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Post-COVID-19 Associated Cardiovascular Complications: A Scoping Review

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes the extremely infectious sickness known as coronavirus disease 2019 (COVID-19). Globally, COVID-19 (simply, COVID) has had a terrible impact, killing more than 6 million people. SARS-CoV-2 spread quickly around the globe since the first instance of this respiratory viral infection was discovered in Wuhan, Hubei Province, China, on 31 December 2019. Keeping given epidemiological estimates, the World Health Organization (WHO) declared COVID-19 as a global pandemic on March 11, 2020. Post-COVID is a clinical condition characterized by the development of totally new COVID-19 symptoms three months after the initial SARS-CoV-2 infection. COVID-19-affected patients have been reporting a range of cardiovascular (CV) abnormalities which include myocardial inflammation, myocardial infarction, right ventricular dysfunction, myocardial hypertrophy, coronary artery atherosclerosis, focal myocardial fibrosis, acute myocardial infarction, cardiac hypertrophy, viral myocarditis, postural orthostatic tachycardia symptom (POTS), aortic and arterial thrombosis, venous thrombosis, and arrhythmias. Cardiopulmonary symptoms include chest pain, shortness of breath, fatigue, hypotension, and POTS are common and associated with significant disability and heightened anxiety. Additionally, the risk of CV side effects has also been reported with currently available COVID-19 vaccines. Pathophysiological mechanisms for post-COVID cardiac complications are still poorly understood. COVID-19 is anticipated to alter the long-term trajectory of many chronic cardiac diseases which are abundant in those at risk of severe disease. This review discusses the definition of post-COVID complications, pathophysiological mechanisms of underlying acute and chronic CV injury, and their impact post-COVID-19 on multiorgan health.

Keywords: Cardiac complications, cardiovascular abnormalities, cardiovascular injury, cardiopulmonary symptoms, COVID-19, SARS-CoV-2

INTRODUCTION

Corona**vi**rus **d**isease **2019** abbreviated as COVID-19 is a viral infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was discovered in Wuhan, Hubei Province, China in December 2019, has spread globally, and created the worst pandemic.[1] severe acute respiratory syndrome (SARS-CoV-2) is from the genus Betacoronavirus, a subfamily of Coronavirinae, which arises from the family Coronaviridae. It is enveloped and a novel single-strand RNA virus with a length of about 29.9 kb which causes COVID-19 infection.[2,3] The USA, the UK, India, Russia, and Vietnam were

among the many principal nations impacted. There have been one million documented deaths by COVID-19 by the end of September 2020. Pfizer and BioNTech vaccination studies concluded in November 2020 with 90% effectiveness. Globally, one billion doses of the COVID-19 vaccine have been administered by April 2021. Three million new cases and over 23,000 deaths were recorded between March 13, 2023, and April 9, 2023, according to the latest data. Over 6.8 million deaths and over 762 million confirmed cases had been recorded worldwide as of April 9, 2023.[4] Infection with SARS-CoV-2 causes coronavirus disease 2019 (COVID-19), which has contributed to a total cumulative of 7,072,509 deaths as of 20 October 2024.[5] The World Health Organization (WHO) proposed a meaningful definition for the "post-COVID-19 condition" in October 2021. Post-COVID-19 is a condition defined as the presence of symptoms lasting for 2 to 3 months from the initial (SARS-CoV-2) infection. "Post-COVID-19 syndrome" was applied to patients experiencing signs and symptoms after 12 weeks of illness onset.[2,6,7] Long COVID-19 (L-C19) is divided into two groups by the National Institute for Health and Care Excellence (NICE): (1) "Ongoing symptomatic C19" refers to symptoms that continue for 4 to 12 weeks and (2) "post-C19" refers to symptoms that continue for more than 12 weeks beyond the start of the disease. L-C19 has also been referred to by several other names, including "post-acute sequelae of SARS-CoV-2 infection," "persistent C19 symptoms," "post-C19 syndrome" (PCS), "long haulers", and "post-C19 signs" based on the duration and persistence of the symptoms.[8] Post-COVID-19 syndrome affects all age groups, it is poorly understood as it affects COVID-19 patients at all levels of disease severity. Over the years, COVID-19-recovered patients may show clinical correlates of collateral damage at primary, secondary, and tertiary levels of CV services and may lead to increased prevalence of co-morbidities owing to long-term complications affecting the CV system (**Fig. 1**). Though there were no reliable preventive vaccines and/or effective curative therapies for COVID-19 during the early period of the recent pandemic, approval of several drugs through the emergency use authorization (EUA) by the US Food and Drug Administration (FDA) was only available therapeutic option.[9-12] Indeed, many researchers have been investigating the potential antiviral and/or lifesaving beneficial effects by repurposing existing drugs to combat COVID-19 and its complications.[11] Parallel to this, virologists and molecular biologists explored and studied the coronavirus genome and developed several vaccines by conducting seamless clinical trials in selected populations for the successful discovery, development, and approval of safe and effective vaccines with the target of massive global vaccination to save humans.[9,13] The approaches of drug repurposing and seamless vaccine trials have potential advantages over developing new drugs, including lower costs and shorter development timelines for drugs and vaccine development and subsequent approvals in overcoming the stringent regulatory requirements during pandemic times.[9-13] However, these approaches have certain limitations in establishing the long-term vital organ safety and the effectiveness of repurposed drugs and novel vaccines on the CV system in COVID-19-recovered patients. Accumulating data strongly suggests that COVID-19 recovered patients are mostly associated with post-discharge dyspnea and fatigue and other symptoms include chest pains, cough, headache, myalgia, palpitations, taste dysfunction, gastrointestinal and cardiac problems including myocarditis, myocardial injury, heart failure, cardiac arrhythmias, thromboembolic events, acute coronary syndrome. These symptoms may persist for up to 6 months from disease onset.[14-17] Additionally, the risk of CV side effects has also been reported with currently available COVID-19 vaccines.[18]

PATHOPHYSIOLOGY

Angiotensin-converting enzyme 2 (ACE2) receptor

ACE2 receptors are the binding sites for SARS-CoV-2 which uses its S-spikes to bind ACE2 as the point of entry into the host cell. The pneumocyte types like type 1 and type 2 are expressed and other cell types, like endothelial cells too. The renin-angiotensin-aldosterone system is inversely regulated by ACE2.[3] ACE2 not only functions as a SARS-CoV-2 receptor,

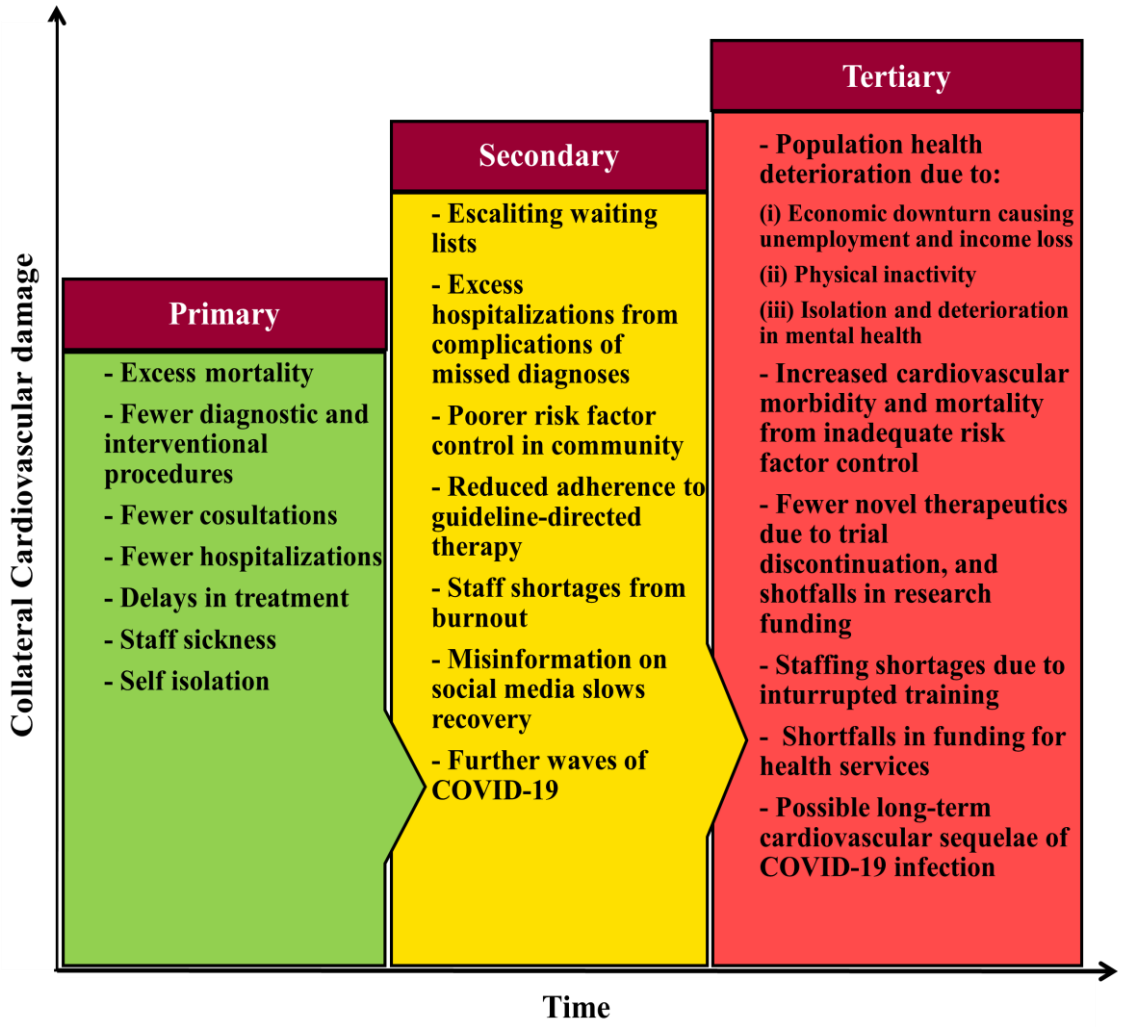

Fig. 1. Predicted potential collateral damage of the COVID-19 pandemic to cardiovascular services. [12,19,20,23]

but it also regulates the renin-angiotensin-aldosterone system (RAAS), avoiding an excess of angiotensin II in tissues. ACE2 catalyzes angiotensin I into angiotensin 1-9 and works on angiotensin II to convert it into angiotensin 1-7. Angiotensin 1-9 and angiotensin 1-7 can both prevent vascular constriction and decrease inflammation. When SARS-CoV-2 attaches to ACE2 through the spike protein, ACE2 on the cell membrane is downregulated. ACE2 downregulation leads to higher angiotensin II levels, which are responsible for greater arterial vasoconstriction and elevated blood pressure, as well as the release of inflammatory cytokines.[24-27] Both innate and adaptive immune systems of the host are activated by SARS-CoV-2 infection. Antigen-specific immune responses are adaptive immune responses but are slower than innate responses. The adaptive immune responses have long-lasting immunological memory, enhance viral clearance, and protect the host from SARS-CoV-2 reinfection. If

any defects occur then the adaptive system works to eliminate the SARS-CoV-2 infection, which leads to systemic organ damage including lung, endothelial cells, the heart, and the kidneys.[27,28] Failure to control viral replication in the early stages results in severe inflammation in the affected organs.[26-30] The European strain of SARS-CoV-2, a rare mutation of S protein (D839Y/N/E) can enhances the virus to interact with T cells.[31] This interaction may lead to hyperinflammatory polyclonal proliferation of T-lymphocytes in MIS-C (multisystem inflammatory syndrome in children), autoimmune IgG reactive to endothelium and other tissue, and hyperactivated cytotoxic CD8+ T cells and NK cells but rare COVID-19 complication.[32] The rapid clonal expansion of antigen-specific T and B lymphocytes is another feature of adaptive immune response, polyclonal activation of lymphocytes leads to activation of innate immune cells causing macrophage activation syndrome (MAS) like syndrome, cytokine storm, and systemic inflammation. Hemophagocytic B may be developed by this mechanism due to COVID-19 infection.[25-32] Innate immunological responses to SARS-CoV-2 infection depend heavily on the complement system, which can potentially set off pro-inflammatory reactions.[33]

Cytokine storm syndrome

Cytokine storm syndrome (cytokine release syndrome) is described as an overactivated immune system, it is associated with various pathological conditions which include tissue damage, hyperinflammation, and multi-organ failure, as observed in infectious diseases like SARS-CoV-2.[19,20,23,276] Cytokines provide regulatory signals that direct, amplify, and resolve the immune response and play a crucial role in coordinating antimicrobial effector cells. Systemic effects and collateral damage to vital organ systems are the adverse events noticed by increased levels of cytokines.[28] At the early stage of SARS-CoV-2 infection release of dendritic cells (DCs), and macrophages occur in respiratory cells and delayed release of cytokines and chemokines. Later, the cells secrete high levels of proinflammatory cytokines like (interleukins (IL)-1β, IL-6) and tumor necrosis factor-alpha (TNF-α) and chemokines like (chemokine ligand (CCL)-2, CCL-3, and CCL-5, also secrete low levels of the antiviral factors interferon (IFNs).[29] SARS-Co-V-2 infects epithelial cells of human airways, which induces a delay in the release of THP-1 cells, human peripheral blood monocyte-derived DCs (dendritic cells), and macrophages, elevates the level of proinflammatory cytokines and chemokines. SARS-CoV-2 activates the proinflammatory response of pathogenic Th1 cells to secrete proinflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and it activates $CD14^{+}CD16^{+}$ inflammatory monocytes produce large amounts of tumor necrosis factor-α (TNF-α) are mediated by membrane-bound immune receptors.[29,30] Additionally, IFN- γ is produced by effector T-cells during antigen-specific immunity, with increased levels of IFN- γ in corroboration with the viral load in COVID-19. This is followed by the infiltration of macrophages and neutrophils into lung tissue, which results in a cytokine storm. [29-31]

POST-COVID-19 ASSOCIATED CARDIOVASCULAR COMPLICATIONS (Fig. 2)

1) Myocarditis, myocardial injury, and elevated cardiac enzymes

In COVID-19 patients, myocarditis is identified as a risk factor for increased mortality, acute myocarditis is a pathological condition usually noticed in viral infections, which generally presents with the hallmark of inflammation and in the absence of overt vascular disease myocardial cell injury unrelated to ischemia.[32] In SARS-CoV-2 infection, various mechanisms of acute myocardial injury have been proposed. The target of SARS-CoV-2's spike protein is expressed heavily on myocardial and

alveolar surfaces through the ACE2 receptor. This is the direct mechanism for myocardial injury, an alternative to this inflammatory response caused by T-cells, and hypoxia during acute infection leads to cytokine storm that can be cardiotoxic.[23,33] The CV injury is measured by an elevated cardiac troponin accompanied by several COVID-19-associated CV complications including viral myocarditis, stress cardiomyopathy, heart failure, pulmonary embolism, and arrhythmias.[19,20,34] The clinical presentation of SARS-CoV-2-related myocarditis is based on abnormal electrocardiographic changes and elevated cardiac troponins, the reported presenting symptoms range from mild (eg., fatigue and dyspnea) to severe (eg., chest pain on excretion and hemodynamic instability). Some patients may develop acute heart failure, cardiogenic shock, and fulminant myocarditis defined as acute ventricular dysfunction and heart failure within 2 to 3 weeks of initial illness (**Fig. 2**).[35] Cardiomyocytes derived from human pluripotent stem cells *in vitro* models show that the interaction between the highly expressed ACE2 receptor and activated SARS-CoV-2 spike protein facilitates the spread of the virus within the myocardial cells.[36]

2) Heart failure

In SARS-CoV-2 infection, silent and progressive cardiac injury contribute to the progression of CV complications, including heart failure, following complete recovery from the initial infection. Irrespective of initial COVID-19 illness, persistent cardiac injury was observed in 78% of 100 recovered COVID-19 survivors after 3 months.[37] Due to acute cardiac injury in early SARS-CoV-2 infection causes a classic form of HF (heart failure) with preserved ejection fraction, whereas HF with systolic dysfunction is developed due to the progression of cytokine storm in the later phase of SARS-CoV-2 infection. Expression of cardiac ACE2 due to SARS-CoV-2 infection increases the risk of heart attack in patients with HF.[19,20,38] The 12 gene alteration is recognized with the role of the immune-inflammatory pathway, especially Toll-like receptor, NF-kappa B, chemokine, and interleukin-related pathways that are primarily related in response to SARS-CoV-2 complicated with HF. TLR4, TLR2, CXCL8, IL10, STAT3, IL-1β, TLR1, TP53, CCL20, and CXCL10) were shown to be the top 10 essential genes that are emphasized in response to SARS-CoV-2.[23,39] Heart failure is a possible clinical manifestation of the post-COVID-19 syndrome in patients with pre-existing HF possibly worsening after COVID-19 and the onset of *de novo* HF in patients recovered from infection is rare.[40] Patients with SARS-CoV-2 infection frequently have CV injury. The severity of the myocyte damage varies, ranging from an early injury with raised troponins to ultimate heart failure indicated by elevated levels of the N-terminal-prohormone brain natriuretic peptide (NT-proBNP).[41,42] Since COVID-19 is becoming more and more dangerous, HF from SARS-CoV-2 infection seems to be a possible risk, especially in older individuals who already have concomitant conditions including diabetes mellitus, ischemic heart disease, and hypertension (**Fig. 2**).

3) Cardiac arrhythmias and sudden cardiac arrest

Many ECG abnormalities are linked to SARS-CoV-2 infection, possibly caused by cytokine storm, hypoxic damage, aberrant electrolyte levels, plaque rupture, coronary spasm, microthrombi, or direct endothelial or myocardial injury in COVID-19.[43] The ECG abnormalities include sinus tachycardia, supraventricular tachycardias such as atrial fibrillation or atrial flutter, ventricular arrhythmias such as ventricular tachycardia or fibrillation, Ventricular premature complexes, and non-sustained ventricular tachycardia, Conduction disturbances, polymorphic ventricular tachycardia (torsade de pointes), with up to 90% severely ill patients reporting at least one abnormality.[19,20,43,44] In hospitalized patients with COVID-19, 16.7% of patients were noted with cardiac arrhythmia and

contributed to 44% of those transferred to the ICU.[45,46] Heart arrhythmia was one of the primary effects of SARS-CoV-2 during the outbreak in China. When patients with elevated troponin T levels were admitted to the intensive care unit (ICU), the incidence of ventricular arrhythmia nearly doubled (7% of patients).[46] Nevertheless, it could be challenging to pinpoint the exact pathophysiology behind the ventricular arrhythmia in COVID-19. Atrial and ventricular arrhythmia due to COVID-19 was associated with fulminant myocarditis with cardiogenic shock. [23,45,47] Post-COVID-19 is associated with orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS).

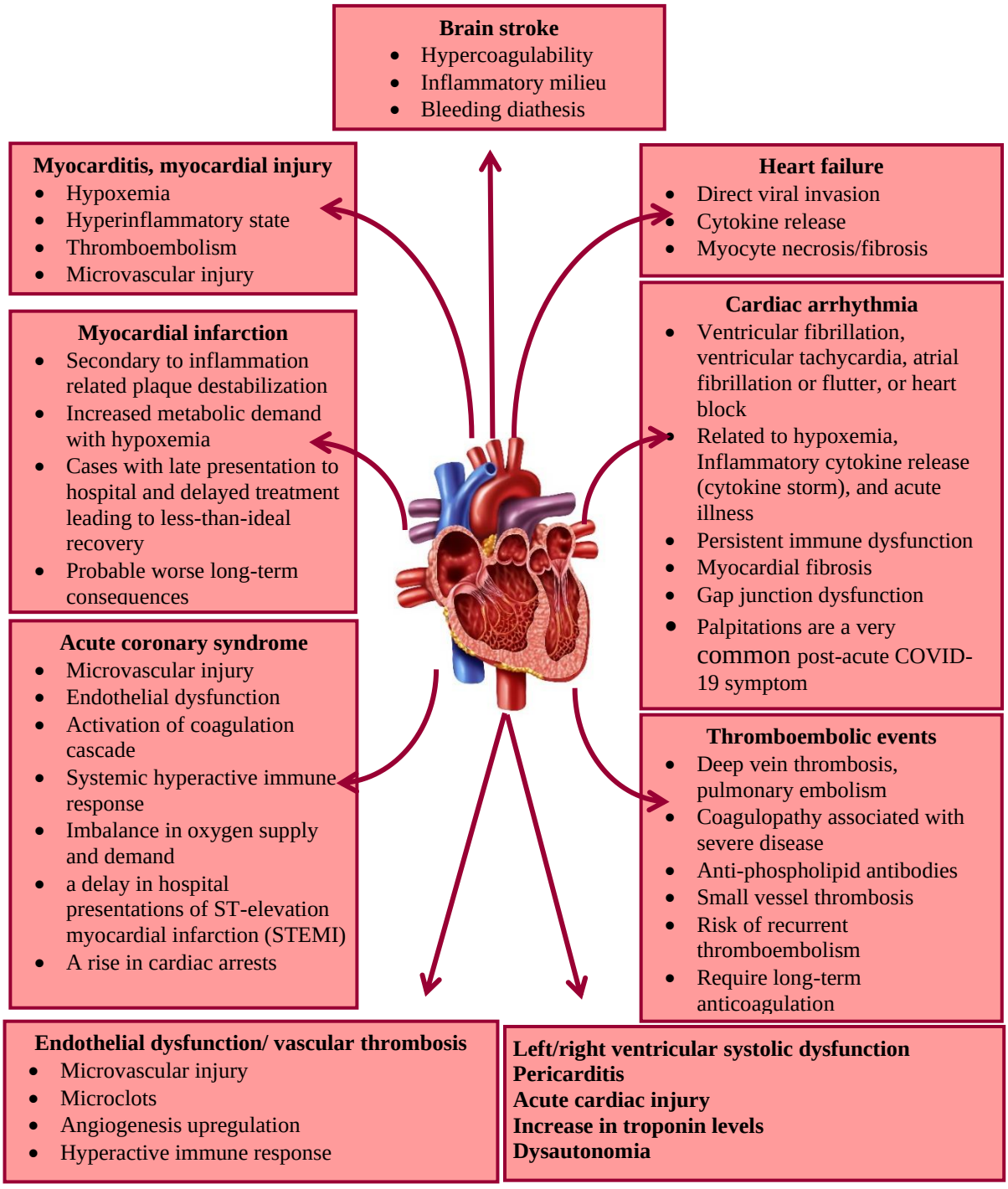

Fig. 2. Post-COVID-19 associated cardiovascular complications. [12,19,20,33,34,38,45,47,53,59,60]

OH is a common autonomic symptom associated with post-COVID which is defined as a systolic and diastolic blood pressure decrease of 20 mm Hg or 10 mm Hg respectively within 3 min of standing.[48] POTS presents with symptoms of palpitations, chest pain, and exercise intolerance, it is defined as a persistent increase in heart rate of at least 30 beats per minute within 10 min of standing. [49] In post-COVID-19 inappropriate sinus tachycardia syndrome (IST) is common it is defined as a sinus heart rate of more than 100 beats per minute at rest and is associated with symptoms of palpitations.[49,50] Atrial fibrillation is one of the common CV disorders noticed in post-COVID syndrome and has a high prevalence in populations with advanced age, CV risk factors, and comorbidities, which significantly increased the mortality rate among inpatients in hospitals (**Fig. 2**).[49-51] Post-COVID ventricular arrhythmias include ventricular tachycardia and are often associated with decreased physical activity and heart rate variability.[52]

4) Thromboembolic events

It has been shown that the elevated risk of CV consequences, such as thromboembolic illness, continues to exist throughout an extended duration of follow-up after the first 30 days following infection (post-COVID-19).[19,20,53] Among COVID-19 patients, thrombotic and thromboembolic events such as myocardial infarction, deep vein thrombosis, pulmonary embolism, and disseminated intravascular coagulation are often described. In patients with moderate and severe COVID-19, the incidence of thrombotic and thromboembolic consequences ranges from 21% to 49%, and it is considerably greater (71%) in individuals who did not survive.[23,54] Even with preventative anticoagulation, patients hospitalized with COVID-19, particularly those in intensive care units, have been documented to have elevated risks of arterial and venous thromboembolism. Higher mortality may also be linked to thromboembolism associated with COVID-19.[55] Additionally, being bedridden and having an illness might raise your chance of developing venous thromboembolism (VTE). Treatment for COVID-19 individuals with deep vein thrombosis (DVT) or lethal pulmonary thromboembolism (PTE) is difficult, and patients with VTE may have worse clinical outcomes.[56] Over time, COVID-19 can cause endothelial dysfunction and the coagulation system to become activated, which can result in a prothrombotic condition. As a result, two of the most serious consequences of this illness are arterial and venous thrombosis. Acute pulmonary embolism is the most prevalent thrombotic symptom of COVID-19, and it lengthens hospital stays and raises morbidity and death rates.[55-58] Acute COVID-19 is mostly caused by the following pathophysiologic mechanisms: the direct toxicity of viruses, endothelial damage, microvascular injury, immune system dysregulation, the development of a hyper-inflammatory state, and hypercoagulability leading to *in situ* thrombosis, macro thrombosis, and abnormalities in the ACE2 mechanism (**Fig. 2**).[57-59]

5) Acute coronary syndrome

Significantly higher rates of acute coronary syndrome (ACS) have been seen in COVID-19 individuals. Many potential mechanisms have been proposed, although the underlying pathogenesis is still unknown.[60] Differential pathophysiological routes are suggested by the features of ACS in COVID-19 patients, including angiographic evidence of unobstructed coronary arteries, stent thrombosis, numerous thrombotic culprit lesions, and significant thrombus load. The most well-known mechanisms include endothelial dysfunction, prothrombotic activation of the coagulation cascade, cytokine-mediated systemic inflammatory response, and hypoxia damage brought on by an imbalance in oxygen supply and demand.[12,19,20,60,61] In addition, the risk of nosocomial COVID-19 transmission in this susceptible patient group may be elevated by

admission with an ACS during the COVID-19 pandemic, when a high number of patients were hospitalized with the virus. It is still difficult to handle patients who arrive with ACS in the context of COVID-19.[62] When comparing the pre-COVID-19 ACS population to the COVID–19–positive group, individuals with acute ACS tend to appear later and have greater rates of cardiogenic shock and in-hospital death (**Fig. 2**).[23,62,63] There has been an increase in CV deaths in 2020 compared to 2019, This increase may be caused by several factors, such as a decrease in hospitalizations for acute coronary syndrome (ACS), a delay in hospital presentations of ST-elevation myocardial infarction (STEMI), a rise in cardiac arrests that occur outside of hospitals, a decrease in coronary revascularization procedures, and a decrease in outpatient surveillance.[64] In the immediate stage of acute coronary syndromes and for secondary prevention after stabilization, antiplatelet medication is an essential part of the treatment plan. Moreover, treatment with aspirin with a P2Y12 inhibitor for at least 12 months after acute coronary syndromes has been demonstrated in prior randomized studies to minimize ischemic events. The extra advantage is observed with the third-generation P2Y12 inhibitors, ticagrelor, and prasugrel when compared to clopidogrel.[65]

6) COVID-19 vaccine-induced cardiac complications

The first modified RNA-based (mRNA) vaccine to be approved for use by the US FDA was the COVID-19 vaccine, BNT162b2. Several randomized control trials showed that mRNA vaccines increased the risk of CV abnormalities including myocarditis, even though their safety profile was satisfactory. Post-marketing surveillance studies eventually confirmed this finding.[66-68] However, diverse beliefs, perceptions, and misinformation about COVID-19 vaccines have been affecting the acceptance of COVID-19 vaccination.[9,12,13,69] In addition, the lack of evidence of the safety and effectiveness of COVID-19 vaccines in women, particularly during pregnancy at the time of the COVID-19 pandemic was one of the causes of distress and speculation about acceptance of COVID-19 vaccination that seriously affected maternal and child health.[9-13,69] Further, following the COVID-19 vaccination, myocarditis, myopericarditis, arrhythmia, and ischemic heart disease were the most frequently reported CV consequences. The majority of these adverse CV events were seen following the second dosage of the vaccine.[70] Through immune-mediated, molecular mimicry, and thrombus development, the COVID-19 vaccination induces myocarditis. The vaccine's mRNA may be recognized by the immune system as an antigen, which triggers immunologically-mediated myocardial inflammation. Both the Th1 response and the delayed hypersensitivity reaction are immune-mediated processes. The immune system is made more sensitive by the first dosage and made more active by the second.[68,71] From a CV perspective, it's crucial to keep in mind that the FDA and the European Medicines Agency (EMA) reported cases of myocarditis and pericarditis as possible, albeit uncommon, side effects of vaccination in the summer of 2021, roughly six months after Pfizer and Moderna authorized the two mRNA vaccines.[68-72] Rare cases of myocarditis have also been documented in SARS-CoV-2 vaccination recipients. Research conducted on clinically evident myocarditis in U.S. military members who had vaccinations with either the Moderna mRNA-1273 vaccine or the Pfizer-BioNTech BNT162b2-mRNA vaccine indicated that the incidence was around 1 in 100,000.[66-68,73] Similar guidelines apply to managing COVID-19 infection as well as vaccine-induced myocarditis: individuals exhibiting symptoms such as chest pain following vaccination ought to be assessed and, if necessary, admitted to the hospital for a potential case of myocarditis; in most cases, however, symptoms are mild to moderate, and NSAIDs, colchicine, and corticosteroids may be prescribed.[72-74] Although several

studies on the incidence of myocarditis after COVID-19 vaccination offer population-wide estimates, the risks are mostly influenced by factors such as age, gender, prior vaccination history, and perhaps the timing and dosage of vaccine administration (**Fig. 2**). The risks for females are around two to three per 100,000 doses, which are higher in young and adolescent girls than in older females. These risks are just marginally higher than predicted rates.[75] Males are at greater risk; this risk is greatest after the second or third vaccination dose and occurs between 12 and 30 years. Additionally, rates seem to be greater after mRNA-1273, even though children have not used this as frequently. Following the second dosage of BNT162b2, rates for teenage men vary from 6.7 to 15 per 100,000. [75,76]

CONCLUSION

After recovering from a COVID-19 infection, a person may experience a variety of CV problems known as post-COVID cardiac complications. Both those with severe COVID-19 instances and those with less severe symptoms may have these problems. Myocarditis, which is inflammation of the heart muscle, pericarditis, which is inflammation of the membrane around the heart, arrhythmias, or abnormal heartbeats, and myocardial infarction, or heart attack, are a few typical post-COVID cardiac problems. These issues may lead to long-term health difficulties and can arise even in people who have never had cardiac issues before. It is important for healthcare practitioners to closely monitor and effectively manage these issues to promote the best possible outcome for the individuals impacted. Post-COVID-19 is becoming a significant problem for public health. Although there is still much to learn about the pathophysiological causes and available treatments, there is reason for optimism as several national and worldwide research programs aim to unravel the complexity of this illness. The necessity for multispecialty input is highlighted by the significant burden of cardiac symptoms combined with other organ presentations; this paradigm is likely to benefit other chronic illnesses as well. Patients' concerns and anxieties may be reduced by proactive screening and inquiry, where necessary. Adding to this, the enormous disparities in healthcare access that COVID-19 revealed will be exacerbated by recurrent complications, rehospitalizations, length of hospitalization, palliative care, survival benefits, risks, longer recovery time, enhanced cost of the treatment, and financial burden to the affected families and public health. Lastly, it takes a lot of work to strike the correct balance between patient benefit and cost-effective research to guarantee sustainable service delivery during these hard economic times.

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