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Molecular Determinants, Clinical Manifestations and Effects of Immunization on Cardiovascular Health During COVID-19 Pandemic Era - A Review

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Abstract: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has enveloped the world into an unprecedented pandemic since 2019. Significant damage to multiple organs, such as the lungs and heart, has been extensively reported. Cardiovascular injury by ACE2 downregulation, hypoxia-induced myocardial injury, and systemic inflammatory responses complicate the disease. This virus causes multisystem inflammatory syndrome in children with similar symptoms to adult SARS-CoV-2-induced myocarditis. While several treatment strategies and immunization programs have been implemented to control the menace of this disease, the risk of long-term cardiovascular damage associated with the disease has not been adequately assessed. In this review, we surveyed and summarized all the available information on the effects of COVID-19 on cardiovascular health as well as comorbidities. We also examined several case reports on post-immunization
Coronavirus disease 2019 (COVID-19) is the first large pandemic after the 1918 Influenza pandemic that caused nearly 15 million deaths. COVID-19 is caused by a novel beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus belongs to the coronaviridae family, members of which have caused similar respiratory diseases in the past. COVID-19 began as a respiratory disease outbreak in Wuhan city of Hubei province in Mainland China, with the index case being discovered in November 2019. The disease was declared as a pandemic by World Health Organization (WHO) on March 11, 2020, primarily due to its rapid community transmission. The COVID-19 etiologic agent, initially designated as 2019-nCoV, was later isolated and classified as a novel coronavirus. After genome sequencing, the virus was named severe acute respiratory syndrome coronavirus-2 by the International Committee for Virus Taxonomy due to its similarity to the virus that triggered the 2003 SARS outbreak. After sequencing 96% of the genome, the SARS-CoV-2 sequence was found to be identical to another coronavirus isolated from bat species (Bat-CoV-RaTG13) from Yunnan province, nearly 2000 km away from Wuhan. Thus, the origin and source of SARS-CoV-2 were suspected to be a horseshoe bat.

According to WHO, fever, cough, tiredness, loss of taste or smell are the most typical signs and symptoms of this viral illness. Shortness of breath, loss of speech or movement, chest discomfort are all severe signs that require rapid medical attention. Sore throat, headache, bodyaches, diarrhoea, skin rash, and red or irritated eyes are some of the less usual symptoms.

COVID-19 has rapidly emerged as a pandemic with over 513,955,910 cases with 6,249,700 deaths globally, as documented in WHO latest on May 06, 2022. The rapid contagion necessitated an immediate understanding of the pathogen and associated comorbidities to find an effective treatment regimen. Primarily affecting lung function, coronavirus infections impair multiple organ systems, including the cardiovascular system and gastrointestinal tract. COVID-19 infected patients have impaired cardiac functions leading to deleterious consequences like myocardial injury, arrhythmias, and heart failure (Fig 1). Further, patients with cardiovascular comorbidities reportedly had a higher mortality rate than non-comorbid patients suffering from COVID-19.
complications in COVID-19 patients include long-term consequences like heart palpitations, loss of breath, persistent cough, chest ache. In a study by Guo et al. 11 35.3% of the total 187 COVID-19 positive patients had a history of cardiovascular comorbidities like hypertension and coronary heart disease, and 27.8% of patients had suffered a myocardial injury. Among a total of 187 patients, 144 patients were discharged from the hospital. In contrast, 43 patients succumbed to the disease. On average, 8%-12% of COVID-19 infected patients reportedly suffered a direct or indirect myocardial injury, systemic inflammation, and acute coronary arterial event.12 According to 1 report, of the 16.7% cases of arrhythmia in COVID-19 patients, 8.9% were mild, and 44.4% were severe, others were moderate. Abnormalities in glucose and lipid metabolism were also noted in a long-term assessment of COVID-19 patients.13 These irregularities necessitate a detailed evaluation of cardiovascular implications related to coronavirus infection. In this review, we have attempted to summarize available knowledge on the impact of SARS-CoV-2 viral infection on the human heart as well as the cardiovascular system through systematic research.

**Mechanism of Virus Entry**

SARS-CoV-2 exhibits a striking surface entry mechanism wherein spike glycoprotein (S) present on the external envelope of the virion facilitates its entry into the host cell. Biochemically, the structure of SARS-CoV-2 consists of an outsized ectodomain, a short C-terminal intercellular tail, and a single pass trans-membrane anchor. The large ectodomain of S protein of a coronavirion is composed of 2 parts: the S1 site, which binds to the receptor and is a measure of the capability of the virus to

![Diagram showing the mechanism of virus entry into the heart.](FIG 1. Cardiovascular pathology due to SARS-CoV-2 infection (Color version of figure is available online.).)
enter a host cell, and another part, the S2, which is the membrane fusion unit (Fig 2). Studies have revealed that SARS-CoV-2 can strongly bind to the human angiotensin-converting enzyme 2 (ACE2) receptor. Although both SARS-CoV and SARS-CoV-2 share a similar binding pattern with ACE2 receptor, minor molecular difference in the receptor-binding domain of the S-unit in SARS-CoV-2 increases its ACE2 binding affinity. Therefore, a quantum increase in pathogenicity and virulence is observed in SARS-CoV-2.15,16

Cells with a high surface ACE2 expression [eg, type II alveolar cells (AT2) of the lungs] are more in the risk of SARS-CoV-2 infection.14 Evidence from single-cell RNA sequencing has suggested that organs like the bladder, esophagus, kidney, heart, and ileum are highly affected by SARS-CoV-2 infection due to the abundant expression of ACE2 receptors on the outer surface of these cells.17

The virus can enter the cells in 2 ways following cell contact, that is, either through endosomes or plasma membrane fusion (Fig 3). The entry of SARS-CoV-2 is facilitated by Spike proteins (S1 and S2) by mediating cell membrane attachment through ACE2 binding. As virions are endocytosed into endosomes, either cathepsin L or trans-membrane protease serine 2 (TMPRSS2) activates spike proteins close to the ACE2 receptor, which initiates viral membrane fusion with the plasma membrane. After endocytosis, the virus releases positive-sense single-stranded genomic RNA. Subsequently, the released RNA is translated into polyproteins.3 The genomic RNA of SARS-CoV-2 encodes nonstructural proteins that play a critical role in synthesizing viral RNA and structural proteins essential for assembling new virions. The process involves the translation of positive-sense single-stranded genomic RNA into nonstructural
FIG. 3. The life cycle of SARS-CoV-2. (1A) virus entry through endosomes, (1B) virus entry through plasma membrane fusion, (2) virions are endocytosed into endosomes, (3) virus releases RNA, (4) Genomic RNAs are then prepared to initiate translation, (5) polyproteins are translated to form polyproteins pp1a and pp1ab, (6) Proteolysis of polyproteins 1a and 1ab to form 16 non-structural proteins (7) formation of helicase and RdRp complex, (8) RdRp complex helps development of negative-sense RNAs, (9) Transcription of mRNAs and Ribosomes translate S-spike, M-membrane, N-nucleocapsid, and E-envelope encoding proteins, (10) The nucleocapsids are assembled along with genomic RNA, (11) The precursor of virions is then transferred by vesicles from the RER via the Golgi apparatus to the cell surface, (12) Virions are released by exocytosis, (13) Virus is released in the extracellular environment.3,4
proteins 1a and 1ab, followed by cleavage of the nonstructural proteins into smaller components, such as RNA-dependent RNA polymerase complex (RdRp) or helicase with the help of 2 enzymes; papain-like protease (PLpro) and 3C-like protease (3CLpro). By both replication and transcription, this complex drives the development of negative-sense RNAs. The ribosomes of the rough endoplasmic reticulum (RER) translate a subset of around 9 subgenomic RNAs, including those that code for all structural proteins. They are transported to the RER surface for virion assembly. The nucleocapsids (N) are assembled with genomic RNA in the cytoplasm. The precursor of virions is then transferred from RER as vesicles via the Golgi apparatus to the cell surface. Lastly, Exocytosis releases virions from infected cells, kicking off a new replication cycle.

**Virus Mediated Pathogenesis**

The clinical course of SARS-CoV-2 infection can be divided into 2 clinical phases. The first phase involves replication of SARS-CoV-2, known as the replicative phase, during which the patient exhibits no symptoms to mild clinical manifestation of the disease. A significant difference between infection caused by old forms of coronaviruses and SARS-CoV-2 infection is the absence of upper respiratory tract infection (e.g., Rhinorrhea) in the case of the latter. A study reported that nearly 18% of COVID-19 patients lacked any symptoms despite having the SARS-CoV-2 infection. The most common symptoms exhibited by most patients are dry cough, shortness of breath, and fever. In addition to these, patients suffering from severe COVID-19 also exhibited pneumonia, and mild respiratory distress, requiring supportive maintenance such as oxygen supplementation. Besides these symptoms, patients suffering from SARS-CoV-2 infection displayed gastrointestinal abnormalities such as diarrhea, abdominal pain, and nausea, along with occasional cases of lymphopenia.

The second phase involves the build-up of adaptive immunity by the body against the virus through an antibody response. This decreases the virus titers and resolution of symptoms in most patients. However, high mortality risk persist in a minority of patients who become critically ill, and around 10% of total patients succumb to the worsening symptoms arising from the support of intensive care for survival. The patients also develop other symptoms such as multiorgan failure, acute cardiac injury, acute respiratory distress, secondary bacterial infections, and viremia. Multiorgan failure is reportedly associated with a marked elevated immune-inflammatory response. The second phase of infection plays a
vital role here as the severity of the infection depends on this phase. While most infected individuals remain asymptomatic or exhibit mild symptoms, patients with comorbidities or old adults with weak immune systems require hospitalization.\textsuperscript{19}

Direct Impact of Coronavirus on the Heart and its Management

We reviewed numerous studies that evaluated the micro- and macrohistopathological changes in the patients’ heart due to SARS-CoV-2 infection through tissue examination. All of them were either autopsies or post-mortem reports. However, only patients with the severe manifestation of the disease have been described here, along with the treatment approach.

Mechanism of COVID-19 Related Cardiovascular Manifestations

Out of the several theories speculating the probable mechanism of COVID-19 related cardiovascular manifestations, the following 5 mechanistic pathways of cardiac damage appear promising: (i) Direct injury; (ii) Cardiovascular injury by ACE2 downregulation, (iii) Hypoxia-induced myocardial injury, (iv) Systemic inflammatory response syndrome and (v) Psychological stress-induced cardiomyopathy.

Direct Injury. The presence of viral RNA in the blood is linked to the severity of COVID-19. As a result, SARS-CoV-2 infect cardiomyocytes directly through circulation. Direct SARS-CoV-2 infection can cause cardiomyocyte inflammation, apoptosis, and necrosis, leading to acute myocardial damage and myocarditis.\textsuperscript{22}

Cardiovascular Injury by ACE2 Downregulation. Cardiomyocytes reportedly sustain direct damage due to the binding of SARS-CoV-2 with the functional receptor ACE2, which is abundantly expressed in the heart and lungs. ACE2, a type 1 transmembrane protein receptor, acts as a regulator of the cardiovascular system by its essential functions like vasodilation, anti-hypertrophic, anti-fibrotic and antioxidant activity.\textsuperscript{23} Though ACE2 is homologous to ACE receptors, it can balance the renin-angiotensin-aldosterone system (RAAS) by converting angiotensin II into angiotensin. Downregulation of ACE2 induces systemic RAAS imbalance via angiotensin II overexpression. A cohort study of SARS-CoV-2
infected patients showed that angiotensin II expression was more remarkable among infected patients than normal. This condition results in RAAS imbalance inducing multiorgan failure.\textsuperscript{12}

**Hypoxia-Induced Myocardial Injury.** A direct attack on the pulmonary epithelial cells by the SARS-CoV-2 might play a potential role in developing acute respiratory distress syndrome (ARDS) and pneumonia.\textsuperscript{24} Additionally, patients suffering from ARDS and severe pneumonia experience hypoxia. The acute respiratory damage-induced severe hypoxia may give rise to oxidative stress and hence an overall increase in oxygen demand in the myocardial tissue (due to the existing acute lung injury). Apart from oxidative stress, intracellular acidosis and mitochondrial damage may lead to myocardial injury (Fig 4). This can further reduce oxygen saturation due to respiratory failure and systemic arterial hypotension, particularly among patients with low ischemic thresholds\textsuperscript{22,25} as described in a retrospective cohort study where 10% of total hospitalised COVID positive patients under cardiovascular treatment in ICU had severe respiratory failure leading to cardiac arrest due to ARDS and sudden pneumonia.

**FIG 4.** The probable mechanism of COVID-19 induced cardiac manifestations: SARS-CoV-2 enters the cells through binding with ACE2 receptors and directly attacking the epithelial cells in the lungs and heart, leading to acute respiratory distress syndrome (ARDS) pneumonia. Along with that, these patients experience hypoxia, which also worsens myocardial damage, causing myocardial infarction, myocarditis, and ischemia (Color version of figure is available online.)
Systemic Inflammatory Response Syndrome. The SARS-CoV-2 infection leaves scope for deregulated immune response where an increase in neutrophil-lymphocyte ratio has been observed, in contrast to the lower concentration of both the T suppressor cells and T helper cells. There is an overall increase in the expression of pro-inflammatory cytokines, such as granulocyte-colony stimulating factor, tumor necrosis factor (TNF)-α, Interleukin (IL)-6, IL-2R, monocyte chemoattractant protein 1 along with interferon-γ inducible protein 10, chemokine (IL-8), macrophage inflammatory protein 1-α. These altered levels of immune mediators generate cytokine storm syndrome. This massive increase in the immune response leads to cardiac microvascular damage, hyperpermeability of blood vessels, and clot formation in the coronary arteries, resulting in acute coronary syndrome (ACS) (as illustrated in Fig 5). This systemic inflammatory response can also cause plaque rupture leading to epicardial coronary artery occlusions.

Psychological Stress-Induced Cardiomyopathy. During SARS-CoV-2 infection, infected patients suffer from severe stress disorders like depression and anxiety. Physical and psychological stress stimulates sympathetic nerve activity and increases catecholamines release. This fear or stress causes several cardiac manifestations like hypertension due to coronary artery vasoconstriction, myocardial injury, and arrhythmia. These conditions might play a significant role in cardiovascular damage, causing vascular leakage with peripheral and pulmonary edema, direct cardiac toxicity, or rapid onset of severe cardiac dysfunction.

Diagnostic Markers for Cardiac Manifestations

To manage COVID-19 induced cardiac complications, the primary diagnosis is made by laboratory tests, echocardiography, and electrocardiography (ECG). Coronary angiogram by computerized tomography (CT) and magnetic resonance imaging (MRI) is a highly preferred diagnosis technique to identify the early manifestations of cardio dysfunction. Evaluation for cardiac biomarkers like N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponin (cTn) is also equally essential to identify the cardiomyopathy in COVID-19 infections. NT-proBNP is secreted by the heart during myocardial wall stress, and the heart is working hard to pump. A higher level of NT-proBNP indicates the risk of cardiomyopathy. Frequently elevated blood troponin level is an interesting but common observation in COVID-19 patients. Elevated cTn levels can be widely connected with augmented severity of
FIG 5. Mechanisms implicated in the pathogenesis of myocardial injuries related to COVID-19 infection. (1) SARS-CoV-2 enter through the ACE2 receptors; (2) Viruses attack alveolar epithelial cells in lungs; (3) Viruses are then recognized by dendritic cells and macrophages followed by the release of large amounts of cytokines; (4) Increased level of proinflammatory cytokines like IL-1, IL-6, IL-8, TNF-α, NF-κB induce cytokine storm; (5) Cytokine storm stimulates the production of ROS in the cells; (6) ROS lead to lung injury, pulmonary edema and acute respiratory distress syndrome (ARDS); (7) Lung injury causes an imbalance between oxygen demand and supply resulting in arterial hypotension causing cardiovascular damage; (8) Cytokine storm-induced ROS causes systemic inflammation leading to cardiac microvascular damage and acute coronary syndrome.
cardiovascular disease and consequent risk of death.\textsuperscript{30} The rise in cTn level in COVID-19 patients also be noted due to arrhythmia, heart failure, hypotension, hypoxemia and renal failure, and other common factors, which must be clinically evaluated.\textsuperscript{31} Myocardial infarction is characterized by an elevation of the cTn value above the 99th percentile, according to the fourth universal concept of myocardial infarction. If there is a rise and/or decline in cTn values, the injury is considered acute. In a retrospective single-center case series, Guo et al.\textsuperscript{11} analyzed that SARS-CoV-2 infected hospitalized patients with elevated cTn levels had more frequent malignant arrhythmias than normal patients. Reasons other than systemic inflammation, myocardial infarction, direct myocardial inflammation, plasma troponin concentration elevation can result due to SARS-CoV-2 infection associated thromboembolism leading to coronary microvascular ischemia.

The myocardial zymogram, including the measurement of D-Dimer, C-reactive protein (CRP), IL-6, Creatine Kinase (CK), or more specifically creatine kinase-myocardial band (CK-MB) and lactate dehydrogenase (LDH) activities, was frequently described in COVID-19 cohort studies.\textsuperscript{24,32,33} CK-MB isoenzyme level signifies injured myocardial cell wall,\textsuperscript{30} and D-Dimer level indicates formation and dissolution of a clot in the body. CRP and LDH, inflammatory markers are associated with cardiac arteries inflammation.\textsuperscript{29} The rise of CK (≥200 U/L) and LDH (≥250 U/L) serum levels accounted for 13.7 \% and 41 \% respectively, in a large multicenter retrospective analysis involving 1099 COVID-19 confirmed patients from 552 hospitals throughout 31 Chinese regions. Critically ill patients had higher CK and LDH levels (19 \% and 58.1 \%, respectively) and those with significant composite endpoint events, such as admission in ICU, invasive mechanical ventilation, and death.\textsuperscript{24}

**Cardiovascular Manifestations**

**COVID-19 and Myocardial Infarction and Myocarditis.** SARS-CoV-2 infection induces clinical manifestations of myocardial infarction, which can be diagnosed as ST-segment elevation myocardial infarction (STEMI), which helps in further treatment approach.\textsuperscript{34} An imbalance between myocardial oxygen demand and supply can cause myocardial infarction type 2.\textsuperscript{11} In our literature search, we also found that some authors have argued a direct connection between COVID-19 with myocardial infarction and myocarditis manifestations. In contrast, an autopsy of a patient who died of cardiac arrest and was simultaneously suffering
from COVID-19 revealed no indication of involvement of any myocardial structure, suggesting no direct impact on cardiac tissue due to COVID-19.\textsuperscript{35} Contrastingly, another case study revealed low-grade inflammation of the myocardium along with localization of SARS-CoV-2 particles in the myocardium outside of cardiomyocytes (estimated by endomyocardial biopsy) indicate towards the direct deleterious consequence of COVID-19 on the myocardium.\textsuperscript{36} The presence of viral RNA and mild inflammation in the heart of patients suffering from COVID-19 was confirmed by autopsy reports. SARS-CoV-2 infection is known to cause systemic inflammation, which probably may, in turn, augment the excessive risk of developing myocardial infarction of type 1, by destabilizing the coronary atheromatous plaques, leading to an increase in aggregation of platelets and consequently posing a greater risk of stent thrombosis.\textsuperscript{12} In another study, 64 SARS-CoV-2 infected patients were assessed for left ventricular ejection fraction (LVEF). COVID-19 patients showed low LVEF leading to cardiac failure, which is scored by heart failure with preserved ejection fraction or HFA-PEFF. As a higher HFA-PEFF score signifies that patients are suffering from myocardial injury, it was observed that the score was higher in COVID-19 patients along with left ventricular diastolic dysfunction.\textsuperscript{28} Anticoagulation therapy with low-molecular-weight-heparin was used to treat myocarditis, but this therapy could not be continued in 1 patient due to profuse bleeding in the coronary artery.\textsuperscript{33} A tentative mechanism and effect on the myocardium have been summarized in Figure 6.

Available clinical data suggest that progressive systemic inflammation caused by the SARS-CoV-2 may be attributed to myocardial injury, along with a direct infection of the myocardium, causing viral myocarditis, as evident in the fraction of patients already suffered from COVID-19.

**COVID-19 and Acute Coronary Syndrome (ACS).** Initiation of acute coronary syndrome following COVID-19 might be attributed to microthrombi formation, which may arise due to the cytokine storm or systemic inflammation, coronary spasm, or rapture of concomitant plaque\textsuperscript{37} (Fig 6). In a case study in New York, 18 patients with COVID-19 infection and simultaneous elevation of ST-segment (suggestive of potential acute myocardial infarction), 5 out of a total of 6 patients suffering from myocardial infarction required urgent percutaneous coronary intervention.\textsuperscript{38} A case study from Portugal reported that though the number of ACS patients hospitalized was less, cases were severe with a larger acute STEMI, increased troponin level, and left ventricular systolic dysfunction.\textsuperscript{39} In another report from Italy, 24 patients out of 28 patients with
COVID-19 had elevated ST-segment during myocardial infarction as the primary clinical manifestation. However, they were found to be negative in the COVID-19 test during coronary angiography. Salinas et al. reported a comparative cohort analysis where invasively managed ACS patients in 2020 were compared in the same time frame of 2019. This study analyzed the effect of SARS-CoV-2 infection on 30 days mortality rate in ACS patients. A total of 118 ACS patients were hospitalized, and 11% were COVID positive. Of these, 23.1% of COVID positive ACS patients and 5% COVID negative ACS patients died in 2020. This study showed that 30 days mortality rate in COVID positive ACS patients was greater than COVID negative ACS patients. A positive SARS-CoV-2 test was shown to be related with 30-day mortality in the multivariable

FIG 6. Detailed overview of the bidirectional correlation between COVID-19 and cardiovascular manifestations. Cardiovascular comorbidities in patients with COVID-19, like coronary artery disease and hypertension are associated with heart failure. COVID-19 is most commonly associated with viral pneumonia, but it can also cause cardiac damages like myocarditis, arrhythmias, acute coronary syndrome, and thromboembolism in the cardiovascular system. Finally, several of the drugs that have been recommended as COVID-19 therapies have pro-arrhythmic properties. (Color version of figure is available online.)
analysis. These observations put forward substantial evidence on how COVID-19 may be a precedent cause for the ACS, even when no systemic inflammation occurred. On the other hand, the global pandemic has changed the ACS treatment approach, Morishita et al. observed a change in the ACS treatment of in-hospital patients in Japan, like reduction in primary percutaneous coronary intervention and increased in the use of fibrinolytic therapy (use of thrombolytic agent), and coronary artery bypass graft surgery had ceased.

**COVID-19 and Arrhythmia.** The 2 most common clinical manifestations of COVID-19 are sudden cardiac arrest and arrhythmias. In COVID-19 patients devoid of cough or fever, heart palpitations have emerged as the primary clinical symptom. In a study on a group of 138 COVID-19 patients from Wuhan, China, 17% of the patients (44% patients in the ICU) reportedly developed arrhythmia; however, no records have stated the type of arrhythmia. In another study from Wuhan, the cohort of 187 hospitalized patients suffering from COVID-19, found with raised levels of troponin T. They had a greater risk of developing malignant arrhythmias, like ventricular fibrillation and tachycardia, as compared to the population having normal plasma concentration of troponin T (12% vs 5%). Myocardial injuries or other systemic factors like sepsis, fever, electrolyte imbalance, and hypoxia can trigger arrhythmias, especially atrial as well as ventricular fibrillation and tachycardia. Generally, cardiac depolarization and repolarization time or QTc interval prolongation is directly related to a high risk of ventricular arrhythmias and cardiac failure (Fig 6). In a report, Guo et al. showed that QTc interval was prolonged in SARS-CoV-2 infected patients with preserved ejection fraction-like syndromes and leading to heart failure.

During this pandemic, not only did the patients with a history of cardiovascular complications have experienced severe COVID-19 induced cardiac arrhythmia, but it has also been observed in patients without any pre-existing syndrome. Zylla et al. described a study where 34 patients were hospitalized due to arrhythmia, where atrial fibrillation was the most common type. In 10.2% of patients, arrhythmia was diagnosed before SARS-CoV-2 infection, where 16 patients had a history of atrial fibrillation, and 1 patient had bradycardia. In contrast, 13.3% of patients had new-onset arrhythmia, and 9.6% had no previous history before contracting COVID-19 and hospitalization. Four patients were administered amiodarone to manage the arrhythmic complications, and 3 received chronic antiarrhythmic therapy.
Since many patients with atrial fibrillation type of arrhythmia have been found with new or previously diagnosed venous thrombosis or pulmonary embolism, they received anticoagulation therapy. To maintain oxygen supply in blood or support blood circulation in the body, patients receive oxygen, vasopressors, and noninvasive ventilation. In severe respiratory failure due to cardiac arrhythmia, patients require mechanical ventilation. Duration of mechanical ventilation was not related to new or previously diagnosed COVID-19 infected arrhythmic patients. In addition, the antibiotic and antiviral treatments (Hydroxychloroquine, Tocilizumab, Remdesivir, Favipiravir) were administered to patients suffering from advanced COVID-19 infections induce arrhythmias or other cardioxicities (Table 1) in a few patients. Stählberg et al. highlighted the presence of tachycardia within 4-12 weeks after a SARS-CoV-2 infection as a symptom of post-acute COVID-19 syndrome.

**Impact of COVID-19 on the Heart of Children**

The severity of SARS-CoV-2 infection is reportedly low among children with mild symptoms compared to adults. However, it reportedly has severe manifestations like pneumonia, acute injury in the kidney and heart leading to a multisystem inflammatory syndrome in children (MIS-C) in a few children. MIS-C reportedly affects children below 21 years of age, and half of the patients are above 10 years. Some symptoms of MIS-C are similar to Kawasaki disease, and some are with SARS-CoV-2 associated cardiovascular complications in adults due to the elevation of inflammatory markers. Symptoms like fever, abdominal pain, mucocutaneous diseases, and coronary artery dilation are similar to Kawasaki disease, where elevated cTn, acute systolic biventricular heart failure, cardiogenic shock, ST-segment elevation in ECG finding are the symptoms similar to adult SARS-CoV-2-induced myocarditis. Thrombocytopenia is another common symptom of MIS-C.

Association for European Paediatric and Congenital Cardiologists had conducted a multicentre survey to document MIS-C associated cardiovascular clinical manifestations in 286 children with an average age of 8.4 years in 17 European countries from 55 centers. A majority had elevated cTn value and reduced LVEF with elevated inflammation markers like CRP, NT-proBNP, IL-6, serum ferritin, procalcitonin, and D-dimer in blood. Cardiovascular complications included were cardiogenic shock, arrhythmias, pericardial effusion, coronary artery dilatation. Another retrospective case report analyzed 4 children and adolescents 6-12 years of age admitted to the ICU with acute myocarditis. All patients were...
### Table 1. Updated drug therapies for cardiovascular complications in COVID-19 patients

| Class of drug | Name          | Mechanism of action                                                                 | Role of the drug on COVID-19 infected patients                                                                 | Adverse effects or contraindications                                                                 |
|---------------|---------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Antiviral drugs | Remdesivir    | □ It is a nucleotide prodrug of an adenosine analog; administered intravenously.       | □ Remdesivir shortened the recovery time of hospitalized patients, as the treated patients had reduced respiratory infection. | □ Hepatotoxicity, renal toxicity are common.                                                     |
|               |               | □ The drug inhibits viral replication as it terminates RNA transcription prematurely by binding to the viral RNA-dependent RNA polymerase. | □ Patients who received at least 1 dose of remdesivir had improved oxygen support.                           | □ Cardiotoxicity has been reported in rare cases or in higher doses.                               |
|               | Ritonavir/ Lopinavir | □ Binds and inhibits 3C-like proteinase enzyme and suppresses SARS-CoV-2 viral replication. | The median time for clinical advancements in the lopinavir-ritonavir treatment group was 1 day less than the standard group in an open level randomized control trial conducted with 199 COVID positive patients, where 99 patients were allotted in the lopinavir-ritonavir group. | □ Cardiovascular risks have been reported for QT and PR interval prolongation in healthy adults, and there are rare reports of atrioventricular blockage in patients with pre-existing conduction abnormalities. |
|               | Favipiravir    | □ Inhibits RNA-dependent RNA polymerase enzyme, thus                                  | Favipiravir group have a shorter viral clearance median time and significantly improved                      | □ Hepatotoxicity, pancreatitis, and neurotoxicity are the main reported adverse effects.          |

(continued on next page)
| Class of drug | Name       | Mechanism of action                                                                 | Role of the drug on COVID-19 infected patients                                                                 | Adverse effects or contraindications                                                                 |
|--------------|------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Antiparasitic drug | Ivermectin | - Inhibits the nuclear import of proteins of virus and host as well.                | - Patients on ivermectin treatment resolved all the symptoms of COVID-19 on the 21st day of infection.       | - Headache, vomiting, diarrhea, abdominal discomfort is common adverse effects.                      |
|              |            | - It could bind to 3CL protease, RNA-dependent-RNA polymerase, and helicase, and nucleocapsid protein. | - Combining ivermectin and doxycycline increased viral clearance and recovery.                                 | - Cardiovascular risk reports in COVID-19 patients showed tachycardia and PR interval prolongation in rare cases. |
|              |            |                                                                                      | chest CT compared with the ritonavir/lopinavir group in a preliminary clinical study where 35 patients received favipiravir along with interferon (IFN)α and 45 patients were treated with ritonavir/lopinavir along with IFNα. | - Severe adverse effects, mainly in men above 64 years of age, are blood and lymphatic disorders, cardiac disorders. |
|              |            |                                                                                      |                                                                                                               | nausea, vomiting, tachycardia, and diarrhoea.                                                      |
| Class of drug | Name | Mechanism of action | Role of the drug on COVID-19 infected patients | Adverse effects or contraindications |
|--------------|------|---------------------|-----------------------------------------------|-------------------------------------|
| Antibiotics  | Fluoroquinolones, Cephalosporins, Azithromycin, and Ornidazole. | □ Cephalosporins bind to the penicillin-binding protein and inhibit bacterial cell wall synthesis.\(^{68}\)  
□ Azithromycin inhibits bacterial protein synthesis in bacterial coinfection associated with COVID-19 viral infection and stimulates human immune and epithelial cells.\(^{69}\)  
□ Ornidazole acts via reduction of the nitro group, produces toxic derivatives and free radicals.\(^{70}\)  
□ Fluoroquinolones act by inhibiting 2 enzymes involved in bacterial DNA synthesis.\(^{71}\) | In a retrospective case-control study where 65 COVID positive patients with nosocomial infection were evaluated against 260 COVID positive non-nosocomial infection patients as control. In the univariate and multivariate analysis, significant positive associations between nosocomial infection and antibiotics were seen. These antibiotics significantly inhibited bacterial infection in patients with several comorbidities like hypertension, cardiovascular diseases, liver, and chronic kidney diseases, diabetes, and respiratory diseases.\(^{72}\) | □ Common adverse reactions are nausea, vomiting, lack of appetite, dry mouth.  
□ Some reports showed Azithromycin as arrhythmogenic.\(^{68,73}\) |
Wang et al.\textsuperscript{18} described a retrospective, single-center case report from Wuhan, China, of 138 COVID positive hospitalized patients with confirmed pneumonia, and 46.4\% among them had one or more comorbidities. 14.5\% of the total comorbid patients with pneumonia were suffering from pre-existing cardiovascular diseases, and 31.2\% had hypertension. Moxifloxacin was given to 64.4\% patients; ceftriaxone to 24.6\%; azithromycin to 18.1\% of patients among total patients who received antibiotic therapy. These therapies significantly reduced the median hospital stay of patients by reducing disease severity.

Common adverse reactions are nausea, vomiting, lack of appetite, headache, and dizziness. Acute thrombocytopenia with epistaxis and petechiae occurred during treatment with ceftriaxone, levofloxacin, and lopinavir/ritonavir in a COVID positive patient and recovered gradually with withdrawal.\textsuperscript{74,75}
| Class of drug                  | Name        | Mechanism of action                                                                 | Role of the drug on COVID-19 infected patients                                                                 | Adverse effects or contraindications                                                                 |
|-------------------------------|-------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Immuno-modulatory regimens    | Tocilizumab | □ This anti-IL-6 receptor monoclonal antibody blocks IL-6 receptor-mediated signal transduction. |
|                               |             | □ It prevents the cytokine storm syndromes caused due to the elevation of IL-6 during COVID-19. |
|                               |             | □ Tocilizumab treatment among COVID-19 infected patients suffering from severe pneumonia showed a reduced risk of invasive mechanical ventilation or death. |
|                               |             | □ Hospital mortality was less in the patients who received tocilizumab in the first 2 d of ICU admission. |
|                               |             | It may increase the severity of atherosclerotic cardiovascular disease as it increases serum LDL, cholesterol, and triglyceride levels. |
| Hypolipidemic drug            | Statins     | Used for secondary prevention of coronary heart disease in COVID-19 infected patients. |
|                               |             | A retrospective cohort analysis of COVID-19 patients conducted on 1296 patients (648 statin users, 648 non-statin users) reported that antecedent statin use was associated with lower inpatient mortality. |
|                               |             | □ Cause elevation in serum glucose level, CK, and liver enzymes. |
|                               |             | □ Antiviral drugs Ritonavir/ Lopinavir may have serious side effects like rhabdomyolysis. |

(continued on next page)
| Class of drug     | Name                                                                 | Mechanism of action                                                                 | Role of the drug on COVID-19 infected patients                                                                 | Adverse effects or contraindications                           |
|------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Antihypertensive drugs | Renin-angiotensin-aldosterone system inhibitors or RAAS inhibitors include ACE inhibitors (ACEIs) and Angiotensin II receptor blockers (ARBs) | □ Commonly used to treat hypertension, myocardial infarction, and heart failure.  
□ In the COVID-19 treatment approach, the favourable action of RAAS inhibitors is blocking ACE2 receptors and preventing viral entry into the heart and lungs.  
□ Also, decrease IL-6 and CRP levels in peripheral blood.  
□ These drugs also reduce peak viral load by increasing CD3+ and CD8+ T cells.  
□ There were some different opinions regarding the withdrawn of RAAS inhibitors for their negative impact on SARS-CoV-2 infected patients, but Chouchana et al. found no association between the use of RAAS inhibitors with in-hospital mortality. | □ ACEIs or ARBs can reduce severity in COVID-19 patients with hypertension.  
□ Also, decrease IL-6 and CRP levels in peripheral blood. | □ Hypotension, hyperkalaemia, rash, angioedema, diarrhoea. |
| Class of drug | Name | Mechanism of action | Role of the drug on COVID-19 infected patients | Adverse effects or contraindications |
|--------------|------|---------------------|---------------------------------------------|-------------------------------------|
| β-blockers    | β-blockers | Act via slowing down conduction velocity and prolonging the refractory period, as it indirectly prevents calcium ions from entering into myocardial cells. | CCB treatment reduced mortality in elderly patients with cardiovascular comorbidity. | Bradycardia, hypotension, fatigue, nausea, and constipation. |
| Calcium channel blockers (CCB) | CCBs prevent calcium ions from entering into the cells of the heart and arteries, leading to hypotension in the blood vessels. | CCB treatment reduced mortality in elderly patients with cardiovascular comorbidity. | Constipation, bradycardia, and headache. |
| Antiplatelet blood-thinning agents | Aspirin | Prevent the formation of a blood clot, inhibiting platelet aggregation via blocking thromboxane A2 formation in platelets. | Combination therapy of enoxaparin injection, ivermectin solution, aspirin 250 mg tablets and dexamethasone 4-mg injection significantly lowered the overall mortality rate of the infected population in Argentina and did not allow the disease to progress from mild to moderate symptoms. | Gastrointestinal ulcer, abdominal pain, stomach upset, and rash. |

In another case, study patients over 60 years who received aspirin showed lower cumulative in-hospital death.
hospitalized within a week from the onset of initial symptoms of SARS-CoV-2 infection, that is, fever, gastric irritation, rash, conjunctivitis. Tachycardia, systolic dysfunction, and vasoplegia with low-normal LVEF were reported from ECG findings in most of these patients. Elevated brain natriuretic peptide (BNP), cTn, and CRP were also reported. Postinfectious diffuse myocardial edema was found in cardiac MRI. Intravenous immunoglobulin therapy was the treatment approach. In another meta-analysis of cardiac markers reported by Zhao et al., in 1613 hospitalized children diagnosed with MIS-C, BNP level was significantly higher in patients with MIS-C than patients with mild or moderate symptoms. BNP is a protein made by heart and blood vessels, and a higher level of it indicates the risk of heart failure. In a retrospective single-center study reported by Theocharis et al., 20 patients of average age 10.6 ± 3.8 years were admitted at Evelina London Children’s Hospital with MIS-C associated cardiovascular complications. All patients showed abnormality in the Doppler echocardiography, and ejection fraction resulted in low-normal echocardiography in half of the patients. Uniform coronary artery dilation in CT and myocardial edema in MRI had been reported in 50% of patients. Similar to ECG findings in adults with myocardial infarction or arrhythmias, ST-segment elevation and QTc interval prolongation were seen in patients with MIS-C-associated cardiovascular manifestations.

These findings suggest that though the percentage of infected children is very low, SARS-CoV-2 infection injures and alters the functions of vital organs, and the findings on the extent of cardiac involvement are increasing day by day from the initial reports. ACS, cardiac edema, and other cardiovascular changes can persist in the future despite the normalization of cardiac and inflammatory markers. There has been no WHO-approved vaccine available for children till now. So, detailed screening using advanced techniques on the changes in patients with infection and pharmacovigilance monitoring should be continued to manage this condition.

Management of COVID-19 Induced Cardiovascular Complications

For the treatment of COVID-19, no specific effective therapies have yet passed FDA screening in the United States. The World Health Organization’s “Solidarity” international clinical trial aimed to recognize medicines with therapeutic promise for COVID-19 involves 14,200 hospitalized patients from 600 hospitals of 52 countries. Still the
approach of medication has been towards “repurposing” or “repositioning” of other drugs for the treatment of COVID-19. The aim of “repurposing” or “repositioning” is to quickly assess the effectiveness of current antiviral, antiparasitic and immunomodulatory drugs that have not yet been registered for the treatment of COVID-19. Many drug candidates have been screened, and many are currently being investigated, including antiviral drugs (eg, remdesivir, ritonavir/lopinavir, Favipiravir), antibiotics (eg, fluoroquinolones, cephalosporins, azithromycin, ornidazole), antiparasitic drug (eg, ivermectin), immunomodulatory regimens (eg, tocilizumab), and supporting agents (vitamin B complex, C and D). For specific cardiac manifestations, symptomatic treatment approach has been considered like antihypertensive drugs (β-blockers, renin-angiotensin-aldosterone system inhibitors), hypolipidemic drug (statins), and antiplatelet blood-thinning agents (aspirin, warfarin, heparin, and clopidogrel). For different cardiovascular manifestations with COVID-19, possible anti-SARS-CoV-2 regimens have been summarized in Table 1.

Recently, WHO has announced the start of next phase of the Solidarity trial where SARS-CoV-2 infected hospitalized patients will be tested for a new treatment approach with 3 new drug therapies. Artesunate, Imatinib, and Infliximab are the 3 new drugs of choice that will be tested for their efficacy in reducing severity and mortality in COVID-19 hospitalized patients. These drugs are already being used for other diseases like severe malaria, cancers, and immune disorders (Crohn’s Disease, rheumatoid arthritis) respectively.

Immunization and post-immunization cardiovascular complications

COVID-19 vaccines are being produced faster than conventional vaccines and are being approved internationally through Emergency Use Authorization (EUA). According to a report published by WHO, as of May 06, 2022, there are 351 vaccines to be developed for COVID-19, 197 are in preclinical development, and almost 154 vaccines are under human clinical trials. There are 3 main approaches to vaccine design: (1) use a whole virus (inactivated virus, live-attenuated virus, and viral vector); (2) use a part of the viral particle to trigger the immune system; (3) use the virus genetic material (nucleic acid). These immunization processes are meant to boost the immune response by various mechanisms. Both T and B cells have an adaptive immune response to SARS-CoV-2. At about 10 days after viral infection, IgG and IgM antibodies appear in
the infected host. The antibodies have neutralizing activity and are made against the virion’s internal nucleoprotein and spike protein.96 Total 11,598,144,093 vaccine doses have been administered worldwide till May 07, 2022.8

Individuals receiving the influenza vaccine within a year of contracting the infection reportedly had significant protection and experienced mild clinical conditions, including the patients with various comorbidities who received this vaccine. Influenza vaccine activated natural killer cells within the body after viral entry. Thus influenza immunized patients had fewer hospitalization and ICU admission risks than non-vaccinated COVID infected patients.97 Behrouzi et al.98 have shown that influenza immunization could reduce cardiovascular manifestations in COVID-positive patients leading to a reduction in morbidity and mortality.

Comirnaty and Covishield vaccines reportedly have mild side effects like- headache, fever, muscle pain, fatigue, joint pain and pain or redness or swelling at the injection site.99 Experiencing these side effects following vaccination is indicative of an active immune response. However, there are also some alarming cardiovascular complications during this process. Advisory Committee on Immunization Practices reviewed the safety data of Pfizer-BioNTech and Moderna mRNA-COVID-19 vaccine and observed that males were more prone to post-immunization myocarditis than females.100 Chest pain, dyspnea, or palpitations in infants, young adults, and adolescents were most common. They were diagnosed with myocarditis by the cardiac MRI result, elevated cTn, CRP levels, and abnormal ECG with ST-segment elevations along with abnormal echocardiogram report.101 According to a report, a 96-year-old female suffered myocardial infarction nearly 1 hour after her first Moderna COVID-19 vaccination, having no known cardiac history.102 Older adults and young people were equally prone to the cardiovascular effects post-immunization. A 24-years man experienced chest pain 4 days after his second dose of Moderna vaccine and was diagnosed with myocarditis via Cardiac MRI.103 Mouch et al.104 showed that 6 patients with a median age of 23 years were diagnosed with myocarditis, 5 patients received the second dose, and 1 received the first dose of BNT162b2-mRNA COVID-19 vaccine (Pfizer-BioNTech). Due to some symptoms like chest pain or discomfort, cardiac markers were checked, and cTn and CRP levels were found higher than normal. All of them were without any history of COVID-19 infection or cardiovascular problems. Similar symptoms with cardiac dysfunction and cardiac MRI evidencing myocarditis were found
in a report by Kim et al.\textsuperscript{105} where 4 patients (23-36 years aged 3 younger males and a 70-year-old female) had experienced myocarditis 3-5 days after receiving the second dose of mRNA-COVID-19 vaccine (where 2 of them received BNT162b2-mRNA vaccine and other 2 received mRNA-1273 vaccine).

In a case report from US Military Health System, 23 participants had acute myocarditis during their active duty, and 20 of them experienced it 4 days after receiving of mRNA COVID-19 vaccine.\textsuperscript{106} Supporting the observations of the Advisory Committee on Immunization Practices, Marshall et al.,\textsuperscript{107} reported that 7 males (14-19 year-old adolescents) experienced post-immunization myocarditis and myopericarditis after 4 days of receiving the BNT162b2-mRNA vaccine. After mRNA vaccines, another case of acute myocarditis in 28 years male patient came from the US after being vaccinated by EUA approved adenovirus vaccine (Johnson and Johnson). 5 days after vaccination, the subject experienced chest pain, and ST-segment elevation in the prostate ECG was found along with elevated cTn. In the same case series of 7 patients from US another report on mRNA vaccines by Moderna or Pfizer/BioNTech came where 6 patients had acute chest pain with biochemical evidence of myocardial injury 3-7 days after the second dose of vaccination. Cardiac MRI had no evidence of sustained arrhythmia.\textsuperscript{108} Another case report by Chamling et al.\textsuperscript{109} on another approved vaccine Covishield, showed that a 68-year-old lady experienced acute chest pain after her first dose of the vaccine. Elevated cardiac enzymes (cTn, CK, CK-MB) and cardiac MRI report suggested it as non-ischemic myocardial damage or vaccine-associated autoimmune myocarditis with active inflammation in basal and apical segments of the septal wall. In the same case series report, a healthy young man (25 years) had acute chest pain after 10 days of receiving the first dose of Pfizer–BioNTech mRNA vaccine. Elevated cTn, CK values, and ST-segment elevation in ECG finding along with cardiac MRI report evidenced it to be vaccination-associated non-ischemic autoimmune myocarditis. Similar clinical manifestations were reported in a 20-year-old, very healthy young police officer after 3 days of receiving his second dose of the Pfizer–BioNTech mRNA vaccine.

Finding a direct link between myocarditis and COVID-19 vaccination remains challenging.\textsuperscript{105} However, the limited observations on cardiac complications suggest that despite the safety data for all the approved COVID-19 vaccines, critical observation and thorough worldwide pharmacovigilance will be required to manage post-immunization complications.
Conclusion

The SARS-CoV-2 induced novel COVID-19 has numerous similarities with other pre-existing beta coronavirus infections like middle east respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). However, the infection has been found to be more severe, along with the involvement of multiple organs, including the cardiovascular system, as reported in many autopsies of COVID-19 infected patients. A systemic inflammation triggered by the infection may have implications on the heart. Reports of viral particles being present in the heart suggest the spread and reach of the COVID-19 virus into the cardiovascular system. It has now been reported that the ACE2 receptor is the primary interacting site both for the SARS-CoV and SARS-CoV-2 in the host cell, with 6.5% of all the myocardial cells have been reported to express this ACE2 receptor. Various animals and human studies regarding hypertension and diabetes suggest that the concentration of ACE2 receptors increased in those receiving medication with angiotensin-converting enzyme 2 inhibitors or angiotensin receptor blockers. These treatments up-regulate ACE2 receptors in the body, which further assists the entry of SARS-CoV-2 into the target cells. In contrast, an increase in the number or sensitivity of ACE2 receptors decreases the SARS-CoV-2 binding affinity to that present on the membrane. The soluble ACE2 receptor, when up-regulated consecutively, facilitates a reduction in the activity of angiotensin II, exerting a protective effect against the inflammation, and thus vasoconstriction, caused by the COVID-19 infection. This available information can be further explored and researched to treat COVID-19 and concomitant cardiovascular manifestations associated with COVID-19 infection. Also, the advent of different immunization schedules and stringent pharmacovigilance worldwide may provide more insights into the cardiovascular effects of the vaccination.

CRediT Authorship Contribution Statement

Amrita Chatterjee: Literature Search, Writing-original draft; Writing-review & editing; Rajdeep Saha: Literature Search, Writing-original draft; Arpita Mishra: Conceptualization, Literature Search, Writing-original draft; Deepak Shilkar: Writing-review & editing; Editing and Revision; Venkatesan Jayaprakash: Conceptualization and Supervision; Biswatrish Sarkar: Conceptualization, Supervision, Writing-review & editing; Editing and Revision; Pawan Sharma: Supervision, Writing-review & editing.
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