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ACUTE CORONARY SYNDROME AS A POST-COVID-19 COMPLICATION: A REVIEW ON ITS PREVALENCE, POTENTIAL MECHANISMS, AND TREATMENT

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ABSTRACT

Coronavirus disease (COVID-19) is a major medical concern worldwide. The lung infection and respiratory failure that are linked to SARS-CoV-2 can result in considerable mortality and morbidity. Moreover, it has a similar inflammatory effect on different organ systems**.** The S proteins bind through the S1 subunit to angiotensin-converting enzyme 2 (ACE2) expressed on host cells, but merely binding to ACE2 is not sufficient for cell infection.22 Viral cell entry requires the transmembrane serine protease 2 (TMPRSS2) expressed on host cells to perform critical protein priming that leads to conformational changes, viral cell entry, and cell infection. Several COVID-19 individuals have been documented to have acute coronary syndrome (ACS). Even though the underlying pathophysiology is yet unknown. The most well-known mechanisms include oxygen supply/demand imbalance, endothelial dysfunction, prothrombotic activation of the coagulation cascade, and systemic inflammatory response mediated by cytokines. In addition, viral respiratory infections have been linked to a higher risk of MI due to gene expression that is prone to stimulating platelet activation. Further in-depth research on the relationship between COVID-19 and ACS is required to see whether there is a direct causative or

instigating link between them. Although many experimental therapies are used, standard therapy should be established. Acknowledging this connection could result in fresh research and ACS patient treatment alternatives.

KEYWORDS: Covid -19, Cytokine storm, ACE -2 Receptor, inflammatory response, transmembrane serine protease 2.

INTRODUCTION

Coronavirus is a single-stranded enclosed positive sense RNA virus in the order Nidovireles of the Coronaviridae family.[1] The Coronavirus which affects the lungs caused by SARS-CoV-2 has a wide clinical spectrum, from asymptomatic infection to mild upper respiratory illness, severe viral pneumonia, respiratory failure, shock, and, in some cases, death. This clinical presentation doesn't stop at the respiratory level different studies have shown manifestations in different other body systems.[2]

Many research studies have shown that the virus is linked to major cardiovascular complications and also worsens the outcome of patients infected with Covid-19.[3] Among all the cardiac complications patients with acute coronary syndrome are major.[4]

The acute coronary syndrome refers to acute myocardial ischemia, which encompasses unstable angina, ST elevated MI, and Non-ST elevated MI, the most prevalent cardiovascular disease. These are closely related in their pathophysiology but differ in severity.[5]

In those with underlying heart illness or proinflammatory cardiovascular risk factors, Covid-19-induced Myocardial damage is deadly.[3] This is largely owing to the possibility of a link between respiratory infections and Myocardial infarction.[6] Covid-19 may enhance atherosclerotic plaque instability and thrombus development, which can lead to acute coronary syndrome.

Laboratory findings in Covid-19 patients have shown decreased levels of lymph count, increased levels of troponin, interleukins, and a prolonged prothrombin time. The etiology of ACS in sars-cov-2 virus-affected patients is unclear even though many hypotheses developed none of them are fully understood.[7] some study shows direct cardiac injury by the virus itself.[8]

EPIDEMIOLOGY OF COVID-19

Since its outbreak in Wuhan, China in 2019 December covid-19 (sars-cov-2), it evolved into a global pandemic affecting healthcare systems worldwide.[1] and the total number of cases is 13 million as of march 29, 2021, including 2.8 million confirmed death. In India from 2020 January to 2021 July total of 2 million samples was collected all over India. 1.7 million were positive cases and 37,947 death cases were recorded during that period.[9,10]

EPIDEMIOLOGY OF ACS

According to recent data, there are 1.3 million ACS-related emergency visits per year in the US. Among them, 21% had ST-elevated MI, 36% had non-ST-elevated MI, and 46% had unstable angina. The world's largest ACS burden is found in India. Current information on 20,468 patients from 89 sites across 10 regions and 50 Indian cities has been made available via the CREATE registry.[5,11]

EPIDEMIOLOGY OF ACS IN COVID-19 PATIENTS

Huang *et al.*, reported myocardial injury as a major complication in sars-cov-2 patients at the rate of 12% in 41 hospitalized patients.[1] *wang et al*., found 7.2% of patients had acute myocardial dysfunction in 138 hospitalized patients with covid-19 and 22.2% of them were admitted to ICU. As li *et al*. reported acute myocardial injury in at least 8% of the patients with 13 folds a higher risk in patients with severe clinical presentation admitted to the critical care unit.[2]

CLINICAL PRESENTATION OF COVID-19 & ACUTE CORONARY SYNDROME

Inhaling respiratory droplets from a SARS-COV-2 infected person while they cough, sneeze, talk, or exhale is a major factor in both disease symptoms and transmission methods.[12] Common signs and symptoms include a temperature or chills, cough, shortness of breath or difficulty breathing, exhaustion, a sore throat, runny nose or congestion, diarrhoea, body aches, and a loss of taste or smell.[13]

Shortness of breath, fatigue, lethargy, indigestion, palpitations and chest pain are examples of atypical ACS symptoms. Moreover, silence ischemia can happen in the absence of any standard ACS symptoms.[14]

CLINICAL QUIRKS OF THE ACS IN COVID-19

The challenge is that the distinguishing characteristics of the course of the infectious disease itself can mask the clinical presentation of acute coronary syndrome in a patient with COVID-19. Acute respiratory failure and tachyarrhythmia in COVID-19 patients may result in an imbalance between myocardial oxygen demand and oxygen supply (type 2 MI).[15] According to the findings, the risk of acquiring ischemic stroke increased by three to seven times and the chance of developing an AMI increased by three to eight times in COVID-19, with the peak incidence occurring in the first two weeks following infection.[16] According to the Danish National Registry, compared to the time before infection, the incidence of AMI is five times greater in the first 14 days after a diagnosis of COVID-19 infection.[17] Arrhythmias in COVID-19 individuals are influenced by hypoxemia, enhanced adrenergic stimulation, acid-base and electrolyte disturbances, and hypomagnesemia which worsen the condition.

Risk factors

Traditional risk variables like age, male sex, obesity, smoking, and diabetes, have less of an impact on acute myocardial injury patients.[18] Simultaneously, sars-cov-2 is a unique issue, and it is obvious that the viral infection, the existence of hypoxia, and systemic inflammation are all distinct risk factors that might destabilize pre-existing cardiovascular diseases (CVD).[16]

COVID INDUCED ACS

The ACS in COVID-19 may have a number of underlying processes, some of which are yet not fully understood. (12). As MI was the initial sign of the illness, it is reasonable to assume that ACS represents a distinct thrombotic consequence of SARS-CoV-2 infection. The most well-known mechanisms include the systemic inflammatory response mediated by cytokines, prothrombotic activation of the coagulation cascade, endothelial dysfunction, and hypoxia damage brought on by an imbalance in oxygen supply and demand.[17]

➢ ENDOTHELIAL DYSFUNCTION

A healthy endothelium has several beneficial characteristics that control vasomotion, inflammation, platelet reactivity, coagulation, vascular permeability, and host defense.[6] Conventional cardiovascular risk factors including smoking, diabetes, hypertension, and advanced age, and hypertension may harm the endothelium through various mechanisms, including oxidative stress brought on by elevated quantities of superoxide anions inside the

cells.[17] Current research shows that endothelial dysfunction is one of the most harmful processes behind covid-19 pathogenesis. Venous, arterial, and microvascular thrombosis may be caused by both inflammatory cell build-up and direct viral impact, as shown by the presence of viral components inside the endothelium. A vasodilator/vasoconstrictor imbalance, platelet aggregation, and eventually myocardial ischemia may all be favoured by increased endothelin-1 synthesis, a strong prothrombotic and vasoconstrictor agent.[6,17] Vascular endothelial glycocalyx (VEGLX) damage caused by sars-cov-2 may be another pathophysiological mechanism for endothelial dysfunction. VEGLX damage has been linked to several diseases, including Inflammation, Hypoxia, Hyperglycemia, and ischemia/reperfusion injury.

➢ INFLAMMATORY RESPONSE

Studies have shown that sars-cov-2 (acute respiratory infection) causes elevated troponin levels, inflammation, and release of cytokines which progress the disease.[3] The release of macrophages and t cells into the atherosclerotic plaques is stimulated by the hyper-inflammatory response brought on by circulating cytokines, interleukin (Il-1, Il-6, And Il-8), and tumor necrosis factor-alpha (TNF-alpha) produced at the infection site. IL-1 supports the production of other proinflammatory mediators, and IL-6 causes the synthesis of acute reactants like fibrinogen and supports a prothrombotic and anti-fibrinolytic imbalance.[19] These cells stimulate matrix metalloproteinase and peptidase which, along with enhanced vascular permeability, encourage the production of fibrous caps.[6] In response to intraplaque inflammatory activity, the extracellular matrix degrades and undergoes an oxidative burst, releasing phospholipids, tissue factor, collagen, and components of the platelet-adhesive matrix that help to stabilize the plaque and generate thrombi which is a typical pathogenesis.

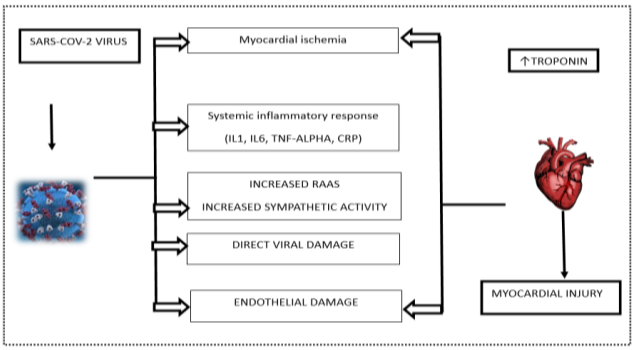

Fig: 1 possible mechanisms of myocardial injury in patients with SARS-CoV-2 2 (IL-1: Interleukin 1, IL-6: Interleukin 6, TNF-ALPHA (Tumor Necrosis Factor, CRP: C Reactive Protein).

➢ MYOCARDIAL ISCHEMIA CAUSED BY HYPOXIA

Via the spike (S) protein, COVID-19 interacts with the angiotensin-converting enzyme receptor, which is widely expressed in the epithelium of the heart and lungs. Angiotensin II receptor on the endothelium ACE then transforms angiotensin 1 to angiotensin 2, increasing inflammatory cell build-up and vasoconstriction.[6] Patients with acute respiratory infections have a 17-fold increased chance of developing myocardial ischemia, which is largely brought on by the disruption of ventilation-perfusion ratios, a functional effect of underlying hypoxemia, and the absence of the hypoxic Vaso-constrictive reflex.[16] The sympathetic nervous system is then activated by a decrease in oxygen supply, which raises heart rate and cardiac contractility while stressing myocardial oxygen demand, resulting in myocardial infarction.[6]

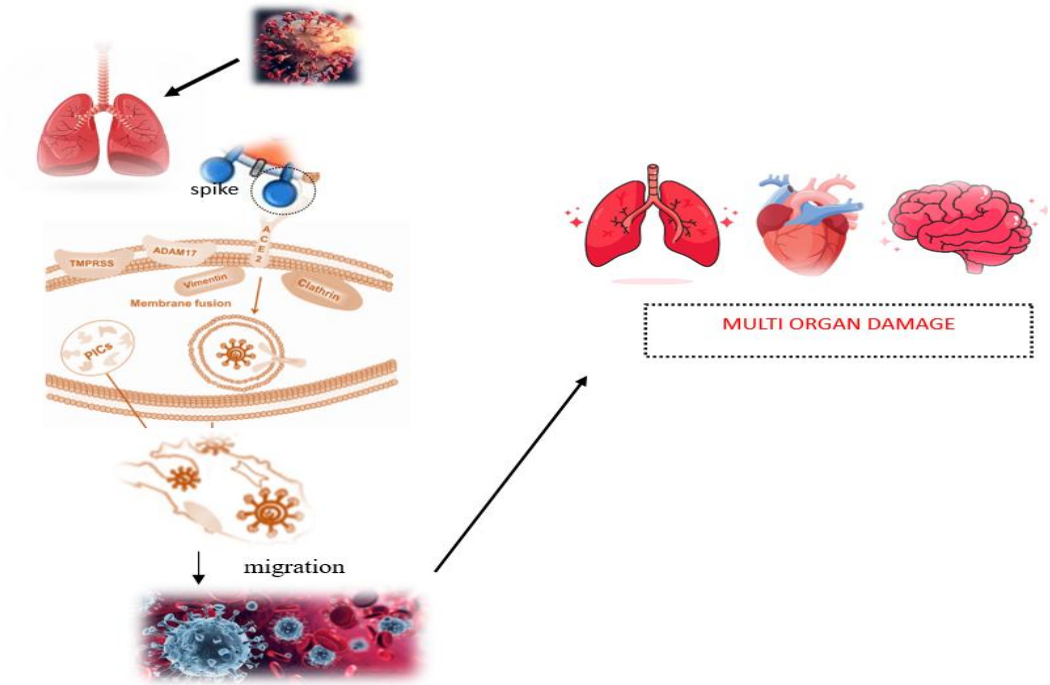

Fig. 2: Possible Mechanism for Multi-Organ Damage Through ACE Receptor.

➢ HEMOSTATIC ABNORMALITIES

COVID-19 has been associated with several hemostatic disorders. Studies imply that the cytokine storm (CS) plays a significant part in the coagulopathy caused by COVID-19.[6,15] Ultra-large von Willebrand factor multimers (ULVWF) and tissue factors are overexpressed as a result of cytokines released during the systemic inflammatory response (TF).[16] These elements may serve as significant catalysts for the activation of the coagulation cascade, resulting in a hypercoagulability state marked by enhanced thrombin generation. The

prevalence of thrombotic complications like acute coronary syndrome, which can be fatal, is frequently seen because of this multifactorial coagulopathy.[13]

TREATMENT OF COVID-19 INDUCED ACS

Treatment for patients with ACS who have covid-19 infection has been delayed. Several patients with ACS were discharged from hospitals sooner than permitted by ACS protocol as a result of the covid-19 pandemic, which led to greater difficulties with AMI. Controlling the sars-cov-2 infection and striking a balance between the risk associated with delaying treatment for ACS patients has become a global challenge during the pandemic.[20]

In addition to their ability to prevent thrombosis, anticoagulant medications also have anti-inflammatory properties that may have a positive therapeutic impact. Both unfarctional and low molecular weight Heparin have pleiotropic Anti-Inflammatory actions that include preventing the interaction between platelets and neutrophils and decreasing the release of interleukin (IL-1, IL-6).[17]

The therapy of ACS in covid-19 may involve antiviral medications. In 199 patients, Cao b, *et al.,* 2020 prospectively examined the use of lopinavir/ritonavir for severe covid-19; regrettably, neither the viral load nor the symptoms of ACS were significantly reduced.[20]

Wang m *et al,*. in his study concluded that QTC prolongation, hydroxychloroquine, and antiviral treatments can both raise the risk for torsade's de pointes. If there are abnormalities of cardiac structure or function, concurrent ventricular arrhythmias, or a longer QT interval at baseline, this risk may be exacerbated in those with ACS in covid-19.[21]

Mason JW *et al.*, has suggested immunosuppression as a potential therapy for myocardial damage in ACS in covid-19.

Interleukin-6 and other inflammatory markers are markedly elevated in severe covid-19 sickness and ACS in covid-19, and cytokine activation appears to be a prominent feature. Interleukin-6 inhibitors sarilumab, Siltuximab, and tocilizumab may help to treat ACS in covid-19 and severe covid-19, according to ascierto pa, *et al*., In 2020. In patients with covid-19, trials with the drugs sarilumab, Siltuximab, and tocilizumab are now being conducted. These trials will provide further details on the effectiveness and safety of the drugs as well as their effects on the ACS in covid-19.[22]

Many current randomized clinical studies are investigating the effectiveness of antithrombotic treatment in covid-19. In the context of covid-related endothelial damage and thrombin inflammation, antiplatelet medications may play a significant function in addition to being a pharmacological therapy for acs. The systemic inflammatory response is further exacerbated by the production of various inflammatory mediators from activated platelets, including cytokines, chemokines, and metalloproteinases.[17]

Beta2-adrenergic receptors are widely expressed on immune cells such as macrophages, dendritic cells, and t and b lymphocytes and seem to play a relevant role in promoting macrophage activation and proinflammatory cytokine production (IL-6, TNF-α, and on) large multicentre trials are required to prove the -blockers' potential positive cardiac and anti-inflammatory benefits. Statins have pleiotropic effects on the immune response, in addition to their influence on circulating lipids, via altering immune cell adhesion and migration, antigen presentation, and cytokine generation. Statins have pleiotropic effects on the immune response, in addition to their influence on circulating lipids, these effects are achieved by their capacity to suppress the synthesis of small GTPases and alter the plasma level of the initial response to myeloid differentiation, which results in the downregulation of transcriptional factors involved in inflammation, such as NF-B. Moreover, statins lower reactive oxygen species and produce more antioxidants, re-establishing the normal endothelium function.[17]

CONCLUSION

Due to its pathogenesis, the COVID-19 disease is often the cause of CVD, which is why it is even more often followed by a higher mortality rate. The association between COVID-19 and acute coronary syndrome leads to increased mortality, morbidity, hospitalization rates, and decrease quality of life. Acute coronary syndrome is a potentially life-threatening complication of COVID-19. Patients with chronic CVD who are infected by COVID-19 frequently experience an abrupt worsening of their condition, a higher risk of developing ACS, and a poor prognosis. Patients with ACS and SARS-CoV-2 infection exhibit different clinical and anatomical characteristics in comparison to non-COVID-19 individuals. The use of pharmacological agents, such as anti-platelets, anticoagulants, ACE inhibitors, beta-blockers, and statins, appears to be a valuable strategy not only in the treatment of ACS but also as a preventive strategy in high CV-risk subjects with COVID-19. International global registries and randomized trials from a global perspective can aid in the development of a

standardized approach to ACS diagnosis and treatment to optimize early morbidity and mortality while also documenting the actual prevalence of ACS. Waiting for the findings of upcoming, big, multicentre trials that would ensure the better survival of these patients may be essential to address all issues in the approach, diagnosis, and treatment of patients with COVID-19 and ACS.

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