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COVID-19 beyond the lungs: Unraveling its vascular impact and cardiovascular complications—mechanisms and therapeutic implications

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Abstract

COVID-19, caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), is primarily a respiratory illness but significantly affects the cardiovascular system as well. After entering the body through the respiratory tract, the virus directly and indirectly disrupts the vascular system. Vascular endothelial cells (ECs), which express ACE2 and TMPRSS2, are targets for viral invasion. However, the predominant cause of widespread vascular damage is the "cytokine storm" induced by the immune response. This leads to EC activation, inflammation, neutrophil activation, and neutrophil–platelet aggregation, causing endothelial injury. Additionally, increased expression of plasminogen activator inhibitor-1 disrupts the balance between prothrombotic and fibrinolytic processes, while activation of the renin–angiotensin–aldosterone system adds oxidative stress to the vascular endothelium. In the heart, SARS-CoV-2 invades ECs, leading to apoptosis and pyroptosis, exacerbated by inflammation and elevated catecholamines. These factors contribute to arrhythmias, strokes, and myocardial infarction in severe cases of COVID-19. This narrative review aims to explore the mechanisms by

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which SARS-CoV-2 affects the cardiovascular system and to highlight the resulting complications. It also identifies research gaps and discusses potential therapeutic strategies to mitigate the cardiovascular impacts of COVID-19.

Keywords
COVID-19, cardiovascular complications, vascular injury, cytokine storm, endothelial dysfunction

Introduction

COVID-19 is a communicable disease caused by a virus belonging to coronavirus family named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).[1] The virus was identified in early December 2019, in lung tissue of patients with symptoms resembling severe bilateral pneumonia, including acute respiratory distress syndrome (ARDS). COVID-19 pandemic totally changed the fabric of our life as it had brought the world to a standstill. The number of cases skyrocketed catching the nation's off-guard. The total number of COVID 19 cases till date are 704,753,890 with 7,010,681 being dead so far. In case of our country the death toll reached 533,570.[2]

In the earlier days of the epidemic, COVID-19 was considered to be restricted to the respiratory machineries of the body. The affected population were being considered only for upper and lower respiratory tract infections. Interventions were also designed to combat respiratory symptoms and signs like—sore throat, dyspnea, low SpO_2, fever, and so on.[2] Gradually constellations of accumulated evidence from basic sciences, imaging, clinical observations and biomarker studies have clarified COVID-19 as a vascular disease. In general COVID-19 is characterized by three overlapping phases of disease progression—the phase of early infection (Stage I), pulmonary phase (Stage II), and phase of hyperinflammation (Stage III). In Phase I, viral infection in respiratory tissues trigger reactivation of innate immune system in the host body along with vasodilatation and vessel leakage. This is followed by pulmonary restrictions as well as consequent hypoxemia.[2] Vascular involvement and cardiovascular stress take place simultaneously in the second phase of the disease. The third phase is characterized by severe inflammation leading to pan-vascular inflammation and serious cardiovascular insult. In this review here, we try to shed light on the multiorgan vascular involvement caused by SARS CoV2 virus and try to emphasize on potential therapeutic avenues that might be adapted to check the infection at several steps of its propagation.

This narrative review follows the guidelines of the Scale for the Assessment of Narrative Review Articles as described by Baethge et al. (2019).[3] The literature search strategy utilized a combination of keywords and controlled vocabulary, including MeSH terms, to ensure comprehensive coverage. The keywords used were: COVID-19, SARS-CoV-2, cardiovascular system, vascular endothelial cells (ECs), ACE2 expression, TMPRSS2, cytokine storm, endothelial activation, neutrophil–platelet aggregation, plasminogen activator inhibitor-1, renin–angiotensin–aldosterone system (RAAS), oxidative stress, endothelial injury, myocardial infarction, arrhythmias in COVID-19, stroke and COVID-19, cardiovascular complications, therapeutic strategies

for COVID-19, inflammation and thrombosis, and apoptosis and pyroptosis. Searches were conducted in PubMed and the World Health Organization Global Literature Database on Coronavirus Disease.

Structure of SARS CoV2

Corona viruses belong to the family of Coronaviridae. The subfamily is coronavirinae which contains four genera (Figure 1). SARS CoV2 belongs to the β-coronavirus family with very close similarity in genomic sequence with the coronaviruses isolated from bats and Malaysian pangolins. According to several studies, bats have been implicated as a natural reservoir of the virus whereas pangolins have been indicated to be the intermediate hosts.[4,5] The virus is a single-stranded RNA (+ssRNA) virus where the nucleocapsid protein (N) encircles the viral genome. It is further packed in layers of membrane protein (M), envelope protein (E), and spike protein (S).[6,7] These four structural proteins (N, M, E, and S) are supported by presence of a number of nonstructural proteins (Nsp 1-16). Among the nonstructural proteins, the Nsp12 exhibits RNA-dependent RNA polymerase activity (RdRp) which is critical for corona virus replication/transcription.[8] The virus gains entry into the human cells via angiotensin converting enzyme2 (ACE2) receptors.[9] The viral spike protein or S protein (the S1 subunit, to be precise) plays a major role in binding with the ACE2 on target cell surface.[10,11] The spike protein is facilitated by host cell membrane proteases, such as furin, transmembrane protease and serine 2 (TMPRSS2), and disintegrin metalloproteinase 17 (ADAM-17).[12]

Distribution of host cell membrane proteases

The preference of SARS CoV2 for respiratory epithelium (Type II pneumocytes) is well established. But vascular ECs, vascular smooth muscle cells and pericytes

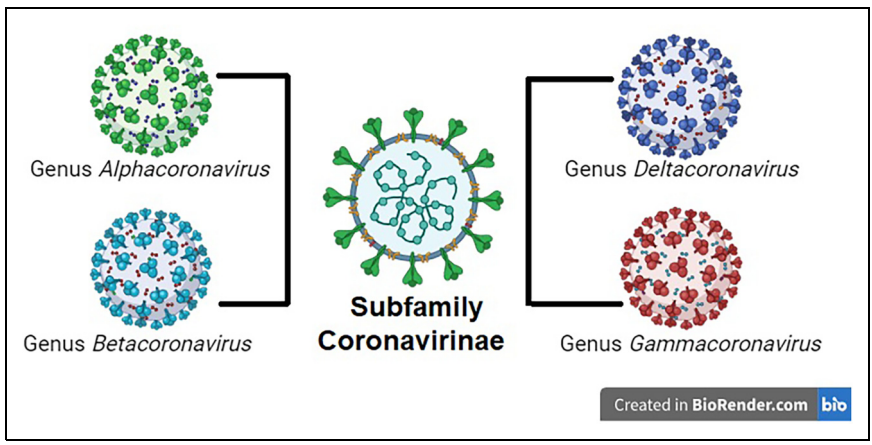

Figure 1. The four genera of coronavirinae.

become easy targets for SARS CoV2 owing to abundant expression of host cell membrane proteases like ACE2, TMPRSS2, and ADAM17.[13]

ACE2, a Type I transmembrane carboxymetallopeptidase protein, is present ubiquitously in ECs of cardiovascular, digestive, respiratory, and genitourinary systems. The ACE2 [soluble ACE2 (sACE2) to be precise], not only acts as a receptor for SARS CoV2, but also plays a cardiovascular protective role by reducing activity of renin–angiotensin system.

ADAM17 proteinase, on the other hand, is a membrane "sheddase" protease that removes membrane protein ectodomain including that of ACE2 (sACE2).[14] ADAM17 proteinase genes are expressed in the tissues of respiratory and cardiovascular system along with other parts of the body.

TMPRSS2 is another serine protease and a host cell membrane protein suggested being involved in pathogenesis of COVID-19. Vascular ECs, smooth muscle cells, and pericytes coexpress TMPRSS2 abundantly with ACE2. According to several studies, the coexpression of ACE2, TMPRSS2 and furin is utmost necessary for a human cell to be infected by SARS CoV2.[15,16] Accumulated evidences suggest that the virus can invade the ECs in the lungs, heart, kidneys, liver, and intestines of patients with COVID-19 infection. Infection with SARS CoV2 leads to endothelial inflammations throughout the body and it is probably the single most important reason for multiorgan involvement in COVID-19.[17] Macro and microvasculature of lungs, kidney, intestine as well as brain have been evidenced for the presence of endothelitis and viral inclusion bodies in several postmortem studies. Expression studies also demonstrated presence of ACE2 and TMPRSS2 in ECs and vascular pericytes. Of course, there are exceptions to these findings.

Mechanism of viral entry into the host cell

During SARS-CoV-2 infection, the viral spike protein is cleaved into two subunits, S1 and S2, which activates the virus and primes the spike protein for entry into the host cell. This priming is achieved through proteolytic cleavage at two distinct sites: the proprotein convertase furin cleaves the spike protein at the S1/S2 site, while the transmembrane serine protease 2 (TMPRSS2) cleaves it at the S2′ site.[2,6]

S1 subunit of SARS CoV2 has the receptor-binding domain which binds with the ACE2 receptor in its peptidase domain. The S2 subunit, on the other hand, takes part in fusion of the viral particle with host cell membrane.[7,8] In most instances, S2 subunit gets cleaved by TMPRSS2 and exposes the fusion peptide which in turn leads to fusion of virus with host cell. The fusion of viral and host cell membranes facilitate the entry of the virus into the host cell.[9] ADAM17, for its protease activity might play useful role in fusion of virus and host cell membranes and thus facilitating the entry of virus in human cells.

Once SARS-CoV2-ACE2 complex is internalized, there is upregulation of ADAM17. The pathway of this gene upregulation is not properly elucidated yet. However, once ADAM17 upregulation takes place, there is proteolytic cleavage of ACE2 ectodomain leading to generation of sACE2, that is the soluble and biologically active form of ACE2. A soluble ACE2 formed in the cytoplasm would prevent entry of viral particles

into pulmonary and cardiac tissues by blocking them. On the other hand, this proteolytic cleavage of ACE2 might also trigger procoagulant and proinflammatory pathways by downregulation of ACE2 and activation of RAS. At this juncture, role of AngII is very crucial for release of inflammatory mediators and induction of "cytokine storm."[18]

TMPRSS2 is also capable of cleaving ACE2, but at sites that differ from that of ADAM17.[19] As a consequence of TMPRSS2-mediated cleavage, no sACE2 is formed. Therefore, there is no way that TMPRSS2 mediated viral entry would exert any cardioprotective potential.

Another pathway of viral entry into host cells is via endosomal entry pathway.[10] Here, following viral binding with ACE2, the virus–ACE2 complex is internalized into an endosome. The S protein is primed using cathepsin B and cathepsin L instead of TMPRSS2.[10,11] Although this endosomal pathway of entry of SARS CoV2 is explored extensively in vitro, the importance of the same in living organisms is still dubious.

After viral entry into host cells, there is replication of viral genomic RNA. Further amplification of several structural and nonstructural proteins also takes place at the same time. These proteins are then translocated via endoplasmic reticulum and Golgi complex of the host cell and finally they are assembled to form new viral particles and are released from the host cell by the process of exocytosis.[12]

SARS CoV2 infection and endothelial injury

COVID-19 has been evidenced to evoke endotheliopathy and coagulopathy in human. In normal physiological circumstances, vascular endothelium maintains a delicate balance between coagulation and anticoagulation. This balance is essential for the arrest of bleeding in one hand and maintenance of free flow of blood through the healed vessel on the other hand. This vascular homeostasis is maintained by the regulation of inflammatory equilibrium, immune activation, tight junctional barriers, and hemodynamic stability by vascular endothelium. Initially, it was thought that the endothelial insult in COVID-19 was due to direct invasion of ECs by the virus. But, mounting evidences changed the view in recent times. Infection with SARS CoV2 leads to disruption of immune balance, RAAS and balance between thrombotic and fibrinolytic pathway.[14,20] All these deregulated pathways, severely impact macro- and microvascular endothelium in conjugation.

The endothelium acts as a general barrier protecting blood vessels from various insults. However, the infiltration of perivascular immune cells can disrupt this natural barrier function. This is supported by multiple studies and observed findings. In a study by D'agnillo et al. (2020)[21] alveolar capillary barrier was found to be disrupted as evidenced by discontinuous immunoreactivity of components of endothelial tight junctions and endothelial basement membrane. Another study records a three case series of compromised blood–brain barrier as evidenced by fibrinogen leakage into brain parenchyma.[22] In another study, analysis of cerebrospinal fluid revealed elevated albumin levels suggesting impaired endothelial integrity.[7]

Vascular ECs are influenced by cytokines such as IL-1 and IL-6. These damages are linked to various pathogen-associated molecular patterns. These activated ECs take part in host defense by producing an ambience of localized inflammation. This is achieved by

proinflammatory gene expression and recruiting inflammatory cells to infected tissues. Increased endothelial permeability leads to vascular leaks. Local activation of neutrophils leads to the formation of neutrophil extracellular traps (NETs) by a process called NETosis.[11,23] NETs are decondensed chromatin structures mixed with antimicrobial proteins and released in response to infections.[7] Patients with severe disease in COVID-19 had elevated markers of NET in blood. The increased level of neutrophil–platelet aggregation that has been evidenced in these patients is associated with thrombotic events.[24] Another avenue of EC injury that has been suggested by many authors is activation of Toll-like receptors following viral RNA recognition. As a consequence, there is production of reactive oxygen species and further EC injury.

Interaction of SARS-CoV-2 with ACE2 receptor has been evidenced to evoke NLRP3 inflammasome/IL-1β signaling pathway. Activation of the pathway is associated with subsequent release of IL-1β and other inflammatory cytokines like IL-1Ra, IL-18, and IL-18-binding protein (IL-18BP) which lead to hyperinflammation, inflammatory cell death and diffuse organ damage.[25,26] Several studies have found massive NLRP3 expression along with promotion of procoagulant pathways in exosomes derived from individuals with severe SARS-CoV2 infections.[25] However, the resolution of inflammatory processes relies on active mechanisms driven by lipid mediator (LM) molecules, known as specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins, and maresins.[27,28] These SPMs actively regulate inflammation by reducing proinflammatory cytokines and chemokines and limiting neutrophil influx at infection sites.[29] In SARS-CoV-2 patients, the LM profile has been linked to disease severity, with notable differences in LM derivatives observed between severe and moderate cases. It is speculated that preexisting conditions like diabetes, heart disease, or altered lipid profiles may disrupt LM balance, impairing the ability to resolve inflammation and contributing to severe COVID-19 outcomes.[29]

Activated EC also overexpress plasminogen activator inhibitor-1 which is an important suppressor of endogenous fibrinolysis. Under stressful condition, the endothelium also promotes release of tissue factors and von Willebrand factor (vWF). Both of them happen to have prothrombotic actions. There is also decreased activity of thrombomodulin and plasmiogen activator.[30] The culmination of all these factors leads to generation of a hypercoagulable state and production of intravascular thrombi in case of uninterrupted severe disease. These thrombi have been evidenced to be formed both in large vessels as well as microvasculatures of different organs resulting in pan-vascular involvement in COVID-19. Thrombotic complications, particularly pulmonary thrombosis, are key contributors to severe COVID-19 pathology and mortality. Pulmonary thrombi play a role in early ARDS-related hypoxemia and may account for up to 10% of COVID-19 deaths.[31] A meta-analysis reported venous thromboembolism incidence as 28% in ICU patients and 10% in non-ICU settings.[32] While less common, arterial events like stroke and myocardial infarction have also been observed. Autopsy studies frequently note increased pulmonary arterial thrombi in COVID-19 patients.[33]

Studies on COVID-19, conducted all over the world, observed deregulated blood levels of fibrinogen, fibrin degradation products, D-dimer, and vWF indicating tendency toward thrombotic episodes.[34] These prothombotic events in SARS-CoV2 infection might explain the episodes of myocardial ischemia, myocarditis and venous

thromboembolism in seriously ill patients or in patients not treated with prophylactic or therapeutic doses of anticoagulants. A number of articles reported myocardial infarction occurring in COVID-19 patients without any evidence of ruptured atherosclerotic plaque in angiography or left ventricular dysfunction in electrocardiogram.[35] Some patients developed these cardiac symptoms even after recovery and being discharged from hospitals. Coronary microvascular thrombi generation is considered to be the main culprit behind these complications of COVID-19. Evidences of significant numbers of large-vessel strokes and pulmonary embolisms further reinforces the fact that SARS-COV2 infection is complicated with a disruption of natural prothrombotic and fibrinolytic balance. Further, pregnant women with severe COVID-19 disease presented symptoms like HELLP syndrome which comprised of hemolysis, elevated liver enzymes, and low platelet count. Different studies conducted, have established the fact that syndromes like HELLP and preeclampsia are associated with significant vascular dysfunction at the core.[36] So, these findings also support the theory of pan-vascular dysfunction in SARS-CoV2 infection.[37]

Another avenue of vascular endothelial tissue damage by SARS-CoV2 infection is via activation of the RAAS axis. Normally, ACE2 plays key role in maintaining vascular homeostasis in body by exerting antiinflammatory, antioxidant, and antifibrotic effects. Accumulated evidences suggest that SARS-CoV2 inhibit the expression of ACE2 in the infected subjects.[11,14] It is achieved by excess cleavage of ACE2 by a specialized proteinase A—disintegrin and metalloproteinase-17 (ADAM17). As a result, the protein is shed from the EC surface and the protective function of ACE2 is lost. Increased amount of circulating angiotensin II have also been reported in studies. This downregulation of ACE2 and resultant increase in angiotensin II concentration, together, lead to vascular dysfunction via nitric oxide mediated oxidative stress.

SARS-CoV2 infection and myocardial injury

Heart, especially the myocardium and the endothelium, was one of the most affected organs during SARS-CoV2 infection. The incidence of cardiac involvement has been evidenced to be around 46.3%.[38] Organic heart damage in COVID-19 is being implicated as one of the major factor leading to adverse disease outcome.

Cardiac insult in COVID-19 takes place via direct and indirect pathways.[38] Studies involving postmortem cardiac tissues and in vitro studies observed presence of SARS-CoV2 inside myocardial cells. Direct invasion of virus particles into cardiac cells occurs via ACE2 receptors as well as cathepsin mediated endocytosis. Invasion of cells with virus is soon followed by infiltration of immune cell like, lymphocytes and macrophages into the cardiac tissue. The apoptosis and pyroptosis imparted by host immune system is the major cause of direct cardiac tissue damage in COVID-19.[39] Inflammatory cytokines as a consequence of "cytokine storm" also contribute immensely in cardiac tissue injury and myocardial dysfunction. Indirect pathways of cardiac tissue injury include increased myocardial oxygen demand, dysfunction of left ventricular pumping action and thrombogenic changes in vasculature. Myocardial oxygen demand is increased in tachycardia and hypotension owing to COVID-19-induced sepsis and hypoxemia. Derangement of ventricular pumping might

lead to arrythmogenic complications in SARS-CoV2 infection. Acute atherothrombosis and formation of microthrombi have been evidenced to be leading causes of acute myocardial infarction during infection and in post COVID phase as well.[40] Moreover nonjudicial usage of potentially "QT prolonging" drugs as well as drug–drug interactions are of no slouch when it comes to cardiac insults in COVID-19. As suggested by several authors, another potential pathway of myocardial injury in SARS-CoV2 infection is high level of physiological and psychological stress. Takotsubo syndrome, a stress-induced cardiomyopathy, has been evidenced to be associated with high circulating catecholamines in acute phase of the infection.[41]

Biomarkers of endothelial damage in SARS-CoV2 infection

D-dimer

It is a fibrin degradation product, was probably the most important biomarker of endothelial insults in SARS-CoV2 infections. Seriously ill and hospitalized COVID-19 patients have been observed to have elevated D-dimer levels in their blood.[42] As a result, D-dimer tests have become one of the most frequently requested laboratory tests during the COVID-19 era.

However, it is important to note that elevated D-dimer levels do not always indicate thrombosis; they can also be a sign of inflammation, which is a very common finding in COVID-19.[43] Thus, while high D-dimer levels in COVID-19 patients often warrant further investigation for potential thrombotic complications, they should also be considered a marker of the extensive inflammatory processes and endothelial damage caused by the virus. This understanding underscores the complexity of COVID-19 and the importance of comprehensive clinical evaluation in managing affected patients.

vWF and ADAMTS13 (a protein that cleaves ultralarge multimers of vWF)

COVID-19 has brought attention to various biomarkers and mechanisms involved in the disease's pathophysiology, particularly concerning endothelial damage. Two critical factors in this context are vWF and ADAMTS13. vWF and ADAMTS13, both expressed by ECs, become dysregulated during acute hyperinflammation. This leads to excess VWF release and reduced ADAMTS13 activity, contributing to a prothrombotic state.

These two are noted to be altered in blood of COVID-19 patients indicating a procoagulant milieu.[44] Earlier studies also observed accentuated ratio of vWF to ADAMTS13 in patients with fatal adverse outcome.[45,46]

Angiopoietin 2

It is a surrogate marker of endothelial activation, is observed to be deregulated in COVID-19 patients and has been reported to be correlated with disease severity by many authors. This factor is known to act as a vessel destabilizing agent that might be responsible for adverse circulatory outcome of the disease.[30]

Perivascular immune cell infiltrates

Evidence of endothelial inflammation is further supported by findings of perivascular immune cell infiltrates in the lungs of COVID-19 patients.[47] Additionally, cell adhesion molecules like P-selectin and E-selectin have been associated with severe disease in SARS-CoV-2 infection, indicating Type-2 endothelial activation. This form of activation is characterized by increased leukocyte adhesion and vascular inflammation, contributing to the pathogenesis of severe COVID-19.[30]

Glycocalyx degradation and enzymatic activity

Severe COVID-19 cases have also shown elevated levels of circulating glycocalyx degradation products, including syndecan-1, chondroitin sulfate, and hyaluronic acid. Correspondingly, the activity of glycocalyx-modifying enzymes such as heparinase and hyaluronidase is increased, which further damages the endothelial barrier and exacerbates vascular inflammation.[48]

Postmortem evidence of vascular involvement

Direct evidence of vascular involvement in COVID-19 has been observed in several postmortem studies. Notably, narrowing of the pulmonary arterial lumen due to vascular smooth muscle cell hypertrophy has been reported in patients who succumbed to SARS-CoV-2 infection. Such vascular pathologies have not been documented in cases of infections with other influenza viruses, such as influenza A/H1N1/2009.[7,47,49]

EC detachment and long COVID

Free ECs detached from the vascular endothelium have been detected in the circulation of COVID-19 patients, with a reported correlation to adverse disease outcomes.[17] This EC detachment also exposes sub-endothelial collagen to circulating vWF, creating a prothrombotic environment. Remarkably, these detached cells have also been found during the convalescent period, suggesting a potential role for ongoing vascular inflammation in the development of "long COVID" syndrome.[50]

Imaging techniques for identifying and localizing vascular pathologies

In addition to blood biochemical markers like D-dimer, advanced imaging techniques have emerged that can precisely identify and localize vascular pathologies involved in COVID-19. These imaging modalities hold promise as efficient screening tools for identifying high-risk patients, allowing for timely and appropriate therapeutic interventions.

Compression ultrasonography

It has been reported to be the first-line imaging test in diagnosis and treatment of COVID 19 patients complicated with venous thrombosis (DVT). Compression ultrasonography (CUS) is being preached as a powerful ultrasound biomarker by many authors worldwide.[51] In patients who are symptomatic for DVT (presenting with rapidly deteriorating disproportionate hypoxemia or acute onset of unexplained right ventricular dysfunction), the suspected vessel is compressed real time with ultrasound probe looking for compressibility of the vessel. A normally collapsing vessel is negative for DVT. On the other hand, a vessel not demonstrating collapse on compression, suggests underlying venous thrombosis.

Repeated CUS

It has also been prescribed to be useful in monitoring the progress of a distal DVT into a more proximal vein. Typically, repeated CUS is performed 5 to 7 days after an initial negative ultrasound in patients with a high pretest probability of DVT.[52] It reduces the risk of false negatives and provides a more definitive diagnosis without exposing patients to ionizing radiation, which is particularly beneficial compared to other imaging modalities like CT venography.

Contrast enhanced ultrasound of lungs

It is being considered as a diagnostic tool for identifying areas of consolidation due to pulmonary embolism.[53] It is an advanced imaging technique that enhances the capabilities of traditional lung ultrasound by using microbubble contrast agents. These agents improve the visualization of blood flow and tissue vascularity, making it particularly useful for assessing various pulmonary conditions.

From acute COVID-19 to post-COVID syndrome: Implications and insights

Acute COVID-19 disease can have significant implications for the development of post-COVID syndrome, also known as long COVID.[54] The intense immune response triggered during the acute phase, including cytokine storms and widespread inflammation, can lead to prolonged tissue damage and immune dysregulation. This sustained inflammation can affect multiple organ systems, including the lungs, heart, brain, and vascular system, contributing to chronic symptoms that persist long after the initial infection has cleared.[55] Patients who experienced severe or critical COVID-19 are at higher risk of developing post-COVID syndrome, with symptoms such as fatigue, shortness of breath, cognitive impairments, and cardiovascular issues. Additionally, endothelial dysfunction, thrombosis, and persistent immune activation during acute illness can perpetuate a cycle of inflammation and tissue repair imbalance, prolonging recovery, and impacting quality of life.[56] Understanding these implications underscores the importance of early management strategies aimed at reducing the acute inflammatory response and protecting organ function to potentially minimize the risk of long-term complications.

Role of therapeutic agents in COVID-19-induced vascular pathology

The different mechanisms, by which SARS-CoV2 exerts vascular damage and produce disseminated disease, have been proposed as potential target pathways for therapeutic agents by investigators from all over the world. Since the detection of the infection, several agents have been tried including repurposed drugs as well as novel agents.

Immunomodulatory therapy

So far, it has been proved to be very efficient in checking flare up of host reaction and subsequent cytokine storm. Along-side oral and injectable corticosteroids, several new regimens are also being investigated. Examples of such agents are antagonists of NLRP3 inflammasome and IL-1, IL-6 like-Tocilizumab, Anakinra, etc.[57]

Antithrombotic medications and anticoagulation therapy

Both of these therapies have also been reported to be very effective in mitigating thrombotic complications in COVID-19 patients either by inhibiting endothelial inflammations as well as suppressing the enzymatic activation of coagulation factors. Antithrombotic drugs like aspirin, dipyridamole, and P2Y12 (ADP receptor on platelet) receptor inhibitors as well as anticoagulants such as heparin, direct thrombin inhibitors and oral anticoagulants, all are being tried in various parts of the world.[58] Further, the occurrence of arterial thrombosis in COVID-19 (SARS-CoV-2 Omicron variant) patients requiring artificial lung ventilation is a significant predictor of high mortality risk. For patients receiving nasal cannula oxygen supplementation or noninvasive lung ventilation, open thrombectomy combined with anticoagulant and antiplatelet therapy has proven to be the most effective treatment approach.[59]

Although prophylactic dose of anticoagulation therapy is beneficial in COVID-19 administration of therapeutic dose have been reported to cause hemorrhagic complications and increased mortality. Moreover, selection of agent, determination of dose and duration of the therapy should be guided by regular estimation of blood biomarkers like fibrinogen, FDP, D-dimer, and CRP as of course the coagulation profile.

RAAS system inhibitors

RAAS system inhibitors, such as ACE inhibitors (ACEi) and angiotensin receptor blockers, are recommended for COVID-19 patients with cardiovascular conditions like hypertension. While these drugs have not demonstrated a clear benefit in these patients, they have also not been shown to increase morbidity.[60,61]

Statins

Statins are beneficial in SARS-CoV-2 infection primarily due to their antiinflammatory and immunomodulatory effects on the vascular endothelium rather than their

lipid-lowering properties. COVID-19 often causes endothelial inflammation, a cytokine storm, and thromboembolic events, all of which contribute to severe complications like ARDS and multiorgan failure.[62] Statins help stabilize the endothelium by reducing proinflammatory cytokines and adhesion molecules, modulating immune responses, and inhibiting key inflammatory pathways such as NF-kB and the NLRP3 inflammasome.[63] They also have antithrombotic effects that reduce the risk of thromboembolism by improving endothelial function and decreasing platelet aggregation. Observational studies have suggested that statin use in COVID-19 patients is associated with lower mortality and better clinical outcomes, highlighting their potential as adjunct therapy due to their pleiotropic effects beyond lipid lowering, especially in patients with cardiovascular risk factors.[64]

Anti-VEGF drugs and/or immune-checkpoint blockers

Munn et al. (2021)[65] suggest that androgen deprivation therapy (ADT) may offer benefits beyond reducing TMPRSS2-mediated viral entry into cells. ADT could help restore endothelial barrier function, thereby reducing the risk of thrombosis, a key complication in severe COVID-19. Additionally, early-stage treatment with anti-VEGF drugs or immune-checkpoint blockers may normalize vascular function by mitigating viral-induced endothelial damage. This normalization not only supports vascular repair but also helps prevent thrombosis. These therapies hold promise for dual benefits—modifying the disease's progression while addressing its vascular complications, potentially improving outcomes in COVID-19 patients.

Specialized pro-resolving mediators

Reducing the overall inflammatory drive in COVID-19 patients, particularly in the early stages before the disease progresses to severe or critical phases, has the potential to significantly alter the disease's trajectory.[66] Early intervention to modulate inflammation could prevent the escalation of immune responses, such as cytokine storms, which are often responsible for severe complications. By controlling inflammation early, it may be possible to minimize tissue damage, improve patient outcomes, and reduce the likelihood of long-term sequelae associated with severe COVID-19.[11]

A recent study by Gracia Aznar et al. (2024)[29] highlighted the potential therapeutic benefits of a 12-week supplementation with marine oil enriched in SPMs for managing severe COVID-19. SPMs were shown to support the pro-resolutive axis of inflammation, potentially preventing the cytokine storm that characterizes severe disease manifestations. This intervention not only addresses acute inflammation but also offers benefits for chronic conditions involving persistent heart and lung tissue inflammation. Furthermore, supplementation with SPMs or their precursor metabolites may enhance recovery outcomes for individuals who have recovered from COVID-19 or have been vaccinated, by mitigating residual or vaccine-related inflammation. The study also emphasized the broader applicability of selective pro-resolving mediators, such as monohydroxylates, which show promise in managing a variety of acute and chronic inflammatory conditions. These findings underline the therapeutic potential of SPMs in regulating immune responses and promoting tissue repair across diverse medical scenarios.

Conclusion

COVID-19 caused by SARS-CoV2 virus is primarily a disease of respiratory machinery, but it insults the surrounding organ systems too. As evidenced so far, these multisystem impacts of SARS-CoV2 infection is immunologically mediated. Sometimes the defense system of host body reacts to the respiratory pathogen in overwhelming manner leading to "cytokine storm" and consequent damage to vascular system all over the body. Gradually, the pan-vasculitis in COVID-19 results in damage to the vital organs and multiorgan failure. This study here is an attempt to review the cardiovascular spectrum of SARS-COV2 infection in human. But, the study has got its own pitfalls. The number of scientific articles (original research article, review article, meta-analysis as well as newspaper reports) consulted is not extensive owing to man power limitation and time constraint. However, studies like this will encourage investigators to undertake more detailed and extensive researches focusing on cardiovascular manifestations of COVID-19. This will not only open new therapeutic avenues but also will enrich the world COVID 19 database. This might bridge also the gap between the research laboratory and clinical settings as well as provide solution to many unanswered questions in the domain of epidemiology.

Author contribution

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