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Focused REVIEW

COVID-19 and the Cardiovascular System: How the First Post-Modern Pandemic 'Weakened' our Hearts

*Syeda Tasneem Towhid[1, #], Nadira Naznin Rakhi[2, #], ASM Shamsul Arefin[3], Otun Saha[4], Sumaiya Mamun[5], Mohammad Moniruzzaman[6], Md. Mizanur Rahaman[4, *]*

[1]Department of Microbiology, Jagannath University, Dhaka, Bangladesh
[2]Department of Biotechnology and Genetic Engineering, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj, Bangladesh
[3]Department of Biomedical Physics and Technology, University of Dhaka, Dhaka 1000, Bangladesh
[4] Department of Microbiology, University of Dhaka, Dhaka 1000, Bangladesh
[5]Institute of food and Nutrition, University of Dhaka, Dhaka 1000, Bangladesh
[6] Department of Biology, Virginia Polytechnic Institute and State University, Blacksburgh, VA 24060, USA
# Equal Contribution

* *Corresponding authors*: Md. Mizanur Rahaman, Associate Professor, Department of Microbiology, University of Dhaka, Dhaka 1000; Email: razu002@du.ac.bd; Phone: +8801796585290.

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ABSTRACT

The global spread of SARS-CoV-2 with its diverse signs and symptoms manifested in COVID-19 patients across different age groups and geographic locations perplexed the clinicians and public health experts. Emerging variants of SARS-CoV-2 through continuous mutation with a limited arsenal of treatment made the study of viral pathogenesis and factors associated with disease outcomes in a holistic approach inevitable, among which pre-existing cardiovascular complications were found to be significantly associated with adverse outcome of COVID-19. In addition, COVID-19 has already been reported to cause cardiac injury and different cardiovascular complications in patients irrespective of preexisting cardiovascular complications, which highlights the importance of recognizing the complications at the onset, although these arising complications might be an indirect effect of SARS-CoV-2 induced cytokine storm or hypoxia rather the virus itself. Also, the drugs used for the clinical management of the patients may have an impact on the induced cardiac complications. Thus, the effect of SARS-CoV-2 on the cardiovascular system needs to be investigated in order to predict the clinical outcome and to devise a proper treatment strategy. Besides, the interaction of vaccines or therapeutics to be approved with the cardiovascular system needs to be evaluated to avoid confounding effects leading to cardiovascular complications followed by post-approval retraction. However, potential biomarkers (eg. troponin, D-dimers, fibrin) associated with cardiac injury may be potentially useful in predicting life-threatening conditions early enough to save lives. In conclusion, this review summarizes the molecular pathogenesis of cardiovascular damage caused by SARS-CoV-2 in COVID-19 patients, as well as prescribed treatment and preventative measures.

Abbreviations

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); Coronavirus Disease-19 (COVID-19); Fibrin-degraded product dimer (D-dimer); Milligram (mg); Microgram (µg); Nanogram (ng); Calculated

probability value (P); Transmembrane protease serine 2 (TMPRSS2); Cluster of Differentiation 209 Ligand (CD209L); Interleukin-6 (IL-6); Interferon- γ (IFN-γ); Tumor Necrosis Factor-α (TNF-α); Interleukin-2 (IL-2); Interleukin-7 (IL-7); Interleukin-10 (IL-10); Granulocyte Colony Stimulating Factor (GCSF); Interferon induced Protein-10 (IP-10); Monocyte Chemoattractant Protein-1 (MCP-1); Macrophage Inflammatory Protein- 1α (MIP1α); International Unit (IU); Chimpanzee Adenovirus Oxford 1 (ChAdOx1); new Coronavirus-19 (nCoV-19); National Health System, UK (NHS); Messenger ribonucleic acid (mRNA); Cluster of Differentiation 8^+ ($CD8^+$); T Helper cell type 1 (T_H1); Intensive Care Unit (ICU); troponin (cTnI); creatine kinase-myocardial band (CK-MB).

Keywords: COVID-19 pandemic, myocardial injury, cardiovascular complications, blood clot.

SUMMARY

1. Introduction

The current Coronavirus Disease 2019 (COVID-19) pandemic, so far the biggest pandemic of the 21st century, first caught worldwide attention in November 2019, after the medical facilities in Wuhan, China had reported multiple atypical pneumonia cases with fatalities that could not be managed with contemporary medical guidelines[1]. Later, the causative agent was characterized as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is closely related to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) causing outbreaks in 2002 and 2012 respectively[2]. Currently, COVID-19 is affecting more than 79 million people from 218 countries and territories, with 1,749,606 deaths as of December 25, 2020[3].

In similarity to the closely related viruses like SARS and MERS-CoV, cardiovascular complications are being frequently reported among COVID-19 patients[4]. The meta-data analysis showed that MERS-CoV was more likely to occur in the patients with underlying cardiovascular diseases[5] and tachycardiac cardiovascular complications were more common in patients with SARS[6]. Similarly, COVID-19-induced cardiovascular complications include myocarditis, arrhythmia, hypertension, cardiomyopathy, cardiac and cardiovascular injury, cardiac arrest, and acute heart failure[7]. Moreover, the onset of cardiovascular complications in the patients infected with SARS-CoV-2 and the increased severity and mortality among patients with pre-existing cardiovascular diseases have also been reported[6]. Most importantly, SARS-CoV-2 induced cardiac injury was found to cause a significantly higher rate of fatality compared to either MERS or SARS[6]. While this high rate of morbidity and mortality in the patients with cardiovascular complications surely urge the immediate attention to explore the mechanism of the SARS-CoV-2 affecting the cardiovascular system, the impact of COVID-19 associated cardiac injury on the high mortality among the patients with cardiovascular complications have not been fully determined. Besides, COVID-19 may act as the confounding variable behind the mortality data, as the comorbidities including hypertension, diabetes, coronary heart / cerebrovascular disease, chronic heart failure, chronic obstructive pulmonary disease and even cancer were more frequently present among COVID-19 patients with cardiac injury (all $P < .001$)[6]. Hence, the patients with a history of cardiac disease may develop impaired functionality leading to myocardial infarction or increased myocardial demand causing ischemia and necrosis

or ultimately increased metabolic demand resulting in heart failure or death due to COVID-19[7]. However, it is yet to be determined if the cardiac complications among COVID-19 patients are directly linked to SARS-CoV-2 or typical of any pathology with higher cardio-metabolic demand independent of the virus. Also, some of the drugs used for COVID-19 management may cause myocardial injury[8].

In this context, this study aimed to explore the concurrent literature to develop a deeper understanding of pathogenic mechanisms of SARS-CoV-2 in the cardiovascular system and to investigate the association of COVID-19 severity with cardiovascular disease conditions. Furthermore, the effects of COVID-19 management drugs and the prognostic importance of biomarkers in the cardiovascular system were discussed, summarizing the most important findings in this regard, in order to recommend the best ways forward.

2. Pathogenesis of SARS-CoV-2

SARS-CoV-2 is primarily transmitted via droplets in the air and is inhaled by a susceptible host[9]. The infectious form of viral particle is assumed to persist on fomite surfaces up to 72 hours and can be transmitted to a new host on fingertips[10]. But so far, the SARS-CoV-2-infected persons, including both symptomatic and asymptomatic cases, have been recognized as the major infection source and the virus is transmitted mainly via respiratory droplets along with aerial droplets and close contact[11]. However, upon entering through the portal of entry, SARS-CoV-2 uses Angiotensin Converting Enzyme 2 (ACE-2) as receptors[11] to penetrate the host cell. The spike protein (S protein) on the viral envelope contains a receptor-binding region compatible with the extracellular domain of ACE2 with a high affinity of 15 nM[11]. Viral internalization by endocytosis requires the cleavage of the S protein by the host protease TMPRSS2 into S1 and S2 subunit, which leads to the S2-induced membrane fusion with ACE2 in the pulmonary epithelium[12]. ACE2 internalization by SARS-CoV-2 down-regulates the ACE2 expression on cell surface voiding an important pathway to degenerate Angiotensin II (ANG II) and to initiate cardiovascular disease protective Ang (1-7) causing the damage of pulmonary function[13].

Upon entering into the human body through the nose, SARS-CoV-2 reaches the nasal epithelia, attaches to ACE2, enters epithelia and multiplies itself in the nasopharynx for up to 3 days without producing any symptoms and negligible immune response. After the 3rd days, the viral load in the throat increases, viruses descend towards the lungs and infect the alveolar epithelial cells in the lungs[14]. The alveolar epithelial cells are the major target of the SARS-CoV-2 and release β- and λ-interferons upon infection. Simultaneously, the type II alveolar cells release CXCL10 (C-X-C motif chemokine ligand 10) in response to the epithelial infection, indicating a significant impact on the outcome of the infection[15]. The infected individuals become infectious at this stage showing common symptoms such as fever, breathing trouble and dry cough. Eventually, the alveolar macrophages and cells become active in clearing the infection leading to the recovery of 80% of the infected patients[15]. For the rest of the patients who are unable to produce sufficient immunity against the virus, SARS-CoV-2 migrates towards the gas exchange units in the lungs, where they infect the type II alveolar cells via CD209L receptor[16]. Finally, the apoptosis of alveolar cells results in diffuse alveolar damage, fibrosis and death of multinuclear giant cells, increased pulmonary permeability, neutrophil infiltration and edema, causing chest pain, pneumonia, breathing difficulty and breakdown of gas-exchange in the lungs in the patients. At this stage, X-ray and CT-scan can detect lung damage, and patients might need respiratory support, CPAP (Continuous Positive Airway Pressure) and oxygen[17]. Patients survive when the alveolar regeneration is quick, pneumonia is resolved, and pulmonary inflammation is reversed. However, death occurs when cardiopulmonary complications arise.

On the contrary, another pathological study suggested direct damage to pneumocytes via SARS-CoV-2 occurs when viral cytopathic effect leads to acute respiratory distress syndrome (ARDS). Some other studies showed that increased inflammatory markers upon infection[18] such as CRP, IL-6, IFN-γ, to TNF-α along with IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α cause cytokine storm that might be responsible for multi-organ failure and disseminated intravascular coagulation (DIC)[19]. In addition, the hypoxic condition induced by severe pneumonia and ARDS may also result in end-organ dysfunction

followed by death in critically ill patients[20]. Lymphopenia is also common among critically ill patients, indicating the invasion and subsequent destruction of lymphocytes by SARS-CoV-2, along with high C-reactive protein count (CRP), high erythrocyte sedimentation rate (ESR), as well as high D-dimer protein[20].

3. Mechanisms of COVID-19 induced complications in the cardiovascular system

COVID-19 manifests itself differently among the infected individuals, depending upon their immune response. The majority of the patients experience mild illness such as fever, dry cough, nasal congestion, headache, diarrhea, vomiting, while several patients show mild pneumonia without the need for oxygen supplementation[21]. On the other hand, severe pneumonia cases are characterized by low oxyhemoglobin saturation (SpO_2) of less than 93% and an increased respiratory rate of more than 30 breaths per minute. Ventilation becomes unavoidable when the ratio between the partial pressure of arterial oxygen (PaO_2) and the percentage of inspired O_2 (FiO_2), PaO_2/FiO_2 drops below 100mm Hg pressure. The other serious symptoms are evident in adults, such as coagulopathy, fast breathing, thrombocytopenia, low O_2 saturation, raised serum lactate, reduced urination, tachycardia, weak pulse and low blood pressure, with potential organ failure[22]. However, analyzing the deaths from COVID-19 demonstrated that the differences in the time points of death resulted into two distinct groups that might give an insight into the pathogenesis and disease progression among the patients[23]. It has been hypothesized that the group of patients dying around 14 days after the onset of the disease might have died of respiratory failure, whereas the myocardial damage and cardiovascular collapse possibly leading to myocarditis is responsible for death on and around 22 days after the onset of the disease in the other group[23]. Even though the mechanism of cardiac injury has yet not been elucidated, both cardiac injury characterized by elevated troponin level[24], cardiomyopathy and cardiovascular injury characterized by elevations in troponin levels and N-terminal pro B-type natriuretic peptide levels[24] have been reported especially among the critically ill patients. Besides, the actual mechanism and possible role of COVID-19 on the onset of fulminant myocarditis is yet to be determined[24], although there have been reports of COVID-19 induced myocarditis[25].

Figure 1 depicts different proposed mechanisms to explain the COVID-19 induced cardiac injury among COVID-19 patients. Among the mechanisms, the expression of ACE2 in the heart supports the possibility of the heart being a potential target organ for SARS-CoV-2, as ACE2 expression is not exclusively unique to lung epithelia[26]. In addition, the ACE2 expression in the heart is higher than in the lung corroborating the ACE2 mediated damage to the cardiovascular system[26]. Thus, SARS-CoV-2 may invade the cardiomyocytes through ACE2 and directly damage them. Nevertheless, the pathological evidence is still scant[21]. The positive correlation of COVID-19 severity among the patients with pre-existing cardiovascular diseases with higher expression of ACE2 among those individuals indicates the possible role of ACE2. However, it is still unclear if the binding of SARS-CoV-2 to ACE2 alters its expression or impairs the regulatory role of ACE2 in the RAAS (renin-angiotensin-aldosterone system) pathway producing ANG II[27]. The increase of ANG II (ACE1) axis in SARS-Cov-2 is thought to be responsible for high blood pressure and cardiac failure[28]. However, ANG II upregulates ANG II type 1 receptor promoting vasoconstriction, hypertension, inflammation, fibrosis and eventually leading to heart failure, while Angiotensin 1-7 (Ang 1-7) regulates anti-hypertensive action, vasodilation, down-regulation of cardiac fibrosis and reduced thrombosis[9]. Thus, the balance between ANG II and Ang 1-7 has a significant impact on cardiac damage and the clinical outcome of COVID-19.

The recent pathological study showed scarce interstitial mononuclear inflammatory infiltrates in heart tissue without significant myocardial damage in COVID-19 patients, challenging the plausibility of the direct injury hypothesis despite the necessity of magnetic resonance imaging or echocardiography for confirmation[21]. On the other hand, the cytokine storm produced during the SARS-CoV-2 infection is characterized by higher plasma level of cytokines such as interleukin (IL)–2, IL-7, IL-10, granulocyte-colony stimulating factor, IgG-induced protein 10 (also known as C-X-C motif chemokine-10), monocyte chemoattractant protein-1, macrophage inflammatory protein 1 α, TNF-α along with other markers of inflammatory response including C-reactive protein, procalcitonin, and leukocytes were

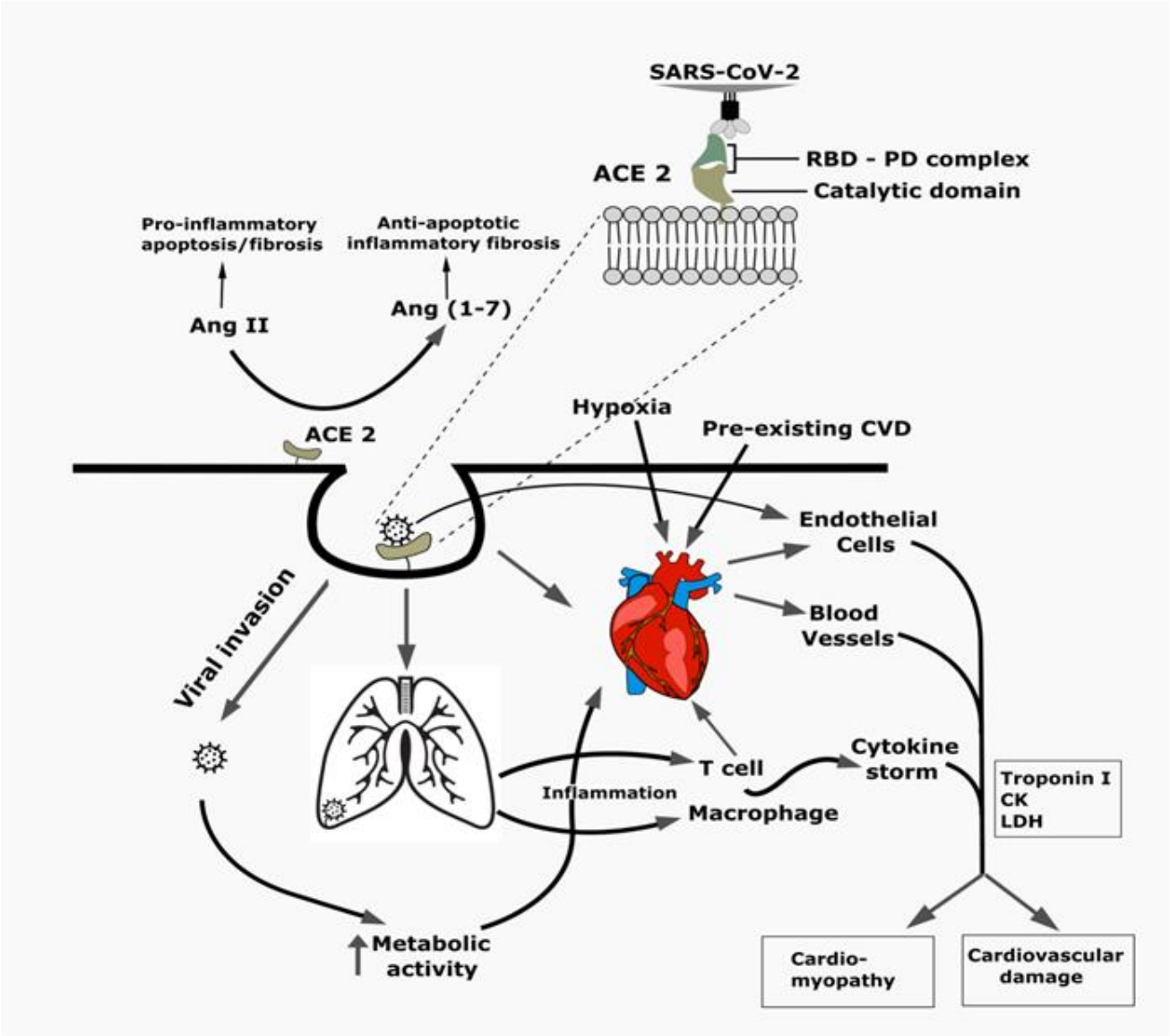

Figure 1. Pathogenesis of SARS-CoV-2 mediated cardiac complications among COVID-19 patients
The receptor binding domain (RBD) of SARS-CoV-2 spike protein interacts with peptidase domain (PD) of ACE2 to penetrate the host cells and impairs the regulation of the RAAS (renin-angiotensin-aldosterone system) pathway producing high ANG II. An increased level of ANG II causes vasoconstriction, hypertension, inflammation, fibrosis and eventually leading to heart failure, while Angiotension 1-7 (Ang 1-7) is responsible for anti-hypertensive action, vasodilation, down-regulation of cardiac fibrosis. SARS-CoV-2 may damage the cardiovascular system directly by invading cardiocytes through ACE2 or indirectly by causing the increased myocardial oxygen demand due to hypoxia induced by SARS-CoV-2 mediated lung injury. Pre-existing cardiovascular diseases with elevated expression of ACE2 may increase the susceptibility to cardiac injury. Infection of endothelial cells is of also great importance causing micro- and macrovascular dysfunction. On the other hand, activated T cell and macrophages release diverse cytokines including IL–2, IL-7, IL-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein-1 etc. leading to the cytokine storms which may result in fulminant myocarditis and contribute to the development of arrhythmia. Ultimately, the prognostic biomarkers like troponin I, lactate dehydrogenase (LDH), creatine kinase-myocardial band (CK) level get elevated indicating the injury.

noticed among the patients with cardiac injury[6]. So, the activation or the upregulation of these inflammatory cytokines might be possibly leading to apoptosis or necrosis of myocardial cells[6].

According to another proposition, cardiac injury among the COVID-19 patients is the result of increased myocardial oxygen demand due to hypoxic condition caused by SARS-CoV-2 induced

acute lung injury (ARDS), rather than direct viral infection or cytokine storm[28].

However, the 'out of the box' aspect of SARS-CoV-2 pathogenesis was to consider COVID-19 as an endothelitis through viral entry into endothelial cells through ACE2, which ultimately damages several organs, including heart vessels, without any sign of lymphocytic myocarditis[29]. Endothelial dysfunction associated apoptosis can be either by a direct viral infection of endothelium or by the host inflammatory response, leading to endothelitis in transversing organs[29]. Hence, along with the myocardial injury, the increased susceptibility to COVID-19 due to old age, male gender, smoking, hypertension, diabetes and especially pre-existent cardiovascular disease can also be explained from the perspective of COVID-19 induced endothelial cell dysfunction.

4. Impact of cardiovascular complications on COVID-19 morbidity and mortality

The susceptibility to COVID-19 is reported high among elderly people with underlying comorbidities, especially cardiovascular complications such as hypertension, coronary heart disease or diabetes, among whom individuals with cardiovascular diseases are more likely to develop severe symptoms[8]. While these complications include myocarditis, cardiac arrest and acute heart failure; many individuals among SARS-CoV-2-infected patients had prior cardiovascular disease history, such as 58% with hypertension, 25% with heart disease and 44% with arrhythmia[7]. Likewise, a significantly greater percentage of patients with cardiac injury has been reported in need of invasive and non-invasive mechanical ventilation than those without cardiac injury[6]. Besides, the relative risk ratio for the COVID-19 patients with hypertension and coronary artery/cerebrovascular diseases is 2.03% and 3.3% respectively leading to a higher chance of developing severe disease or requiring ICU than those without the aforementioned conditions[30]. Consequently, the rate of mortality is also reported higher among these patients with cardiac injury by the National Health Commission of China (NHC), which reported pre-existing hypertension and coronary heart disease among 35% and 17% of COVID-19 patients respectively[8]. This report was corroborated by the analysis of 44,672 confirmed COVID-19 cases showing that the case fatality rate (CFR) was 6% and even up to 10.5% among the patients with hypertension and cardiovascular diseases respectively, while the overall CFR of COVID-19 has been reported only 2.3%[31]. Even though the patients with pre-existing cardiovascular diseases account for only 4.2% of the total COVID-19 cases, cardiovascular diseases were responsible for 18.3% of the COVID-19 deaths[32]. Moreover, studies showed the onset of cardiac injury among 12% of the COVID-19 patients with no prior heart disease evidenced by an ejection fraction decline and troponin I elevation[32]. The radiological findings of those patients showed also a high prevalence of bilateral pneumonia and multiple mottling and ground-glass opacity compared to the patients without cardiac injury[6]. However, myocardial infarction along with acute pulmonary embolism and deep vein thrombosis might have resulted from thrombotic complications among COVID-19 cases, which is characterized by abnormally higher levels of D-dimer, fibrin degradation products, longer prothrombin time and activated partial thromboplastin time[33]. However, disseminated intravascular coagulation was reported as the major cause of COVID-19 fatality in one study[34]. The trigger for thrombotic disorder might come directly from the virus itself and might be facilitated by the immobility of patients and/or administration in-dwelling devices[34]. The post-mortem histopathology from 5 subjects from the USA showed that the fatal vascular injury in SARS-CoV-2 infection resulted from sustained systemic activation and deposition of complement proteins C5b-9 membrane attack complex, subsequent inflammation and coagulation inside vascular endothelia[35].

5. Cardiovascular implications of drugs used in COVID-19 management

While US FDA approved remdesivir for the treatment of COVID-19 on October 22, 2020, clinical management is still primarily based on symptom management by supportive care along with the drug repurposing initiatives targeting SARS-CoV-2 for a better therapeutic. As a result, myriads of drugs including different antiviral drugs, glucocorticoids, intravenous immunoglobulin therapy and antibiotic therapy are being preliminarily used to treat COVID-19 cases, some of which might need attention considering the side-

effects. However, the use of antibiotics, glucocorticoids and intravenous immunoglobulin were reported to be significantly higher in patients with cardiac injury than those without cardiac injury[6]. More importantly, cardiac complications among the COVID-19 patients seemed to plausibly arise from the use of those drugs apart from direct SARS-CoV-2 involvement. So, the drugs used for COVID-19 treatment with potential cardiovascular impacts are listed below.

5.1 Antiviral drugs

Lopinavir/Ritonavir used in the COVID-19 treatment regimen is a viral protease inhibitor blocking post-translational processing of viral proteins inside host cells. The recommended dose for lopinavir in viral infection is 400 mg twice daily for 14 days. Lopinavir has been reported to cause hyper-triglyceridemia in patients with pre-existing heart conditions[36]. However, the other promising antiviral drugs include favipiravir or remdesrivir, which are a RNA-dependent RNA polymerase inhibitor and a prodrug inhibiting viral RNA replication respectively. Even though these drugs have not been evidenced to directly cause cardiovascular damages, hepatotoxicity reported in the case of both drugs along with nephrotoxicity in case of remdesivir only might contribute to the COVID-19 severity in the patients of pre-existing complications[37].

5.2 Corticosteroids

Corticosteroids like dexamethasone have been found to reduce early pro-inflammatory events in porcine models of Coronavirus infections. While glucocorticoids together with a quinolone can prevent acute lung injury in COVID-19 patients, prolonged use of steroids can facilitate viral replication, immune suppression and secondary infection. Also, the side-effects of this steroid treatment include hypertension and dyslipidemia[38].

5.3 Renin-Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB)

ACEI and ARB are controversial therapeutics prescribed to terminal COVID-19 cases with embolism[4]. These drugs bind to the spike proteins of SARS-CoV-2 particles in vivo and inhibit viral attachment to the host cell. The usual dosage of ACEI and ARB is 25 mg daily for 28 days. While ACEI and ARS offer efficacy for treating hypertension[39], the safety and potential effect issue considering ACE2 modulation associated with this antihypertensive therapy needs careful attention. Despite the lack of data regarding the effects of specific anti-hypertensive medications on COVID-19 patients, the role of this therapy is controversial, while the preclinical studies in rats showed that treatment of infarcted rats with either ACEI/ARS increases in ACE2 gene expression and activity[40]. Thus, these drugs are being suspected to act like a double-edged sword in COVID-19 simultaneously causing both increased risk of SARS-CoV-2 infection and reduced risk of lung damage[4].

5.4 Paracetamols and ibuprofen

Paracetamol is being regularly recommended to lower fever, which rarely leads to hypertension. On the other hand, a couple of studies have reported that ibuprofen deteriorated conditions in COVID-19 patients, although a large population-based observational cohort or case-control study is needed to reach a conclusive decision regarding its safety[41]. So far ibuprofen has not been excluded by WHO for the treatment of COVID-19 infections.

5.5 Heparin subunits

Considering the myriads of fatal thrombosis in COVID-19 patients, prophylactic use of low molecular-weight heparin subunits in patients with regular platelet counts was suggested. The FDA-approved enoxaparin® is prescribed in 40-60 mg/daily for 7 days, or daily 10000-15000 IU. However, such drugs must not be given to patients already on blood-thinners/ anti-coagulants[42].

5.6 Anti-malarials

Chloroquine and hydroxychloroquine under this category have anti-inflammatory effects, which help control pulmonary infiltration in later stages of COVID-19, while these drugs have severe cardiovascular side-effects such as cardiomyopathy, hypertrophy, arrhythmia and atrioventricular block[43].

5.7 Antibiotics and antiparasitics

Azithromycin is reported to improve early symptoms of COVID-19, though it is not approved for such cases by the US FDA yet. However, it is generally well-tolerated, while the rare side-effects, such as arrhythmia can be severe. Moreover, another

promising drug, ivermectin, showed negative effects in the electrocardiograms on the cardiovascular system in animal models such as guinea pigs[44] along with the report of tachycardia in calves. Similarly, use of doxycycline in horses showed side effects on the cardiovascular system resulting in fatalities[45]. Although there is no sufficient evidence of side effects of these promising drugs in humans, the negative effects in animal models urge the consideration to ensure safe and effective management of COVID-19.

5.8 Plasma therapy

Treating an infectious agent with convalescent plasma containing high titer of neutralizing antibodies from recovering patients is an old approach in managing life-threatening conditions. The US FDA provided emergency use authorization for administering convalescent plasma for severe cases of SARS-CoV-2 infection in August, 2020, though the clinical practitioners have mixed experience and opinion[46]. There are first-hand reports from randomized clinical trials from thousands of patients stating convalescent plasma containing high titer (1:640) of polyclonal Ig against the spike glycoproteins, envelope glycoproteins, membrane glycoproteins and nucleocapsid of SARS-CoV-2 have low-certainty in preventing COVID-19 induced death (relative risk 0.1, odds ratio 1.04 at CI 95%)[47-49]. However, a carefully controlled randomized clinical trial with patients showed that plasma containing 1:640 titers of neutralizing IgG against S1 spike protein of SARS-CoV-2 has therapeutic value on antibody-induced absorption of lung lesions[50, 51]. Plasma therapy also reduced the length of hospitalization and intubation in COVID-19 patients (9.54 days) as compared to the control group (10.88 days)[52, 53]. The major side-effects in terms of health risks of plasma therapy include anaphylactic transfusion reaction, febrile non-hemolytic reaction, transfusion-associated circulatory overload, pulmonary stress following transfusion and post-transfusion purpura[46,54], while the cardiac injury is not among them. However, a meta-analysis on 20,000 hospitalized COVID-19 patients evaluating the safety of plasma therapy revealed that 3% of the patients develop cardiac complications, although this consequence was supposed to be unrelated to receiving plasma therapy[55].

6. Most promising vaccines against SARS-CoV-2

The vaccine race during the COVID-19 pandemic is unprecedented in history. Never in our history there were so many vaccine candidates receiving emergency use authority in multiple countries in multiple continents within one year against the same etiology. The hype and public interest around vaccine development surpassed all other global events. While influenza vaccination[56,57] was reported to significantly decrease major cardiovascular complications among the patient and even reduced cardiovascular mortality in a meta-analysis, this poses the question if the SARS-CoV-2 vaccines-to-be approved have a similar advantage. Scant data are available to date to determine this effect of promising vaccine candidates. Four of the most potent vaccine candidates that have received emergency approval for vaccination around the world as of December, 2020 have been discussed below.

6.1 AZD1222 from Oxford Univ,/AstraZeneca

In April 2020, the University of Oxford, UK, developed a replication-deficient Chimpanzee Adenovirus (ChAdOx1) containing the engineered mRNA of the spike protein S1 of SARS-CoV-2 as a vaccine candidate. Upon intramuscular administration, the mRNA would generate S1 proteins that would show high affinity binding towards B and T cells, followed by the release of neutralizing antibodies that would optimize SARS-CoV-2 upon natural infection[58]. The phase III, single-blinded, multi-center randomized controlled trial was conducted in collaboration with the pharmaceutical giant Astra Zeneca on 60000 participants spanning in Brazil, South Africa and the UK. Participants in the test group received $5x10^{10}$ particles of ChAdOx1 during the primary shot, followed by a booster shot containing $2.5x10^{10}$ particles after 28 days was claimed to be 91% effective in inciting 4-folds increase in neutralizing IgG and IFN-γ as compared to placebo group. Significant immunity was evident after 14 days of application of the booster dose[59-61]. Side-effects appear within 4 days of both shots, manifested as fever, chill, pain on site of injection and myelin-related anomalies in rare cases. Astra Zeneca applied for license from the NHS, UK under the trade name of AZD1222, pending decision. These vaccines

received emergency approval for use in UK in December 2020.

6.2 mRNA-1273 from Moderna, USA

Moderna, a US-based biotechnology company (Cambridge, MA) developed a vaccine candidate designated mRNA-1273, a sequence-optimized transcript for the SARS-CoV-2 spike protein, encased inside a lipid nanoparticle. The phase III trial conducted on 30,000 participants in collaboration with National Institute of Health (NIH), USA, administered a primer shot on 10µg immunogen, followed by a booster of 100µg immunogen after 4 weeks induced B/T cell activity[62]. The ongoing phase III trial documented chill, fever, pain, fatigue and myalgia[63]. The mRNA-1273 needs a storage/ transport cold chain of -20ºC, making it within the reach of resource-limited nations. These vaccines received emergency approval from the US FDA in December 2020.

6.3 Tozinameran from BioNTech SE/Pfizer

BioNTech SE, a Germany-based biotechnology company, developed a panel of nucleoside-modified mRNAs encoding mutated forms of viral spike proteins and envelope proteins encapsulated inside multi-lipid nanoparticle. One candidate mRNA-containing particle designated BNT162b2, was put forward for a randomized, open-label, phase III trial in Germany on 44,000 participants, in collaboration with Pfizer Pharmaceuticals. An intramuscular primer shot with 1 µg of immunogen, followed by a booster dose of 50µg after 21 days, was shown to elicit receptor-binding domain IgG from B cells and promote skewed response from T_H1 as well as from $CD8^+$ T cells releasing INF-γ. As claimed in the license application, 95% of the vaccines presented effective neutralization of pseudovirus particles with IgG titer of 534U/ml on the 43rd day after the booster. IgG titer rose from 0.7 folds to 3.5 folds among recipients of BNT162b2 compared to that of the placebo group[64,65]. BNT162b2 was applied for a license under the trade name of Tozinameran for use on people from 16-55 years of age. Side-effects of this vaccine candidate include pain in the site of injection, headache, chills and severe anaphylactic reactions. This vaccine has no demonstrated efficacy on vulnerable groups (immunocompromised individuals, pregnant and lactating women, children below 16 years and geriatric population older than 55 years)[66]. The vaccine would need a cold chain of -80ºC throughout storage, transport and delivery. These vaccines received emergency approval from the US FDA in December 2020, and it is currently already used in USA and Europe.

6.4 PicoVacc from Sinovac

Sinovac, China, formulated a chemically inactivated whole virus vaccine administered it on 1500 volunteers. A 3µg primer shot followed by a 6µg booster after 28 days showed rise of SARS-CoV-2 neutralizing Ig at 1:8 titer, rise of pseudovirus particles at 1:30 titer and rise of RBD Ig at a titer of 1:160[67]. This vaccine candidate was approved for emergency use in China on individuals between age 18-39 years.

7. Prognostic value of the biomarkers associated with cardiac complications

Despite the heterogeneity in the results, high level of troponin (cTnI), the biomarker candidate for cardiac injury, was found to be associated with a higher rate of COVID-19 severity leading to ICU admission and mortality[30]. Acute myocarditis along with acute coagulopathy leading to sudden cardiac death might explain this association[46,68]. It has been evident that the cTnI concentration rises only marginally among the COVID-19 patients with mild symptoms, while the value exceeds 99th percentile in the upper reference limit (URL) among the patients with severe symptoms accounting for 8-12% of the cases[47,69]. Hence, it was suggested to use cTnI level as the biomarker of COVID-19 severity which would be measured immediately after hospitalization of the COVID-19 patients as well as longitudinal monitoring during hospital stay to estimate the disease progression towards severe clinical outcome[48,70]. However, increased serum concentration of cTnI is also associated with a higher risk of mortality in other infectious diseases such as pneumonia, sepsis and chronic obstructive pulmonary diseases[49, 71] which justifies the rationale behind the prognostic value of this marker. Other than cTnI, two other biomarkers of myocardial injury showed diagnostic value in COVID-19 patients, including the creatine kinase-myocardial band (CK-MB) and brain natriuretic peptide (BNP). The serum BNP level was also found to be raised along with serum cTnI level among the severe patients contrasting the low and stable serum level of BNP among the hospital discharged patients[50,72].

KEY POINTS

- *The COVID-19 pandemic has brought the whole world at a halt, with >1.7 million deaths*
- *The relatively fast-mutating nature of the virus and variety of symptoms across age groups and geographic regions make it difficult to manage and treat*
- *SARS-CoV-2 induced cardiac injury was found to cause a significantly higher rate of fatality compared to either of the closely related viruses: MERS-CoV or SARS-CoV*
- *Preexisting cardiac complications in COVID-19 patients significantly increase the risk of COVID-19 morbidity and mortality*
- *Available therapeutics used for clinical management of COVID-19 may interfere with the cardiovascular system, leading to cardiovascular complications*
- *The biomarkers related to progressive cardiovascular damage may be of diagnostic potential in predicting the outcome of infection and treatment*

Also, the elevated level was reported to be associated with a higher mortality rate of 51.2% in the COVID-19 patients[6]. However, elevated levels of both BNP and CK-MB was evident in the patients admitted to ICU with myocarditis but without pre-existing cardiovascular complications[50,72]. On the other hand, D-dimer protein not directly associated with cardiac injury rather indicating coagulopathy in the COVID-19 patients, can also be considered for its prognostic value of disease severity and mortality.

8. Conclusion

Cardiovascular complications among the COVID-19 patients with or without pre-existing cardiovascular diseases pose a significant risk in disease prognosis and increased risk of mortality. Hence, a clear understanding of the pathogenesis of SARS-CoV-2 and how it damages the cardiac systems, as well as the factors responsible for poor prognosis, play vital roles in the optimal clinical management of the COVID-19 patients. Thorough knowledge of the molecular mechanism of cardiovascular damage is relevant even after mass vaccination, since the efficacy of the vaccine on the vulnerable group (children, immunocompromised and the elderly).

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M.M.R. developed the hypothesis. S.T.T. and N.N.R. drafted and reviewed the manuscript. S.A., O.S., S.M., M.M. reviewed and edited the final draft of the manuscript. M.M.R. supervised the whole work and P.S. critically reviewed the drafted manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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