Pathological Involvement of Cardiovascular System in COVID-19: A Systematic Review

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Abstract: The novel corona virus which was detected for the first time in Wuhan city, Hubei province, China in December, 2019, rapidly spread all over the world to be recognized as pandemic by March, 2020. Although, initially, the major symptoms were related to the respiratory system but gradually several manifestations have surfaced, thus making one believe that the virus is not confined to the lungs, but has its effect all over the body. The Corona virus disease 2019 (COVID-19) is a hyper-inflammatory state having deranged blood parameters and increase in cardiac biomarkers. Here we review clinical manifestations, histopathological and other laboratory findings, impact of age, pathomechanisms, and prevailed therapeutic approaches related to cardiovascular involvement in patients with COVID-19.

Keywords: ACE2, Cardiovascular system, Covid-19, Histopathology, SARS-CoV-2, systematic analysis.

Introduction:The Corona virus disease-2019 (COVID-19), first reported in December 2019 in Hubei province in Wuhan, China, was designated as a pandemic by the World Health Organization (WHO)

on 11 March 2020. This disease, recognized as an infection with a new betacorona virus-Severe Acute Respiratory Distress Syndrome Corona Virus-2 (SARS-CoV-2), has spread rapidly in almost all countries around the world. The epicenter which was initially in China, later spread to other parts of the world by March/April 2020. Until July, 2020 almost two million cases have been reported worldwide and mortality has been more than 0.6 million[1].COVID-19 pandemic has multiple manifestations, but predominantly respiratory, as acute respiratory distress syndrome (ARDS). SARS-CoV-2 is an enveloped positive sense single stranded RNA virus which belongs to genus betacoronaviridae of the family coronaviridae. Genus betacoronaviridae also includes SARS-CoV-1 and MERS-CoV, the viruses which caused previous epidemic of Severe Acute Respiratory syndrome (SARS) in 2002/2003 and Middle East Respiratory Syndrome (MERS) in 2012 respectively. SARS-CoV-2 has more than 80% sequence homology with the previously identified acute respiratory syndrome-associated coronavirus (SARS-CoV), and some essential enzymes having even more than 90% homology[2]. Due to this homology, many of the presenting symptoms of SARS-CoV-2 can be compared to SAR-CoV. To infect an individual, SARS virus (SARS-CoV-1 & 2) with the help of receptor binding domain (RBD) in their spike protein, targets the host angiotensin converting enzyme 2 (ACE2) receptors present in human epithelial cells. In human lung, alveolar cells (predominantly type II pneumocytes) which express ACE2 are the prime viral targets[3]. SARS-CoV-2 requires cleavage of its spike(S) protein (at the intersection of S1/S2 segment) by host proteases like transmembrane protease serine 2 (TMPRSS2), Cathepsin-L (CTS-L) and Furin, which help the viral spike protein to fuse to host cell membrane, a pre condition for successful host cell invasion[4]. Like the previous pandemics of SARS and MERS, common presentations of patients with COVID-19 include fever, sore throat, cough and shortness of breath[5]. However, as reported by various studies, it affects many other systems of body like cardiovascular, nervous, gastro-intestinal and genitor-urinary tract leading to the multi-organ manifestations[6, 7, 8]

As far as pathological involvement of cardiovascular system (CVS) manifestation is concerned, COVID-19 is known to give rise to potential severe cardiac symptoms like hypertension, myocarditis, cardiomyopathy, acute coronary symptoms, pulmonary embolism, palpitation, chest pain, stroke, arrhythmias and cardiogenic shock[3,9]. Cardiovascular involvement in the COVID-19 has been a common reason for the increased mortality, specially, in the elderly patients[10,11]. This systematic review of the published literature is aimed to provide an overview of clinical manifestations, histopathological and other laboratory findings, impact of age, patho-mechanisms, and prevailed therapeutic approaches related to cardiovascular involvement in patients with COVID-19.

Materials and Methods: A comprehensive systematic review was performed as per PRISMA guidelines (supplementary file-1) in order to identify the available published data. The sources opted for the data and observations included PubMed, Medline (EBSCO & Ovid), Google Scholar, Science Direct, Scopus, Bio Medical and Web of Science (WoS). The time period taken to review the data included from January 1, 2020 to July 31, 2020. Additional sources were identified from the publication citations also. We tried to pick up any specific information related to cardiovascular system that met our selected criteria. Full articles which provided information about the mechanism of entry of the SARS-CoV-2 virus into human cells, histological changes in the human cardiac tissues following SARS-CoV-2 infection, changes in blood parameters in COVID-19 patients, radiological and ECG changes in COVID-19 patients and drugs used in COVID-19 patients were included in the study. A few previous studies explaining the mechanism of action of the drugs used in COVID-19, a study on mouse model explaining relation of viral entry and ACE2 receptor, along with letters to editor, brief correspondence and case reports, have also been included in the review. Articles with only abstract, those with no mention of the cardiovascular manifestations and newsletters were excluded from the study. The terms used for the search included COVID-19 and the heart, cardiovascular changes in COVID-19, heart in COVID-19, SARS-CoV-2 and cardiovascular

system, SARS-CoV-2 and heart, COVID-19 and heart, histo-pathological changes in COVID-19 heart, ACE2 receptor in heart, ACE2 receptors in cardiomyocytes, ECG changes in COVID-19 heart, blood parameters in COVID-19 and the heart, 2019-Corona virus, drugs and COVID-19 heart etc.

Results:

Overall 420 studies were identified that matched our selected criteria. After exclusion of the duplicates 368 research articles were finalized for screening, following which 276 articles were excluded due to various reasons (only abstract, no relevant data related to cardiovascular manifestation in COVID-19, studies having no association with changes in blood parameters, radiological changes, histological changes or studies with no particular explanation of the cardiovascular status of patients with COVID-19). Finally 92 articles were available for systematic review and qualitative analysis.

Discussions: The systematic review of the published data unraveled extensive pathological involvement of CVS in patients with COVID-19. Multiple observations were made in this review, which may enhance understanding of laboratory diagnosis, pathogenesis, and therapeutic management of CVS related problems in COVID-19. Firstly, we discussed histo-pathological findings in heart of COVID-19 patients along with various blood parameters related to the cardiovascular manifestations. Then, other CVS related findings like ECG and radiological changes are also been discussed. This is followed by discussing the related patho-mechanism enabling CVS related manifestations in COVID-19. Lastly, we discussed therapeutic measures that are being followed to prevent or treat any cardiovascular injury in patients with COVID-19.

Hypertension and cardiovascular disease (CVD) have been found to be among the common co-morbidities in patients with COVID-19[12]. Liu *et al* reported heart palpitations as presenting symptom in 7.3% of patients[13]. Although fulminant myocarditis and profound cardiogenic shock is low[9], previous morbidity may resurface due to the SARS-CoV-2 infection. Patients with underlying

conditions like diabetes mellitus, hypertension, cardiovascular disease, malignancy etc. have higher risk of complications and death due to COVID-19[14]. Some authors identified that prior history of cardiovascular disease showed more preponderance compared to prior respiratory disease in COVID-19 patients who were admitted in hospital[15]. In a retrospective study, including multiple centers, authors reported that 34.7% (out of 150 cases) had hypertension and 0.09% had cardiovascular disease and all of them did not survive[10]. Evidences suggest wide occurrence of cardiac problems in patients with COVID-19. Clerkin *et al* reported that more than 7% of affected patients experienced myocardial infarction and showed signs of heart damage[9]. Zheng *et al* reported that 35% COVID-19 patients had hypertension and 17 % had coronary heart disease[3]. Grasseli *et al* observed that hypercholesterolaemia (18%) was a major comorbidity after hypertension (49%) and cardiovascular disease (21%) associated with COVID-19 patients[16].

Some patients may even show cardiovascular symptoms as the primary manifestation rather than the respiratory manifestations[3]. Azarkish *et al* reported a case of transient AV- Block in a COVID-19 patient[17]. It remains unexplained in the literature why some patients experience more cardiac effects than others. This can be due to a genetic predisposition[18,19] or it could be because they have higher viral load.

Histo-pathological Findings in Cardiac Tissue in COVID-19: Xu Z *et al*, 2020 observed mononuclear inflammatory infiltrates with no obvious myocyte damage in COVID-19 patients[20] (Figure 1a). In contrary, Tian *et al*, (2020) observed focal presence of irregularly shaped myocardial cells with darkened dense cytoplasm without any inflammatory infiltrates[21]. They observed various degrees of focal edema, interstitial fibrosis, and myocardial hypertrophy which they opined that might be due to an existing cardiovascular disease. However, RT-PCR assay of SARS-CoV-2 in tissue from heart showed variable result[21].

In another study involving a patient who died of non-ischaemic cardiogenic shock, the autopsied heart tissue under light microscope showed low-grade inflammatory infiltrates in the endocardium and interstitium, along with large (>20 μm), vacuolated, CD68+ macrophages[22] (Figure1b). Electron microscopic examination on the cardiac tissue showed cytopathic changes with membrane damage and cytoplasmic vacuoles along with single or small groups of viral particles of variable size (70-120 nm) having morphology of SARS-CoV-2 in the interstitial cells but not in the myocytes[22] (Figure 2). Absence of viral particles in the myocytes suggests against cardiac myotropism and presence of viral particles in the interstitial cells may alternatively indicate extra pulmonary dissemination of the virus. In an in vitro study on human induced pluripotent stem cell derived cardiac myocytes (hiPSC-CMs), authors showed the cytopathic effect of SARS-CoV-2 on the cells following 72 hours of infection[23].

Blood Parameters: Elevated high-sensitivity cardiac troponin I (hs-cTnI), which indicates myocardial injury, was a common finding in COVID-19 patients having cardiac manifestations [3,9,21,22,24,25]. The report from the National Health Commission of China revealed that almost 12% of patients who had underlying cardiovascular disease (CVD) showed increase in troponin levels or cardiac arrest during hospitalization[3]. In an observation involving the patients who succumbed to COVID-19, median hs-cTnI level was found to be 8.8 pg/ml in the initial period rising to 90.6 pg/mL after about three weeks[26]. In another study, median CK-MB level was found to be 18 to 14 U/L and hs-cTnI level to be 11.0 pg/mL to 5.1 pg/mL[15,25]. Further, in a study, it was observed that, among the patients who died of COVID-19, 37.50 % had elevated serum TnT level without underlying CVD, while 69.44 % had both elevated TnT and history of underlying CVD, suggesting the severity of the disease associated with comorbidity[27]. However, level of TnT also has a great influence on the prognosis of the COVID-19 patients as it was observed that patients who had prior CVD but normal TnT had better prognosis compared to those who had elevated TnT even without prior CVD[28].

Although, increase in level of Creatinine kinase (CK-MB)[29] and hs-cTnI (High sensitivity cardiac troponin I) indicate myocardial injury but this rise is also associated with increase in other

inflammatory parameters which makes one believe that the myocardial injury may be secondary to cytokine storm or hemophagocytic lymphohistiocytosis[9,15]**.** Myocardial injury can result from the associated cytokine storm manifested by elevated levels of interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), and D-dimer or myocardial dysfunction can also ensue from the direct effect of SARS-CoV-2 on the heart[9,30]. IL-6 is considered to be clinical predictor of mortality in COVID-19[10]. Also, elevated D-Dimer level which is related to poor prognosis[31], can be used as a surrogate marker for clot formation. Increase in C-reactive protein (CRP) was also observed in the COVID-19 patients[25,27]. Additionally, increase in N-terminal pro B type natriuretic peptide (NT-proBNP) was a common observation, which indicates the importance of the effects of cardiovascular injury on systemic stability[15,25].

Lymphopenia was observed in most patients with COVID-19 with variable levels of WBC[21,22]. CD4+ T cells, CD8+ T and NK cell count were reduced while pro-inflammatory markers like CCR6+ Th17 in CD4 T cells were highly increased[20,32]. The level of lymphopenia can be correlated with the severity of the disease[33]. Additionally, it was found that CD8+ T cells harbored high concentrations of cytotoxic granules, with 31·6% cells being perforin positive, 64·2% cells granulysin positive, and 30·5% cells having both granulysin and perforin positivity, which implied that overactivated-T cells may have caused immune injury to the tissues[20]. Lymphopenia may be caused due to necrosis and apoptosis triggered by SARS-CoV-2 or due to exhaustion of the cells during initial phase of response to viral invasion[32]. Another hypothesis for lymphopenia in COVID-19 patients may be direct viral invasion into the bone marrow stem cell as was earlier observed in SARS-CoV-2 infection[34]. The levels of CD4+ and CD8+ T cells were observed to be inversely proportional to the severity of the disease and can act as important biomarkers to determine prognosis of the disease[35]. Jiang *et al* 2020 observed that the decrease in CD8+ T cells was more severe compared to the CD4+ T cells in COVID-19 patients[36].

Thrombocytopenia has also been observed in COVID-19 patients but the reported rates have been highly variable with wide range (5-53.6%) [32, 37]. However, on observing the prognostic value of platelet count, authors were in the opinion that decreased platelet count was associated with the severity of the disease[38, 39]. Thrombocytopenia may be caused by direct viral invasion of the bone marrow stem cells as was seen in earlier infection by SARS-CoV-1 or due to associated intravascular coagulopathy[32, 34]. Decreased potassium level which has been found in many COVID-19 patients[40] can be a cause of secondary hypertension. On the other hand, Inciardi *et al* found hyperkalemia along with hyponatremia, and hypochloremia in a patient with deranged ECG findings[25].

Low level of calcium (total as well as ionized) has also been observed in COVID-19 patients, which may be due to decrease in intestinal absorption, impaired metabolism involving PTH and D-Vitamin, or due to direct effect caused by SARS-CoV-2[41]. The viruses utilize calcium for the benefit of their replication and propagation[42] which may lead to hypocalcaemia in the host. Again previous study on SARS-CoV has demonstrated alteration in calcium homeostasis and initiation of inflammatory cascade following SARS-CoV infection and increase in inflammatory cytokines[43]. Since SARS-CoV and SARS-CoV-2 have similarity in their genetic structure, the possibility of SARS-CoV-2 following the same pathogenesis of calcium homeostasis in its favor like the former, can very much be expected.

ECG Findings: Variations in ECG findings may indicate injury to the myocardial tissue. Several reports in COVID-19 patients suggested variable ECG abnormalities. ST- elevation has been observed in some COVID-19 patients presenting with chest pain[9, 40]. In an observational study on 18 COVID -19 patients having ECG abnormalities, from six New York Hospitals; authors mentioned that patients having ST- elevation in the ECG had poor prognosis[44]. ST elevation may mimic ST-elevation myocardial ischaemia (STEMI) but without any evident coronary artery blockage[14] and angiography showing apparently normal coronary vasculature[24]. Again ECG changes following hypokalemia can show prolonged QT interval, ST-depression, prominent U-wave and slurring of T-

waves into U-wave[45]. However QT-prolongation , cardiomyopathy and arrhythmia may also occur due to drugs such as hydroxychloroquine, chloroquine or azithromycin[46,47]. Minimal diffuse ST-segment elevation (more prominent in the inferior and lateral leads), and an ST-segment depression with T-wave inversion have also been reported[25].

Echocardiogram: Low ejection fraction (27-32%) with an end diastolic diameter of 5.8-6.1 cm in left ventricle has been observed in echocardiography in addition to other parameters of myocardial injury[9,24]. There are also reports of diffuse hypokinesis, mildly impaired left ventricular diastolic function, no valve involvement, circumferential pericardial effusion[9]. Tavazzi et al reported gradual drop of left ventricular ejection fraction. In another observation, gradual drop of left ventricular ejection fraction (by 25%) with progression of the disease in a 69 year old patient with dilated ventricle (end diastolic diameter of 56 mm) suffering from COVID-19[22].

Radiological Findings: Studies are scarce reporting MRI findings in COVID-19 patients. We came across with only one study in which Inciardi et al reported using MRI, myocardial edema with late gandolium enhancement indicative of myocarditis and pericardial effusion in a COVID-19 patient with cardiac manifestations[25]. In another observation, it was reported that Chest X-Ray and CT examination of a 37 year old patient presenting with chest pain, dyspnea and hypotension showed cardiomegaly[24] (Figure 3).

Other Findings: Bone marrow aspirates in a COVID-19 diabatic and hypertensive patient under anti- diabetic and anti-hypertensive medications showed an increased number of activated macrophages with phagocytic haemopoetic elements within the cells[48] (Figure 4). In a quantitative study for SARS-CoV-2 load in 22 tissue samples taken from patients who died of COVID-19, broad organotropism was observed including the cardiac tissue[49] (Figure 5).

CVS Related Patho-mechanism: Although the exact mechanism for cardiac involvement is still under consideration, the most hypothesized pathogenesis is the involvement of ACE-2

Receptors, which are the convenient passage for the SARS virus including SARS-CoV-2[50]. During the period of SARS-CoV outbreak in 2002, viral RNA was isolated from autopsied cardiac myocytes[50]. ACE2 receptor, the key entry point for SARS-CoV-2, along with the assisting protease TMPRSS2, present on the cell surfaces (Figure 6) facilitate viral entry into the cells. Since ACE2 receptors are found in cardiac tissue[51,52] **(Figure 7a,b)**, the SARS CoV- 2 infection can potentially attack cardiac myocytes and initiate several patho-physiological reactions[3,53]. Another study comparing ACE2 expression in diseased heart with normal (without indication of cardiac dysfunction) heart samples shows increased ACE2 expression in the former leading to the fact that previous cardiovascular disease is a risk factor for viral invasion of the cardiac tissue[54]. In particular, ACE2 receptors are expressed in endothelial lining of coronary arteries, myocytes, fibroblasts and epicardial adipocytes[55]. Direct viral entry into the cardiac myocytes may lead to cellular death which in turn may lead to a series of reactions thus activating the immune cell response[56]. Myocardial injury, which may be detected by level of troponin, can be due to direct viral invasion, in which case viral particles can be seen within the myocytes. In a study, Chen *et al* mentioned that ACE2 expression is more in heart compared to lungs[29], which indicates the potential susceptibility of the SARS-CoV-2 infection in cardiac tissue. Macrophages express CD209, which is another receptor facilitating entry of SARS-CoV-2[57]. Whenever there is an inflammatory condition, these macrophages may act as the carrier of these viruses into the cardiac tissue, thus initiating the cardiac menifestations. These CD209+ macrophages may interact with endothelial cells through specific receptors and facilitate viral entry into the capillary endothelium. They also mentioned about the high expression of ACE2 receptor in the pericytes around the coronary vasculature, thus influencing the coronary microcirculation[57]. Following entry into the cells, a virus can replicate using the host nuclear machinery leading to cellular damage thus causing an imbalance in the micro-environment. Since ACE2 is closely related to renin-angiotensin system (RAS), an imbalance in proper functioning of this system may also lead to cardiovascular injury. Thus presence of ACE2 is an important determinant factor for tissue injury by SARS-CoV-2. The use of ACE2 by SARS-CoV-2 will prevent

conversion of angiotensin 2(AT2) to angiotensin (1-7)(AT_{1-7}) [58]. Now AT2 being a pro-inflammatory and pro-fibrotic factor, it will initiate the cascade by binding to type 1 angiotensin 2 receptor (AT_1) in the cell (Figure 6). However, in some COVID-19 cases, in which cardiac tissue biopsy was performed, no viral particles were observed in the myocytes[20, 21, 22]. In another study by in-situ hybridization, viral RNA was detected in the interstitial cells within the myocardium instead of the myocytes[59]. In such scenario, other causes may come into play leading to myocardial injury.

Plaques formed in the vascular system due to the viral invasion into the endothelium can cause of circulatory collapse. These plaques may get dislodged to form emboli and get lodged in microvasculature of vital organs such as lung, liver, kidney and heart causing multi-organ failure in COVID-19 patients[6, 60].

However, whether the virus affects the cardiac myocytes by direct invasion or indirectly through other mechanism is still under query, as the presence of virus in the myocytes has not been clearly reported yet in COVID-19. In one study involving autopsied heart tissues of COVID-19 patients, RT-PCR assay of SARS-CoV-2 showed variable results[21].

Possible Mechanism Other than Direct Viral Mediated Tissue Injury, Suggested for Cardiac Manifestations in COVID-19: Whether the cardiac pathology is due to direct affect of the viral invasion or a byproduct of the various cascades of reactions taking place in body due to the viral infection, is still under survey and difficult to establish at this initial stage. Normally, in a human body physiologic immune response is a balanced phenomenon, to get rid of any foreign particle entering the body. But if this immune response in uncontrolled, hyper-inflammatory response may come into play leading to an increase in cytokine levels termed as 'cytokine storm'[61]. The most significant patho-mechanism causing cardiovascular manifestations in COVID-19 seems to be the cytokine storm secondary to the viral invasion into the respiratory system evidenced by the various cytokine pro-inflammatory factors in the serum. These pro-inflammatory factors which include interleukin (IL) -1,2,6, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon

(IFN), IFN inducible protein-10, monocyte chemoattractant protein(MCP)-1, macrophage inflammatory protein(MIP) and tumor necrosis factor (TNF), interfere with the complementary cascade and coagulation pathway thus inducing disseminated intravascular coagulation(DIC) [30,61].

Another mechanism by which the cardiovascular manifestations may flare up is the increased level of angiotension-II due to virus mediated downregulation of the ACE2 receptors[62]. Downregulation of ACE2 and increase in angiotensin II will lead to imbalance of the RAS and thus may increase incidences of thrombo-embolism, hypertension and inflammation. Inflammation may cause arterial plaques causing blockage and thus ischemic changes in heart leading to heart failure. However it can also be caused by direct injury to heart by virus through the ACE2 receptors[15].

Electrolyte imbalance also may have an effect upon the cardiac health in COVID-19 patients. Hypokaelimia noticed in some patients of COVID-19 can lead to hyperpolarization of the cardiac myocytes leading to arrhythmia[40]. This hypokaelimia may be caused due to the virus directed myocardial injury which leads to decreased cardiac output thus activating the Renin-aldosterone activating system (RAAS) and renal excretion of potassium ion (K^+) [63] thus continuing the viciuos cycle and ending in heart failure.

In contrast to electrolyte imbalance-induced arrythmia, there are also reports mentioning presence of bradycardia (below 60 bpm > 24 hours) in COVID-19 patients. The cause of bradycardia as mentioned by some authors is drug induced. The antiviral drugs lopinavir and ritonavir (both protease inhibitor) earlier used during SARS-CoV and MERS outbreak and now used in HIV treatment, are also in use during COVID-19 management, can be the cause of bradycardia[64].

Metabolic acidosis and hypoxia have also been observed in COVID-19 patients[22]. Hypoxia induced myocardial damage secondary to acute respiratory distress syndrome should also be kept in mind as one of the causative factors while considering the pathophysioloy. Hypoxia may lead to oxidative stress thus injuring the cellular mechanism of the cardiac tissue thus leading to myocardial

ischaemia[65,66]**.** Increase in intracellular concentration of calcium due to hypoxia may lead to apoptosis of the cardiac myocytes[67]. Myocardial injury can also be initiated by the backpressure secondary to the collapse of the lungs due to fibrosis following SARS-CoV-2 mediated lung tissue injury. This may further lead to cardiac myopathy, arrhythmia and heart failure. Stress induced cardiomyopathy, renal failure and hypovolemia are other factors leading to heart failure[67].

Age Preponderance: Advancing age is an important risk factor for cardiac co-morbidity associated complications in COVID-19 patients [10,67]. In another study, it was observed that out of 416 COVID-19 patients 19.7% cases had cardiac injury, and it was more prevalent in the aged[11]. Antiviral drug induced bradycardia was observed to be more in elderly patients[64]. Lymphopenia was observed more in elderly COVID-19 patients with high mortality compared to infected children[68].

COVID-19 Heart and Its Protection: Paucity of established therapeutic measures and without any specific vaccines till date, in-order to curtail the affect of SARS-CoV-2 infection, has lead the clinicians to depend on symptomatic treatment and interventions as the preferred line of management. A hypertensive COVID-19 patient has every chance of left ventricular hypertrophy and may lead to arrhythmia which may further be exaggerated by imbalance in potassium level due to the concomitant use of diuretics and associated kidney dysfunction due to COVID-19 [69]. Arrhythmia following corona virus infection was first noted in SARS corona virus infection[70] and the same has also been observed in hospitalized COVID-19 patients[71]. According to the European Society of Cardiology, parental antihypertensive therapy is required for patients who are on invasive ventilation and have persistant severe hypertension[67]. A close monitoring of the potassium level is an essential step to prevent arrhythmia in a hypertensive COVID-19 patient[67].

Renin Angiotensin System (RAS) Blockers: Due to the various beneficial effects of Angiotensin Converting Enzyme Inhibitors (ACEI) /Angiotensin II Receptor blocker (ARBs), they have been widely used in heart failure, hypertension, systolic and diastolic left ventricle dysfunction and acute myocardial infarction[72]. Previous it was speculated that treatment of hypertension

with RAS inhibitors may promote binding of SARS-CoV-2 to target cells (via ACE2) and thus help in promoting disease[73]. This was based on some experimental findings regarding compensatory increase in transcription of *ACE2* by RAS inhibitors, which would further increase ACE2 at tissue level[74, 75] and some authors were in the opinion that ACE-inhibitors (ACEI) or ARBs may be detrimental in patients exposed to SARS-CoV-2[76]. However there are also conflicting data regarding the same[77]. No evidence has yet been observed regarding detrimental effect of RAS blockers in COVID-19 patients[67] and thus treatment of hypertension or any other cardiovascular morbidity requiring RAS blockers should preferably be continued. Since ACE2 Receptors is one of the main component factors for the effect of SARS-CoV-2 virus in human body, use of ACEIs or ARBs requires a balance between the advantages and disadvantages of these drugs on the overall mechanism. Phase 2 trials are on the process on the effect of Losartan (ARB) in COVID-19 a patients who haven't received the drug earlier (**NCT04312009)[77]**. Since COVID-19 is seen to be more among patients with underlying cardiovascular disease[38], it is better to continue the RAS inhibitors in the patients, as withdrawal of the drug may cause a progressive decline in otherwise stable condition[25,77]. Besides this, in experimental models ARBs are shown to have potentially protective influence[78,79]. In the present scenario of infection with SARS-CoV-2 which causes pulmonary inflammation and Acute Respiratory Distress Syndrome (ARDS), it has to be kept in mind that angiotensin II also interferes with adaptive immunity by activating cells of immune system including macrophages along with inflammatory cytokines like IL-6 and TNF-α. Considering the various advantages and disadvantages of withholding ACEIs and ARBs, experts recommend not to withdraw the drugs, as it may exacerbate the underlying condition and paradoxically lead to increased mortality [27, 53, 80].

Anti-arrhythmic Drugs: Before administering multiple drugs, drug interactions have to be kept in mind. Drugs like antivirals, anti-arrythmics and anticoagulants may interact with each other which may cause harmful effect in the body[67]. In haemodynamically unstable COVID-19 patients parenteral amiodarone for supraventricular tachyarrhythmia may be given followed low threshold

beta-blockers (or CCBs if beta-blockers are contraindicated) as maintenance therapy [67]. However, considering the risk of QT prolongation, combination of anti-arrhythmic drugs with hydroxychloroquine and azithromycin should be preferably avoided [67]. Since hypokalemia has been observed in patients with COVID-19, it also requires serious attention in order to avoid subsequent cardiac arrhythmias[40]. Previous studies indicate that adequate level of potassium (K^+) in the blood has a protective role in maintaining a healthy myocardium by balancing the polarity of the cells[81]. Thus regular monitoring of serum K^+ level should be carried out in the COVID-19 affected patients and if required K+ supplements can also be provided as precautionary measure. Some authors recommend maintaining the serum K^+ level between 4.5 and 5.5 mmol/L for proper homeostasis[40, 82].

Calcium Channel Blockers: Calcium channel blockers (CCBs), a well known anti-hypertension drugs has the capacity to inhibit the post-entry replication of SARS-CoV-2 in vitro[83]. Compared to the ACE I and ARB, it was seen that amlodipine besylate (a CCB) displayed significant anti-SARS-CoV-2 activity[83]. Again in a retrospective review on COVID-19 patients, Soleimanjadeh observed that COVID-19 patients who were given CCB (mainly amlodipine and nifedipine) had better survival (50%) when compared to the survival rate of non-CCB group (14.6%)[84].

Anticoagulants: COVID-19 is a hypercoagulable state which is a risk factor for thrombo-embolic phenomenon. To avoid the hypercoagulability, prophylactic dose of anticoagulants may be helpful. Unfractionated heparin (UFH), low molecular weight heparin (LMWH) or non-vitamin K antagonist oral anticoagulants (NOAC), may be used to prevent thrombo-embolic phenomenon[67]. Some authors also recommend fibrinolytic to prevent thrombo-embolic phenomenon[85]. However, drug interactions have to be kept in mind, and proper monitoring has to be followed to avoid any drug reactions as it has been observed that non-vitamin K antagonist oral anticoagulants (NOACs) may interact with drugs like lopinavir/ritonavir (antiviral agents) via Cytochrome P450 3A4 (CYP3A4) and/or P-glycoprotein (P-gp) inhibition[86].

Anti-inflammatory Drugs: Since cytokine storm is one of an important mechanism for tissue injury, the cardiac tissue has to be protected from any inflammation. Since IL-6 being a clinical predictor of mortality in COVID-19[10], it can be an important target to curtail the cytokine storm. Inflammatory conditions can be attenuated by use of corticosteroids [25]. Dexamethasone has shown to be effective in rapid decrease in IL-6 in COVID-19 patients[87]. However, certain immunomodulating drug (like Fingolimod) may cause AV/Bundle branch block[67]. Chloroquine also shows some influence on immune regulation by interfering in the production/release of tumour necrosis factor alpha and interleukin 6, which are the mediators of inflammatory outcomes of several viral disease[88]. There are concerns about the use of Nonsteroidal anti-inflammatory drugs (NSAIDs) as these have been identified as a potential risk factor for serious clinical presentation of SARS-CoV-2 infection[89]. However one study in relation to use of NSAIDs in SARS-CoV shows that Indomethacin, apart from having an anti-inflammatory action, also act against the virus by blocking the synthesis of RNA[90]. However, COVID-19 patients with chronic coronary syndromes should not be withdrawn from aspirin due to its anti-inflammatory effect[67].

Antiviral Drugs: Apart from the cardiac specific drugs, to prevent direct viral invasion in the cardiac tissue along with other tissues of the body, drugs that prevent viral entry and replication may be used. Evidence suggests that Remdesivir as an anti viral agent has shown its usefulness in COVID-19 patients, reducing the mortality and morbidity[91,92]. Remdesivir acts by evading the viral RNA and interfering in its RNA synthesis thus bringing an end to its replication.
Hydroxychloroquine and chloroquine have also shown some viricidal effect against SARS-CoV-2 in the laboratory dish. These drugs inhibit viral entry and multiplication within the cell. Chloroquine and Hydroxychloroquine may cause AV-Block or bundle branch block[67] along with bradycardia. Rarely, there is also risk of QTc prolongation and sudden death during COVID-19 infection[67]. There are evidences of drug induced bradycardia by Lopinavir/ Ritonavir treatment in COVID-19 patients. This bradycardia included 88% with sinus rhythm and 12% with atrioventricular block[64]. Thus close

monitoring of the patients treated with these antiviral drugs, keeping in mind the risk-benefit ratio will prevent a further catastrophic event.

Apart from the prophylactic measures and medical managements, if a COVI-19 patient with cardiac manifestations requires invasive interventions for any emergency situations like reperfusion therapy, angiography, bypass surgery etc, the management should be prompt and should not be compromised, but should be done with proper protocol to prevent spread of the infection[67].

Conclusion: Accumulating evidences indicate virus mediated cardiac tissue injury and ACE2 signaling dysregulation, and cytopathic effect of pro-inflammatory markers may lead to cardiovascular manifestations in patients with COVID-19, especially in the elderly and those with existing co-morbidities. Based on the prior experience managing SARS and MERS, and emerging facts about patho-physiological involvement, multiple therapeutic approaches targeting cardiac manifestations are being applied in patients with COVID-19. However evidence regarding survival benefits from these therapeutic approaches are currently preliminary and need more corroboration from the future studies. **Funding: Funding:** Authors received no substantial funding for this work

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Figures:

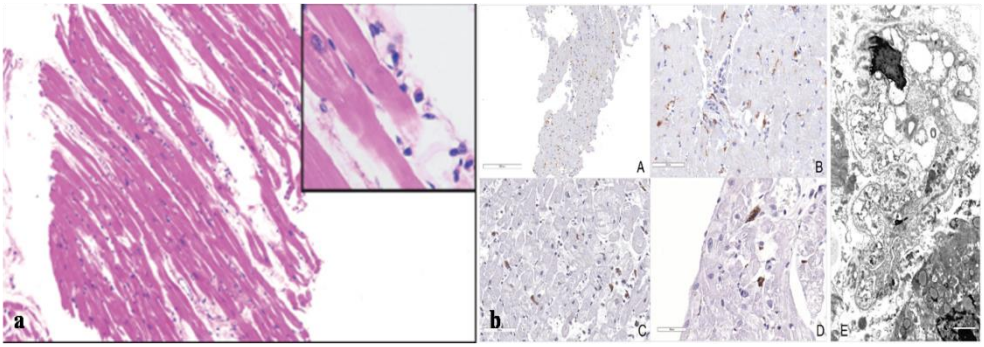


Figure 1(a): Mononuclear inflammatory infiltrates observed in interstitium with apparently normal cardiac myocytes; H& E stain (Reproduced with permission: Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [published correction appears in Lancet Respir Med. 2020 Feb 25]. Lancet Respir Med. 2020;8(4):420-422. doi:10.1016/S2213-2600(20)30076-X)

Figure 1(b): A,B: Few CD45RO positive cells observed in interstitium of biopsied endomyocardial tissue under low (A) and high (B) power light microscopic study; C,D: Large vacuolated CD68+ macrophages also observed in interstitial tissue under low(C) and High (D)power light microscopic observation; E: Large, cytopathic macrophage observed under electron microscopy. Bar scale=2μm (Reproduced with permission: Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;22(5):911-915. doi:10.1002/ejhf.1828)

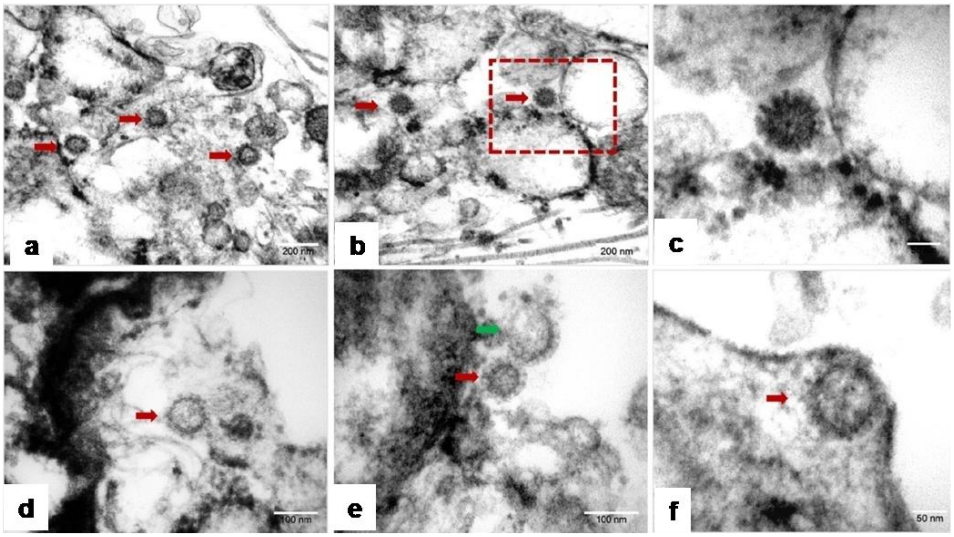


Figure 2: a,b: Small groups of viral particles (red arrow, size 70-120nm) observed under electron microscope, c: Higher magnification of a single viral particle shown on dashed box in b.c,d: Viral particles observed in interstitium of myocardial tissue. Viral particles show spike around them. e: Green arrow shows morphology of viral particle being disrupted f: Red arrow shows the budding pattern of the viral particle. Bar scal=200nm a,b); 50nm (c); 100nm (d,e); 50nm (f). (Reproduced with permission: Tavazzi G, Pellegrini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;22(5):911-915. doi:10.1002/ejhf.1828)

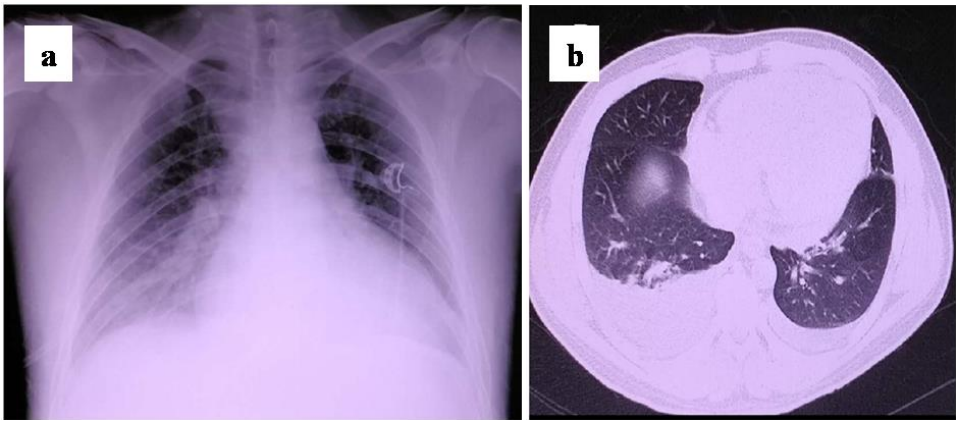


Figure 3: Cardiomegaly observed in Chest X-Ray (a) and CT Scan(b) in a 37 year old male patient who was COVID-19 positive and presented with chest pain and dyspnea (**Reproduced with permission:** Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin [published online ahead of print, 2020 Mar 16]. Eur Heart J. 2020;ehaa190. doi:10.1093/eurheartj/ehaa190)

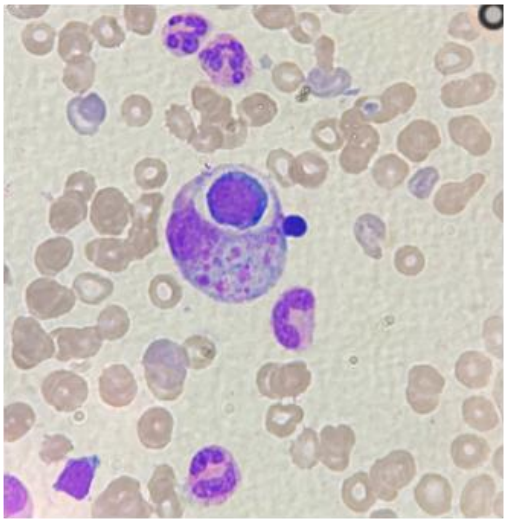


Figure 4: Phagocytosed haemopoetic elements seen in bone marrow aspirate of a diabetic and hypertensive COVID-19 patient (Reproduced with permission: Lima R, Filho CC, Ferreira Filho CM, et al. Hemophagocytic syndrome and COVID-19. Respir Med Case Rep. 2020;31:101162. Published 2020 Jul 10. doi:10.1016/j.rmcr.2020.101162)

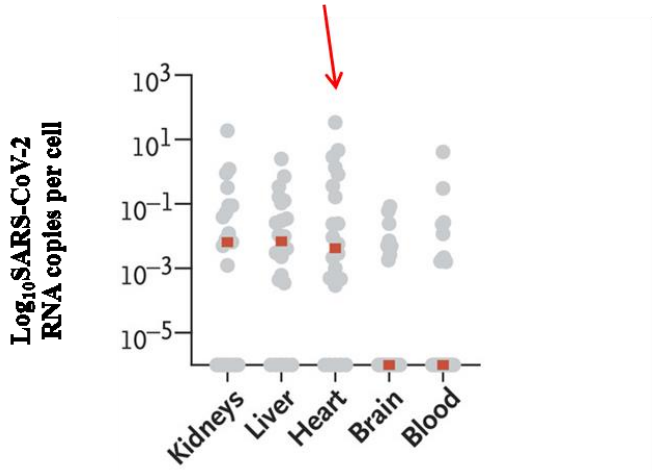
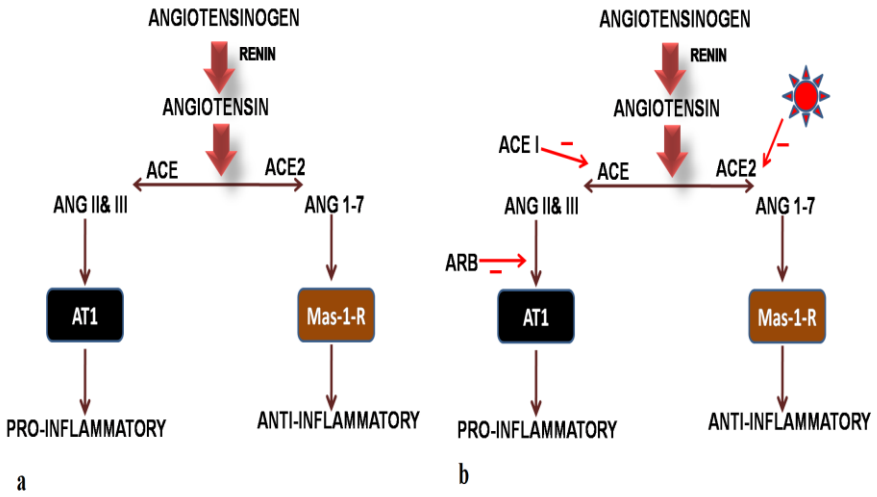


Figure 5: SARS-CoV-2 has tropism for cardiac tissue along with other tissues of the human body. (Reproduced with permission: Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and Renal Tropism of SARS-CoV-2. N Engl J Med. 2020;383(6):590-592. doi:10.1056/NEJMc2011400)



Fugure 6: Mechanism of angiotensin in healthy individual (a) and SARS-CoV-2 infected patient (b) along with site of action of ACE Inhibitor and angiotensin receptor blocker

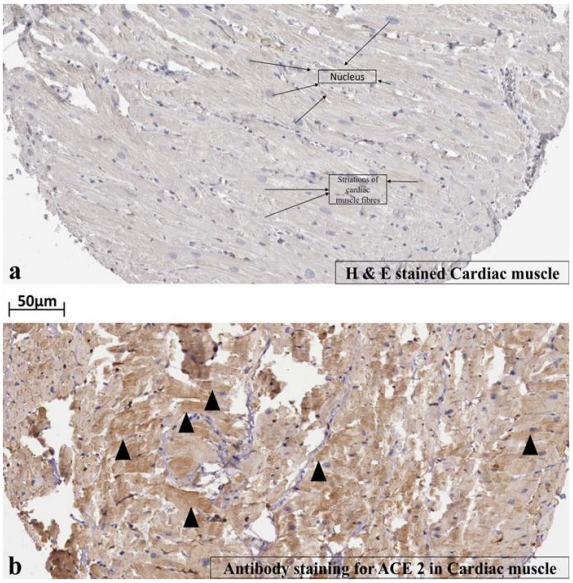


Figure 7(a): H & E stained cardiac muscle fibres (i), Abundant ACE2 positive (black arrowhead) cardiac muscle cells (ii). [Source: Human Protein Atlas, www.proteinatlas.org] (b): Graph showing the consensus normalized expression of ACE2, TMPRSS2, and AT1R on cardiac myocytes.