with various other vital nutrients. Lack of oxygen can trigger hypoxia and multi organ failure as without oxygen the function of each and every organ and organ system is affected in an adverse way [13].

#### **Covid-19 and thromboembolism**

COVID-19 and associated thrombotic events which are mostly proven fatal for the patient occurs among than more a third of patients. It further creates complications and if patients had no prior ailments related to heart or allied system then he or she can acquire one during the course of the treatment. The bidirectional correlation between the cardiovascular ailments and COVID-19 is extremely important to study as it will create more flutters if COVID-19 is creating parallel cardiovascular ailment pandemic which will become tough to manage in future. Venous thromboembolism has been seen among severely ill patients and it has been connected to the immobile nature of the patient. An immune thrombosis can be seen manifested as small sale pulmonary thrombosis, an event attributed to the innate immune stream response. The events linked with thromboembolism during COVID-19 have no clear reason as lack of clarity prevails over innate immune system response generated thrombosis and venous thromboembolism [14]. The analysis of several severely ill patients and autopsies of patients deceased due to

COVID-19 showed some common feature which can be very effective in designing the future course of treatment.

Several enzymes and vital proteins inside the patient's body was found to be out of their tolerance level and showing huge fluctuations in their readings. These are termed as biomarkers as they can be used as indicators for the worsening condition of the patient. Biomarkers such as ferritin, c reactive protein CRP, fibrinogen, D dimer levels were found to be on rise among aforementioned patients which indicates certain pattern. These patterns also point out towards the cardiovascular injury which can worsen the medical condition of the sufferer of COVID-19. A considerable amount of increase in D dimer is directly associated with the fatal clinical outcome and it can independently indicate the deteriorating condition of the patient. Pro inflammatory, increased coagulation response can be seen among the inner layer of the blood vessels known as endothelium. Coagulation and inflammation in important blood vessels can be life threatening. The comorbid patients already suffering from ailments having weak endothelium or inflamed and dysfunctional one can have debilitating impact on them. This can occur via direct proliferation of the novel coronavirus to the endothelium via blood circulation or novel coronavirus causing COVID-19 can have inflammatory response triggering complications [15]. The damage of endothelial layer could trigger another round of triggering of excessive immune response which could further damage the endothelial layer. Pro thrombosis has also been seen among the patients of COVID-19 especially severely and critically ill patients. It is the cumulative effect of immune system, decreased fibrinolysis and coagulation. The previously explained damage to the endothelial layers expose the sub layers and this can trigger the conversion of fibrinogen to fibrin which further leads to forming blood clots along with platelets which also coagulates due to effects of COVID-19. Increase in prothrombin time can have cascading impact of the coagulation as it can trigger more than once.

Haemostatic abnormalities were found to have been stark in severely ill ICU patients than their non-ICU counterparts. The internal bleeding caused due to malfunctioned haemostasis can result into profuse leaking of blood inside the patient body. Cutaneous manifestation has close correlation in such cases as certain patches on skin which indicates worsening of the medical condition of the patient. Innate immune system response and function of the haemostatic function in the body have intimate relation as they together provide a defence against the external pathogenic invasion. Immunothrombosis is a state which is also triggered by the COVID-19 which coagulation and endothelial dysfunction, leads to pro thrombotic state. The vascular damage induced by the COVID-19 initiates cell lysis in which various enzymes along with viral RNA is also spread to nearby cell after the cell bursts due to viral manifestation [16].

As earlier said, biomarkers have been consistent in



indicating the severity of the COVID-19 and among such biomarkers is ferritin. The reports indicating high levels of ferritin could be due to cell damage which triggers inflammation all around the body. As the ACE 2 receptors are expressed by almost every cell on important organs, multi organ failure is the result of such event. The earlier thought to have been the panacea for controlling the inflammation is to block certain inflammatory pathway by inhibitors in the form of medications. But later the over administration of such immunosuppressive drugs or inhibitors have proven more lethal than COVID-19. In fact, side effects due to such over administration of drugs or inhibitors to suppress the immune system response have been backfires and resulted into events like catching deadly fungus like mucormycosis which is extremely easy to fight with normal immune system response. In fact, the mucormycosis can be found in the respiratory pathways of general populace and is extremely harmless. But the immunosuppressant was over administered in some cases and this otherwise manageable fungal infection proved to be deadly. The case fatality rate among the patients of mucormycosis in COVID-19 ranges from 50 to 90 percent. Such is the lethality of the disease. Therefore proper balance must be stroked in order to control the inflammation as well as avoid the overreaction and side effects [17].

#### Preventive measures for Covid-19

Coronavirus disease 2019 or COVID-19 crated many complications for the patients of it. The disease is so unpredictable that patients presenting similar symptoms having almost same clinical history can have different clinical outcome. The panning out of the disease among the patients still cannot be predicted and thus it becomes extremely important to prevent the disease from happening at first place [18]. Also the phenomenon of the long COVID-19, long hauls of isolation and quarantined during the infection period, psychological impact along with socioeconomic impact are some of the adverse impact that patients has to face. Thus more focus is needed on the preventive part rather than curative part. Various methods through which the preventive intervention can be achieved. World Health Organization (WHO) along with other health authorities worldwide has already disseminated the guidelines which enlists the ways by following which one can easily safeguard oneself. These includes wearing of masks, maintaining minimum physical distance among crowd, vaccination, sanitizing hands at regular intervals are some of the preventive measure which can give good results. These measure cannot offer complete protection from infection but the disease severity among the patient after following all such measures will not be there and patient will get easily treated. Also these methods were tested in previous outbreaks where they have proven extremely effective in controlling similar infectious disease. For example in Ebola outbreak, after the introduction of preventive measure like wearing masks and sanitization among health care workers, the detection rate of the disease rose rapidly which in turn

pulled down the fatality rate [19].

#### CONCLUSION

COVID-19 must be dealt with utmost precaution as it is still considered as understudied pathogenic disease. Also its unpredictability can land a patient in precarious situation. The comorbidity has been shown by almost every concerned study to be the worst thing to have in COVID-19. Cardiovascular ailments are one of them and has huge base among people. Thromboembolism is extremely important in COVID-19 as it created multifold impact on patients. Biomarkers are efficient and reliable in indicating the increasing severity of the disease. Therefore, they need to be managing accordingly to lower down the case retaliates occurring due to COVID-19. The bidirectional relationship must be studied as the fall out effect also needs to be tackled professionals. The long term wellbeing of the patients is at stake in such cases. Preventive measures need to be propagated at all costs as it has high efficiency to decongest the ICU units as the severity of the disease can be mellow down. Vaccination drive must be accelerated in order to provide some immune cover to the patient.

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