FUTURE PROGNOSIS FOR CARDIOVASCULAR COMPLICATIONS ASSOCIATED WITH SARS-COV-2: A PHARMACOLOGICAL AND MOLECULAR PERSPECTIVE

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19), which is associated with cardiovascular problems and serious lung damage. COVID-19 patients with comorbid conditions are at a significantly elevated risk of increased morbidity and mortality. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) are the two key host contributing factors for the severity and pathogenesis of COVID-19. The principal SARS-CoV-2 entrance receptor, ACE2, is expressed equally in most organs and produces cardio-protective vasodilators by physically degrading angiotensin II, the main controller of the Renin-Angiotensin Aldosterone System. However, treatment for cardiovascular disease (CVD) commonly involves RAAS inhibitors, which may increase ACE2 expression.

Objective: To summarize the pharmacological molecular discoveries into the processes of viral infection and its consequences for cardiovascular disease and to offer suggestions for the practical management and treatment of COVID-19-related cardiovascular injury.

Methods: This review focuses on the important considerations related to the cardiovascular manifestations of COVID-19 and discusses the various mechanisms of COVID-19 that contribute to its molecular and pharmacological presentation of cardiovascular injury. Results: The host-pathogen relationship began with ACE2’s attachment to the S-protein and proceeded with TMPRSS2’s proteolytic cleavage of the viral spike (S)-protein and ACE2. Currently discovered protein-protein interactions explain the uniqueness of SARS-CoV-2 infection. Conclusion: COVID-19 is associated with cardiovascular problems and serious lung damage. ACE2 and TMPRSS2 are key host contributing factors for the severity and pathogenesis of COVID-19. The molecular discoveries into the processes of viral infection and its consequences for cardiovascular disease provide important considerations for the management and treatment of COVID-19-related cardiovascular injury.
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**Conclusion:** COVID-19 is associated with cardiovascular problems and serious lung damage. ACE2 and TMPRSS2 are key host contributing factors for the severity and pathogenesis of COVID-19. The molecular discoveries into the processes of viral infection and its consequences for cardiovascular disease provide important considerations for the management and treatment of COVID-19-related cardiovascular injury.

**KEYWORDS** - COVID-19, SARS-CoV-2, ACE2, TMPRSS2-S, Cardiovascular Disease, Protein-Protein Interactions.

**GRAPHICAL ABSTRACT**

1. **INTRODUCTION**

The Chinese Wuhan area was where the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially surfaced around late 2019. The 2002 SARS epidemic was brought on by a coronavirus known as Severe acute respiratory syndrome CoV-2 (1). On March 11, 2020, the World Health Organization (WHO) proclaimed a pandemic because the sickness spread throughout the globe.

Acute respiratory failure caused by viral pneumonia predominates when severe COVID-19 infection is clinically present, with the possibility of developing into acute respiratory distress syndrome (ARDS) (2). Numerous studies have indicated that patients with pre-existing co-morbidities such as hypertension, diabetes, cancer, Stroke, Asthma, Prolonged Kidney Damage, Chronic Respiratory Distress Syndrome (CKD), and
cardiovascular disorders are more vulnerable to COVID-19 infection and its after effects on account of the Coronavirus 2 has expanded globally (3). Consequently, the main clinical symptoms of COVID-19 include fever, persistent cough, and tiredness. Sometimes patients exhibit symptoms including diarrhea, cancer, a runny nose, and nasal congestion (4). Patients who had a minor illness only had moderate symptoms, such as a low temperature, light exhaustion, and no signs of pneumonia. Patients who are badly afflicted by the illness possibly have a mild or moderate fever, or maybe not have any temperature at all, as the disease progresses (4, 5).

Cardiovascular diseases in general were shown to have a substantial association with death in COVID-19 individuals. But it has been shown that over around 1/3 of those afflicted, notably those who already have an illness of the heart (CV), have a mix of acute cardiac damage, cardiac dysfunction caused by myocarditis, and dysrhythmias (2).

Covid-19 indications:
- Pyrexia
- Cough
- Fatigue
- Muscle ache
- Headache
- Sore throat
- Shortness of breath

2. STRUCTURE OF CORONA VIRUS AND ITS SPIKE RECEPTOR:

SARS-CoV-2 is composed structurally consisting mainly four protein molecules (Fig.-1): the spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein (6). The transmembrane protein known as the spike, or S glycoprotein, has a molecular mass of around 150 kDa and is situated on the outermost surface of the virus. The angiotensin-converting enzyme 2 (ACE2), which is present in cells of the lower respiratory tract, is drawn to the S protein, which produces homotrimers that protrude from the viral membrane and aid in the adherence of envelope viruses to targeted tissues. A furin-like protease that is expressed in the host cell splits this glycoprotein into the S1 and S2 subunits. Part S2 facilitates viral contact in replicating host cells, whereas Part S1 controls cellular tropism and host-virus spectra with the aid of the receptor-binding domain structure (7-9).
The structural component of CoV that is physically linked to the virus's nucleic acid is known as the nucleocapsid, or commonly the N protein. It may be found near the endoplasmic reticulum and Golgi complex. The protein’s association with RNA shows that it participates in the viral genome, viral replication cycle, and host cell biological responses to viral infections (10, 11).

The membrane protein, often known as the M protein, is another essential element of this virus. It is the most structurally complex protein and affects how the virus’s envelope is shaped. All other structural proteins can bind to this protein. Interacting with the M protein assists in the stability of nucleocapsid or N proteins and facilitates the ability for the viral assembly process to be completed by maintaining the N protein-RNA complex within the intracellular virion. The last element of the SARS-CoV structure is the envelope or E protein which is crucial for the growth and maturity of the virus. It is the smallest protein (12).

3. PATHOPHYSIOLOGICAL LOOK AT THE CARDIOVASCULAR SYSTEM:

There was evidence of degeneration and necrosis in the myocardial cells, and the stroma included a small number of mononuclear cells, lymphocytes, and/or neutrophils. There was some exfoliation of the vascular endothelium, as well as inflammation and thrombosis of the intima. According to certain reports, patients diagnosed with congenital cardiac disease may be regarded to be at a greater risk for problems due to COVID-19 (4, 13). A lot of organs, including the heart, kidneys, gut, lung, brain, and liver, express soluble and cell-associated Angiotensin Converting Enzyme (ACE) 2 receptors (14, 15).

SARS-CoV-2 enters cells via ACE2 receptors and suppresses the production of the enzyme, preventing it from having an organ-protective impact (16). Patients taking ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) have been shown to up-regulate the number of ACE2 receptors on the surface of the myocardium, have a tendency to have lower levels of interleukin-6 (IL-6), have increased CD3 and CD8 T cell counts in the peripheral blood, and have lower peak viral loads (17). As a result, ACEI and ARB medications may be protective in low-level viremia; additionally, studies of losartan on COVID-19 patients are currently being conducted (16, 18-20).

Increasing levels of inflammatory markers such as C-reactive protein, D-dimer, ferritin, IL-6, and lactate dehydrogenase (LDH) have been associated with higher mortality in COVID-19 patients, possibly as a result of cytokine storm or secondary hemophagocytic lymphohistiocytosis. This may be because COVID-19 patients are more likely to develop secondary hemophagocytic (7, 21-24). SARS-CoV-2 has the potential to activate the coagulation cascade, which may result in thrombocytopenia and even severe hypercoagulability, in addition to the sequelae of these conditions, such as ischemia of the fingers and toes (25-27).

3.2 MECHANISM(129)

Mechanism related between CVD and COVID-19, There are several ways in which SARS-CoV-2 interacts with the cardiovascular system. Mainly SARS-CoV-2 adverse outcomes are arrhythmia, cardiomyocyte injury, platelet activation, myocardial fibrosis, atherosclerosis these overall adverse outcome that leads to CVD, few examples are below.

ARRHYTHMIA

Arrhythmia causes by insulin resistance, due to upregulation of RE1 silencing transcription(REST). In several studies shows that COVID-19 can induce that leads to insulin resistance, which related to CVD.

IRON HOMEOSTASIS

An imbalance in intracellular iron accumulation and iron homeostasis brought on by SARS-CoV-2 infection can result in a reduction in the body’s ability to store iron which leads to the ROS production to causes increased oxidative stress and cell damage in cardiomyocytes.

(A significant theoretical foundation for risk assessment and the prognosis of infected patients is provided by the aforementioned study, which also serves as a valuable resource for investigating the mechanism of
interaction between COVID-19 and metabolic diseases.)

LONG IMPACT OF COVID-19

Long impact of COVID-19 that leads to various impairment to patients like chest pain, palpitation, tachycardia, atrial fibrillation, dyspnoea, cough, dysautonomia, postural tachycardia syndrome, orthostatic intolerance, inappropriate sinus, tachycardia. Some main cardiac complications in patients with long COVID are chronic myocarditis, chronic pericarditis, myocardial oedema, myocardial fibrosis or scar, coronary artery disease, and some other newly diagnosed cardiovascular complications are hypertension, diabetes mellitus, stroke venous thromboembolism(130).

4. CARDIOVASCULAR BIOMARKERS RELATED TO SARS-CoV-2.

4.1 Troponin

In certain individuals, an elevated high-sensitivity cardiac troponin I (cTnI) level is the first sign of myocardial damage that may be associated with a COVID-19 infection (7). This conclusion was reached after research was conducted. Patients who were treated in the intensive care unit were more likely to develop cardiac complications and ACCEPTED MANUSCRIPT exhibited an elevation in high-sensitivity TnI levels (5). It was reported that 10 of 138 patients with COVID-19 (7.2% of all patients) had an acute myocardial injury while they were infected with the virus, and those patients were more likely to develop an acute myocardial injury (28). Last but not least, it has been demonstrated that individuals with severe COVID-19 illnesses have significantly greater cTnI concentrations than those with just a moderate form of the sickness (29). The most recent study indicates that 11.8% of dead COVID-19 patients who did not have a history of CVD before hospitalization sustained significant heart damage. This was accompanied by a higher level of cTnI or cardiac arrest while they were being treated in the hospital (28).

4.2 Cytokine storm

When acute heart and lung damage were identified in COVID-19 patients, there was often an overproduction of inflammatory cytokines and chemokines. Further research is necessary to fully understand the possible molecular connections between cardiovascular disorders and COVID-19 effects, as well as the potential significance of the cytokine crisis in the genesis of cardiovascular difficulties after SARS-CoV-2 infection (4). The severity of COVID-19, which may vary from moderate to severe and cause many organs failure, is brought on by the progression of the disease, cardiac impairment, T-helper 1 and T-helper 2 cell abnormalities, also known as cytokine storms. The negative and positive feedback regulation of this system is heightened in the setting of a severe infection brought on by SARS-CoV-2 infection, and the immune regulatory network becomes unbalanced. As a result, levels of various cytokines rise dramatically, and immunological responses are amplified. The effects of the cytokine storm can also affect pulmonary capillary endothelial cells and alveolar epithelial cells, aggravating diffuse damage and resulting in increased lung exudation and low microcirculatory resistance. In addition to acting on vascular endothelial cells to produce platelet aggregation factor, prostaglandins, and leukotrienes that harm the arterial intima. Myocardial ischemia, hypoxia, and necrosis are the ultimate outcomes (30, 31).

4.3 D-dimer

There have been reports of very high levels of circulating endothelial activation indicators (32). Additionally, there is a clear indication of Thromboembolism, with high D-dimers being most conspicuously raised in patients with advanced illness (5, 7, 33-35). When a thrombus is broken down by fibrinolysis, a residue called a D-dimer is left behind. A poorer clinical outcome is also predicted by D-dimer levels upon hospital admission (36, 37). D-dimers are sometimes referred to as powerful acute-phase reactants, even though they are thrombosis biomarkers (38). High D-dimer concentrations continue to stay in these people despite the fact that inflammatory markers like IL-6 have already decreased in advanced COVID-19 patients, demonstrating the fact that their increase is not only a consequence of systemic inflammation (36).

4.4 IL6 and TNF alpha
Compared to the pangolin strain, SARS-CoV-2 is more closely linked to the SARS-CoV strain identified in bats. On the basis of the data we have gathered, we also believe that the human SARS-CoV-2 strain is a naturally evolving variation of the bat SARS-CoV virus. IL-6 and TNF-α, proinflammatory cytokines having human and bat phylogenetic affinities. It is intriguing that these cytokines and the ACE2 corresponding receptor for spike protein share characteristics (39). We chose to investigate the role that TLRs perform in this specific research endeavor since these two cytokines are the byproducts of the TLR signalling pathway. It seems logical to ask how the TLR-3, 7, 8, and 9 receptors work given that SARS-CoV2 is an RNA virus. The link that exists between the SARS-CoV-2 spike protein and the immune cells identified in human alveoli, nevertheless, suggests that perhaps the immunopathological consequences are most probably mediated at the location of the host-virus interface (40). As a result, we investigated the possibility that the surface TLRs that are found on human cells may play a role, in addition, TLRs and the SARS-CoV spike protein interact. Our findings indicate that TLR4 has a strong affinity for spike protein, ranking third after TLR1 and TLR6, and with a binding affinity that is comparable to other receptors. The innate immune system’s TLR4 is its most effective receptor and it is responsible for inducing proinflammatory responses once it has bound with the pathogenic ligand (41). As a result, the immunopathological presentation of COVID-19 may be caused, at least in part, due to TLR4’s association with spike protein. The discovery of drugs that target the same receptor or the use of TLR4 antagonists as corona therapies may both benefit from this connection. We can make informed predictions regarding the nature of these interactions since we used the natural versions of spike proteins and TLRs. However, a real protein-protein interaction investigation utilising surface plasmon resonance might be able to determine the binding constant and intensity. TLR 3, 5, and 6 have all shown positive energy values, indicating a complex interaction that requires more study. This discovery has caught our attention (42).

4.5 ACE2

In the year 2000, an ACE homolog with the name ACE2 was discovered. The fact that the catalytic domains of ACE2 and ACE are 42 percent similar suggests that they originated from the same gene (43). The enzymatic domain of ACE2, which is a type I transmembrane metallopeptidase, is located on the outside surface of the cells (43-46). It may act as a counterpart to ACE since it is involved in the control of heart activity and control of systolic pressure (47). By altering the endogenous amounts of angiotensin I and angiotensin II, ACE2 controls the RAS (44). It breaks down a single angiotensin I residue to produce angiotensin (1–9) and a single angiotensin II residue to produce angiotensin (1–7). ACE may also convert angiotensin (1-9) into angiotensin (1-7). Angiotensin’ (1–7) that bind to the MAS receptor change the balance from angiotensin II’s vasoconstriction to vasodilation, resulting in anti-inflammatory and anti-fibrotic actions, increased no production, and vasodilation (14). Angiotensin II levels rise and cardiac contractility is hampered by ACE2 inactivation (44, 48). Numerous cardiovascular advantages of ACE2 have been reported, involving vasodilation, anti-oxidation, anti-fibrosis, and anti-inflammation (49). This is corroborated by research showing that the loss of ACE2 resulted in Angiotensin II accumulation and impaired cardiac contractile function (50).

A dysfunction of ACE2 is a contributor to inappropriate activation of the RAS as well as systemic endotheliitis, both of which may have a connection to abnormal coagulation and sepsis. In addition, defective coagulation is associated with both the innate immune response and the activation of the inflammatory response. In patients with COVID-19, a significant possibility of really serious illness and mortality is associated with dysfunctional coagulation, which is one of the primary risk factors responsible for this risk (4).

5. COVID WITH ACE2

5.1 Relationship between coronavirus type 2 that causes severe acute respiratory syndrome and the renin-angiotensin-aldosterone system (SARS-CoV-2):

ACE is responsible for the metabolic process that converts angiotensin I into angiotensin II, which primarily binds to AT1R to activate the receptor and cause lung damage. ACE2 can metabolize Ang II, which results in the production of Ang 1–7, and convert Ang I into Ang 1–9, respectively. Ang 1–9 undergoes additional
metabolic processes to produce Ang 1–7 (51). Through its interaction with the receptor MasR, Ang 1–7 contributes to the prevention against pulmonary infection results in lung damage. Additionally, AT2R has a positive impact (52-55). The extracellular domain of surface ACE2 must be cut by ADAM17 (in its capacity as a "sheddase," which leads to the formation of sACE2 and a decrease in the expression of ACE2 that is present on the surface of ACE2). For SARS-CoV-2, recombinant sACE2 may be administered as a treatment. SARS-CoV-2 enters human cells via adhering to its S-protein, and the RBD of the S-protein is also responsible for this (56, 57). The second phase of the procedure, TMPRSS2’s processing of the S-protein, leads to this. After the viral combination is endocytosed, surface ACE2 is further down-regulated, which causes an accumulation of unopposed Ang II. It is possible that viral assaults might cause local renin-angiotensin-aldosterone system activation, which then regulates lung damage responses (56). The virus replicates itself within the cell, which may result in pneumonia and cause inflammatory cytokine storms, all of which might potentially add to the damage sustained by other organs. ACE and ACE2 are enzymes that transform angiotensinogen and angiotensin, respectively (58).

5.2. The function of ACE2 as a COVID-19 treatment candidate:

The effects of SARS-CoV-2 infection alone put the body under a tremendous amount of stress. Given the prevalence of pre-existing conditions among patients and the weakened immune systems of the elderly (25, 59, 60), the severity and possible fatality of a SARS-CoV-2 infection become abundantly obvious. Patients with CVD are often treated with RAAS inhibitors, such as ACE-I and ARBs. The cardiovascular system may be a target organ for cardiovascular SARS-CoV-2 (61, 62). The signalling pathway connected to ACE2 may be crucial in myocardial damage. By suppressing the expression of ACE2, SARS-CoV-2 may influence the control of the (RAS) system, causing or exacerbating cardiac injury (63, 64). The important crucial systems for controlling bodily fluids are RAS. It can control blood pressure, electrolytic balance and maintain homeostasis, all of which play crucial roles in controlling cardiovascular functions. When conditions are physiological, the ACE angiotensin II and ACE2 ANG (1–7) axis maintain dynamic balance. However, expression of ACE2 is downregulated in COVID-19 patients, which lowers Ang (1-7) levels and weakens the impact on alveolar epithelial cells’ ability to combat inflammation, proliferation, fibrosis, and apoptosis as well as the lowering of blood pressure. The aberrant elevation of Angiotensin II levels worsens vasoconstriction, blood pressure, inflammatory responses, cell death, and the spread of pathogens, leading to either the development of new heart injury or the escalation of pre-existing chronic cardiovascular disease (65).

Regarding the recommended course of action for this mechanism, preventing and ameliorating cardiac injury requires preventing the harm done by SARS-CoV-2 to cardiac myocytes and their surrounding environment (4). It is believed that these regions are the major targets for preventing viral entry due to the fact that viral spindles connect to ACE2 via their receptor binding domain. Because ACE2 is represented in a wide range of organs, including vascular endothelium and cardiac tissue, there are a few hypotheses that suggest ACE inhibitors and angiotensin receptor 1 blockers may influence the progression of COVID-19. New vaccinations are a prominent issue in COVID-19 control as well (66).

6. TMPRSS2 WITH COVID

6.1. Mechanism of viral entrance into human cells by SARS-CoV-2:

The spike protein appears as trimers on the corona virus particle’s surface. The S1 and S2 domains are present in each S-protein monomer. The S1 domain interacts with ACE2 receptors, while the S2 domain causes membrane fusion, allowing the viral particle to enter the cell more easily. ACE2 receptors serve as the entrance route for SARS-CoV-2 in human cells. The interaction with ACE2 receptors is mediated by RBD of the S1 domain. The research conducted in-vitro revealed that SARS-CoV-2 was not able to infect Vero E6 and Hela cells that were ACE2 null, indicating a crucial function for this receptor allows the entry of virus inside cells (67). The membrane-bound serine protease TMPRSS2 plays a crucial role in the COVID-19 infectious disease. It is necessary for cleaving ACE2 and S-protein in order to allow viral introduction via merging of the membrane figure in addition to ACE2 and TMPRSS2, coronaviruses also use DPP4 and furin
for MERS-CoV, ANPEP for HCoV-299E, TMPRSS11D for SARS-Co (68-70). The bulk of the remaining positions in the S-protein of SARS-CoV-2 are also conserved, and the virus shares 80% of its sequence with SARS-CoV. The SARS-CoV-2 residue between Leu335 and Phe515 in RBD is the same as the SARS-CoV residue between Leu322 and Phe501, with the difference that Val483 was inserted into the SARS-CoV-2 residue. The amino acid residues of the SARS-CoV have been italicised throughout the text for the purpose of increasing readability. This region contains the SARS-CoV-2 receptor binding motif (RBM) in addition to the three ACE2 interaction regions known as CR1, CR2, and CR3, which are denoted by their respective acronyms (71, 72).

6.2. TMPRSS2 encourages S-protein priming:

Human ACE2 and viral S-protein are the only two proteins that TMPRSS2 interacts outer surface of type II pneumocytes, TMPRSS2 colocalized with ACE2 according to immunofluorescence tests (73).

TMPRSS2 belongs to the serine protease family. The encoded protein has many different functional domains, including the type II transmembrane domain (N-termini), receptor class-A domain, scavenger receptor cysteine-rich domain, and a protease domain. Specific interactions between TMPRSS2 and human ACE2 and viral S-protein have been observed. On the surface of type II pneumocytes, immunofluorescence investigations revealed that TMPRSS2 colocalized with ACE2 (73). The serine protease family includes the TMPRSS2 protein. The type II transmembrane domain (N-termini), receptor class-A domain, scavenger receptor cysteine-rich domain, and protease domain are all present in the encoded protein. The S1-ACE2 complex undergoes conformational changes as a consequence of TMPRSS2 cleaving the trans-membrane C-terminal region of ACE2 (residues 697 to 716) to enable S-protein-increases viral entry (73).

The ACE2 remnant described above overlaps with the ACE2 symmetric dimerization interface, which is coupled to and shielded by B0AT1 from the outside, to form an ACE2-BAT1 hetero-tetramer. Therefore, this hetero-tetramer may be able to prevent TMPRSS2 from accessing the ACE2 cleave site and therefore prevent the spread of covid-19 virus (74).

It’s noteworthy to note that only the kidney and gut co-expressed ACE2 and B0AT1 (75). It has been shown that the S1-S2 condensation site/fusion peptide has many arginine-rich regions where S-protein may be cleaved by TMPRSS2, which is required for SARS-CoV-2 entry into the human cell (76-79). (Arg667 and Arg797) S proteolytic priming refers to the cleavage of such S1-S2 fusion proteins. The S1 domain is released extracellularly as a result of this “priming” on the S2 domain, which creates a mature peptide (S2’) for the fusing of membranes (74, 80, 81). A decrease in pH results in hindering the fusion of membrane that the S2 domain was demonstrated to facilitate because that is dependent on pH (82). On the other hand, when the SARS-CoVs spike (S1) protein binds to ACE2, it triggers an endosomal entrance of the viral particle when membrane proteases are not present (like TMPRSS2). CatL, a cysteine protease, then inside the endosomal vesicle, cleaves the S-protein (81). TMPRSS2 produces S1 fragments that bind to and immobilise neutralising antibodies by cleavage of S1 off the surface of the infected cell (83). Several crucial amino acid residues of TMPRSS2 and S-protein that engage were discovered by in silico molecular docking tests. The S-protein binds with TMPRSS2, in addition to several other residues, and is crucial in ensuring the stability of binding (79, 84-86). Trp64, Thr95, Ala262, Lys187, Arg214, Gly261, Asp215, His66, and Leu are a few of these residues.

6.3. Virus replication and dissemination:

After the release of virion of the RNA genome within the cell, structural and non-structural proteins (NSPs) begin to be translated. The major proteases (Mpro) cleave the pp1a and pp1b polyproteins produced by the translation of ORF1a and ORF1ab to create 16 distinct Nsp proteins (72). An RNA-dependent RNA polymerase (RdRp) uses a positive single-strand RNA as a template to duplicate its genome, producing a complementary RNA strand that joins forces with the template strand to create a dimer. The newly created positive sense genome uses the generated dsRNA as a template to create an independent infectious ssRNA genome (87). Assembly and budding into the endoplasmic reticulum Golgi intermediate compartment occur next (ERGIC). The infected cell subsequently releases virions through exocytosis to further stimulate the
host immune system (88).

7. MANIFESTATION OF CARDIOVASCULAR IN COVID-19

7.1. Myocardial injury:

Cardiac dysfunction is not a common COVID-19 adverse effect. A significant proportion of those infected has had myocardial harm, even though this is not the first time a corona virus has been linked to cardiac issues. Heart failure, arrhythmias, and sudden death from myocardial damage were all caused by systolic and diastolic dysfunction in SARS patients (89, 90). Numerous measures, including high NT-proBNP, increased cTnI, and elevated hs-CRP, markers of cardiac injury and inflammation, were significantly associated with severe illness and critical illness. The non-ischemic condition known as an acute coronary syndrome (ACS: plaque rupture [Type I] or an imbalance between consumption and availability of oxygen may both result in myocardial damage. [Type II]) (i.e., myocarditis, myocardicarditis), both alone or in combination. Troponemia is a common complication of serious illness, especially sepsis, and ARDS, and it shares many pathophysiological pathways with cardiac damage brought on by COVID-19 infection, such as Acute coronary events, systemic inflammation, coagulopathy, and altered myocardial supply-demand ratio (91-93). Critical illness risk factors for myocardial injury include, but are not limited to, old age, diabetes mellitus, and prior cardiovascular disease. (DM). The troponin increase in COVID-19 is highly correlated with disease severity and unfavourable clinical outcomes, much like critical illness unrelated to COVID-19 (91). The uniqueness of myocardial damage and troponin leakage in COVID-19 infection is due to the development of acute viral myocarditis as well as direct viral destruction to myocytes. About one-third of the victims of the 2003 SARS epidemic contained viral ribonucleic acid in myocardial specimens collected from their autopsied hearts. Further, evidence that the COVID-19 virus directly damaged the myocardium came from the discovery of (46) COVID-19 viral particles on an endo-myocardial biopsy of a COVID-19 infected individual (94).

7.2. Arrhythmias:

There are many different arrhythmogenic disorders, including palpitations, bradycardia, sinus tachycardia, atrial fibrillation, ventricular fibrillation (VF), ventricular tachycardia (VT), and sudden cardiac death, have been linked to reports of previous outbreaks and the present COVID-19 pandemic (95, 96). These arrhythmogenic problems may be caused by metabolic disturbances, decreased oxygen levels, direct viral myocardial damage, neurohormonal or inflammatory stress, or changes in the anatomical makeup of the heart (chamber dilation and dilated cardiomyopathy) (90, 97, 98). Approximately 50 percent of the total individuals who tested positive for COVID-19 infection had an acute cardiac injury, showing that variables other than myocardial injury directly increase the likelihood of arrhythmia. Median troponin-I levels were within the normal range in the remaining 50% of this cohort (98). The anti-malarial medications chloroquine and hydroxychloroquine (HCQ), which are currently being studied to be used in COVID-19 therapy, ought to be the main topic of discussion on arrhythmias. Chloroquine is known to disrupt the atrioventricular node (AVN) and lengthen the depolarization amplitude and refractory period of Purkinje fibres, particularly when administered for a prolonged amount of time (99). Atrial arrhythmias induced by drugs, ventricular arrhythmias, and AVN blockage are all connected to chloroquine and HCQ. Similar to chloroquine and quinine (95), By blocking the rapid delayed rectifier channel (IKr), HCQ is known to extend the QT interval. It may also lead to polymorphic VT and sudden cardiac death (100, 101).

7.3. Venus Thromboembolism:

Covid effected persons may have a higher risk of the formation of a blood clot in veins. In addition to extended immobility, vascular inflammation, and endothelial damage can involve in the development of a hypercoagulable condition. The International Society on Thrombosis and Haemostasis has established guidelines for disseminated intravascular coagulation (thrombocyte count, prothrombin time, fibrinogen, D-dimer, antithrombin, and protein C action), and These conditions are met by up to 71.4% of COVID-19 infected individuals who pass away as a result of the illness (DIC) (2). Due to the high prevalence of venous thromboembolism (VTE), elevated concentrations of D-dimer, high fibrinogen, microvascular thrombi within the pulmonary circulation, and enhanced frequencies of vascular thromboembolic events, the DIC that is
present in this scenario is predominantly of the prothrombotic kind. With DIC a factor in the majority of fatalities recorded in one study, the incorporation of D-dimer and fibrin/fibrinogen degradation product levels in pharmaceutical treatment may be recommended because it can be principally good indicators of COVID-19 disease progression (37, 102).

7.4. Heart failure and cardiogenic shock:

Between 23% and 49% of COVID-19-infected individuals also had concurrent heart failure (36, 103). Notably, this illness was almost 5 times more common among patients who died in the hospital (51.9% vs. 11.7%), a rise in B-type natriuretic peptides (BNP/NT-proBNP) is associated with a worse prognosis in ARDS patients, much as a rise in troponin (104). Cardiac arrest and cardiogenic shock linked to COVID-19 infection have several root causes and include aggravation of pre-existing oxygen deprivation, a hyperadrenergic state, new cardiomyopathy (induced by inflammation of the myocardium or stress cardiomyopathy), and greater metabolic needs (91). Consideration should also be given to right-heart failure and related pulmonary HTN, especially in cases of severe parenchymal lung illness, ARDS, or perhaps pulmonary embolism, when right ventricular (RV) dysfunction is frequent (between 25% and 50%) (105, 106). Cardiogenic shock may be caused solely by the heart or by a combination of the heart and lungs. The Berlin parameters may be extended to the onset of symptoms, imaging with bilateral pulmonary opacities, and the absence of fluid overload to distinguish cardiogenic shock from shock with a mixed aetiology. These factors are taken into consideration. Healthcare choices may be supported by BNP (107), echocardiography, and pulmonary artery catheterization given the variety of treatments available for ARDS and cardiogenic shock (for measuring filling pressure, mixed venous oxygenation, and cardiac output) (108).

8. POTENTIAL TREATMENTS AND THEIR IMPLICATIONS

Several medicines for Covid 19 infection are shown in Table 1. Covid 19 has 80% genetic similarity with SARS-CoV (109, 110), demonstrating beyond a reasonable doubt that it is a member of the same family of coronaviruses as SARS-CoV and MERS-CoV. Although the spikes have 76% sequence identity, the protein spike associated with SARS-CoV-2 has a binding domain with ACE2 that is distinct from the one associated with SARS. Drugs that target this protein increase may not be equally effective against both viruses (111).

As opposed to SARS-CoV, SARS-RNA-dependent CoV-2’s RNA polymerase proteins (RDRP) are 96% compatible with one another (111). SARS-CoV-2 is probably susceptible to the same medications that were effective against this polymerase in SARS-CoV. One of these drugs, Remdesivir, which is likely to cure COVID-19 symptoms, has demonstrated some promise in reducing SARS-CoV-2 infection in vitro (110, 112).

Although it is constrained by an internal viral protein called nsp14-ExoN, which may cleave the medication out of the RNA chain before it reaches the RDRP, ribavirin, another RDRP inhibitor, has effectiveness against SARS-CoV-2 (111).

Chloroquine or hydroxychloroquine, a typical anti-malarial treatment, is an alternative to these antiviral medications because it prevents viral entrance by altering endosomes, modulating inflammatory mediators, and changing ACE2 (113). However, there is inconsistent evidence about the effectiveness of these drugs in treating SARS-CoV-2, in addition to legitimate concerns about chloroquine toxicity (114). Ammonium chloride, an acidic drug that suppresses SARS-CoV virus multiplication in vitro, is one more treatment that may work in a manner that is similar to that of this one. Additionally, this drug altered the ACE2 receptor, which could lessen the capacity of the virus to bind (113). Ammonium chloride is a significant problem for the treatment of susceptible individuals because of its restricted therapeutic applications and little research.

Other alternatives being considered at the moment are lopinavir/ritonavir, which lengthens medication half-life by working synergistically to suppress HIV protease and reduce metabolic activity. Based on earlier MERS-CoV and SARS-CoV investigations (115, 116), this medicine may decrease virus titers and minimize
the risk of mortality even if the mechanism in SARS-CoV-2 is unclear. Table 1 lists many drugs used to treat SARS-CoV-2 infection. SARS-CoV-2 has been shown to be in the same coronavirus family as SARS-CoV and MERS-CoV, with 80% genetic affinity to SARS-CoV.

Table 1: The mechanics, cardiovascular complications, benefits and drawbacks of numerous medicines used to treat SARS-CoV-2 infection are:

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### 9. THERAPIES THAT STRAY FROM THE MAINSTREAM:

Various therapeutic approaches have recently been taken into consideration, and some clinical studies have already started. A wide range of fascinating potential pharmacological treatments has been developed as a result of extensive study, the co-operation of several working groups, and the publication of scientific publications internationally. In view of the fact that ACE2 is just one of many potential targets, combination treatments are likely to be both feasible and much more effective. Here, we concentrate on a few of these therapeutic approaches, with a particular emphasis on adjuvant treatments that avoid cardiac damage. High plasmin/plasminogen levels are often present in much co-morbidity, as was previously indicated, and may thus be used as a biomarker to predict risk (122). Specific protease inhibitors have previously been shown in vitro to limit viral entry, and based on these findings (123), the first protease inhibitors are being delivered to COVID-19 patients in China (124, 125). In this regard, Hoffmann et al. discovered that the protease TMPRSS2 is crucial in SARS-CoV-2 cell entrance, suggesting that particular inhibitors or antibodies might be advantageous (79).

### 10. FUTURE PERSPECTIVES:
As the disease spreads, concern well about the state of cardiology as we perceive it’s really growing. The widespread disruption of clinical outpatient consultations, elective treatments, rehab centers, and medical studies is anticipated to have a significant impact on the incidence of cardiovascular illnesses and forthcoming routine practice. Alterations to one’s lifestyle that are unhealthy, reduced availability of cardiovascular care, and decreasing demand for such treatment will all have a cumulative influence on the progression of the cardiac disease over time. Even during the COVID-19 emergency, the public has to be informed on the need of seeking medical attention (126).

The European Society of Cardiology has launched the "you can’t pause your heart" campaign, which urges anybody exhibiting warning signs of a heart attack to get help right once. The number of individuals with post-myocardial infarction issues and cardiac arrest will probably rise since it is more probable that the drop in hospitalizations is caused by a lack of seeking medical help.

In actuality, one of the most crucial indicators of mortality and serious aftereffects while dealing with people who are experiencing an acute myocardial ischemia is the interval between the onset of symptoms and the initial medical assessment (127). High mortality rate, a larger infarct size, and a greater likelihood of mechanical issues are all associated with delayed AMI manifestation (128). A greater morbidity and mortality scenario may come from missed or delayed detection of acute cardiac abnormalities as well as the rapid advancement of chronic difficulties, for which we must be ready.

Recognizing the significant repercussions of less effective cardiologic treatment is critical: Stay-at-home advice is important to prevent illnesses from spreading, but precise knowledge of the need of prompt emergency services engagement is also critical to keep the community as safe as possible. The media must inform the general public that obtaining medical treatment is safe, that virus protection is always available in health centers, and that signs of severe medical diseases need rapid attention. Cardiologists must be ready for the worst.

Nevertheless, the implementation of a healthcare system that includes home-based programmes and remote monitoring will undoubtedly provide a logistical benefit for both patients and carers. A moment of crisis is not simply a time of fear; it is also a time of opportunity, a chance to be better (126).

**Conclusion:**

There have been several attempts to comprehend the diagnosis and prognosis of this respiratory condition before the global health organization (WHO) designated COVID-19 a worldwide emergency at the end of January and a pandemic in March 2020.

It is noteworthy that there are geographical variations in the severity of COVID-19, which seem to be influenced by socioeconomic factors and the capacity of the healthcare systems to handle such a problem. It is yet unknown if COVID-19 has direct or indirect effects on the cardiovascular systems of young or elderly persons since COVID-19 monitoring is still ongoing. This involves the development of precise biomarkers to identify people who are at high risk as well as advanced imaging equipment to track heart re-modelling and inflammation (e.g., MRI). In relation to SARS-CoV-2 and its possible influence on cardiac tissue, ACE2 abundance in particular is of great interest. To accurately clarify the pathophysiology of COVID-19, as well as to find and appropriately assess medications targeting the most relevant pathways that characterize the disease’s severe symptoms, further study is required. Collaboration efforts should use both traditional and innovative methods to provide a fast and efficient worldwide reaction to the COVID-19 epidemic.

**CONSENT –**

I here by gives my consent to publish this article in your journal.

**FUNDING**

None

**CONFLICT OF INTREST**
The author declare no conflict of interest, financial or otherwise.

ACKNOWLEDGMENT

NONE

12. REFERENCES:


viral control by the humoral immune response. Journal of virology. 2011;85(9):4122-34.


Fig. 1: Core structure component of severe acute respiratory syndrome

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