Abstract

Background and aim: Post coronavirus disease 2019 (COVID-19) cardiovascular (CV) pathological changes, myocarditis, and myocardial infarctions (MIs) are major public health issues. This review discusses acute and chronic COVID-19 cardiac manifestations.

Methods: The devastating impact of COVID-19 on global healthcare and economies has likely been one of humanity’s deadliest calamities in recent decades, as multiple literature and databases were searched from 2020 to 2022.

Results: As of April 2022, we identified 73 articles in various electronic databases that discussed the details of COVID-19 and cardiac manifestations. Cardiometabolic risk factors should now, more than ever, be a top priority for clinicians, as their potent role in exacerbating COVID-19 illness severity has been conclusively demonstrated.

Conclusion: This review discusses cardiac pathology changes, CV consequences of acute COVID-19, microvascular injury and cardiac complications linked with SARS-CoV2, COVID-19 linked with chronic CV disease, therapeutic drug effects on heart used in COVID-19, and possible investigational approaches and management strategies for post-COVID-19 CV consequences.

Introduction

The COVID-19 pandemic has infected 466 million people and resulted in 6 million deaths. This crippled the public health infrastructure and the lives of people. COVID-19 patients present with a spectrum of symptoms—asymptomatic, flu symptoms (fever, muscle aches, shortness of breath, headache, altered sensation of taste and smell) to severe complications like acute respiratory distress syndrome, acute kidney injury, thromboembolism, and myocarditis. The complications are instigated and driven by cytokine storm—immunological reaction by macrophages which release proinflammatory cytokines [interferon (IFN) α, IFN-γ, interleukin (IL) 1β, IL-6, IL-12, IL-18, IL-33, tumor necrosis factor (TNF) α, transforming growth factor β, etc.] and chemokines (CCL/CXCL) (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) which damage the epithelial cells lining the blood vessels of various organs leading to organ failures. COVID-19 affects the cardiac system by destabilizing the atherosclerotic plaque through severe inflammatory reactions and microvascular thromboembolic events. Many reports have widely reported poor prognosis in COVID-19 patients with CV complications; this further shows a strong link between COVID-19 and the CV system. Cardiac complications of COVID-19 virus infection include myocarditis, acute coronary syndrome (ACS), and MIs, which is strongly supported by biochemical, biopsy, and autopsy findings. It was reported that myocardial injury due to COVID-19 was attributed to nearly 7% of mortality rates in an early case study.

In this article, we review several clinical studies, articles, and case studies and provide a detailed account of the mechanisms of myocardial injury in COVID-19 patients and its resulting clinical manifestations, and impact on chronic CV patients and further explore myocarditis caused by COVID-19 mRNA vaccine. We have also emphasized different investigation models and management approaches specifically for each case.

Cardiac Pathology Changes: Effect of COVID-19

Coronavirus disease 2019 (COVID-19) CV problems extend from angina to several cardiac and arrhythmias. The majority of problems develop within the first 2 weeks of the presentation. ACS and myocarditis are both major cardiovascular problems that frequently have a poor prognosis as well as a high death rate. Cardiovascular connection in COVID-19 has been attributed to a variety of pathways, including cytokine storm-induced proinflammatory state, direct viral attack to myocytes, hypercoagulable condition with the thromboembolic event, coronary plaque unsteadiness, or a demand-supply disparity contributing to ACS (Fig. 1).

Cardiac symptoms are not confined to the active phase of COVID-19 infection but can also arise during the convalescent phase. During the convalescent phase, affected individuals are at a higher menace for ACS, particularly post-COVID-19 MI may arise as an outcome of coronary plaque unsteadiness caused by persistent inflammation. Furthermore, a chronic hypercoagulable state or endothelial dysfunction following infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be a proposed explanation for an ACS to develop also after healing from coronavirus infection. As previously thought, myocardial inflammation is not exclusively associated with severe COVID-19 as well as symptomatic COVID-19 instances. Puntmann et al. used cardiac magnetic resonance imaging (MRI)/cardiac MRI (CMR) to show persistent myocardial inflammation in 60/100 individuals who had to get well from COVID-19 infection in a recent German cohort. On EMB, three individuals with considerable cardiac involvement revealed active lymphocytic inflammation. Following the remission of their lung problem along with a negative real-time PCR test following a minimum of 2 weeks from the
Post-COVID-19 Cardiovascular Sequelae and Myocarditis

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Post-COVID-19 Cardiovascular Sequelae and Myocarditis

Patients with post-COVID-19 cardiac syndrome have a hypercoagulable state with continuous inflammation, which manifests as ischemia or as sequelae of myocarditis together with left ventricular dysfunction and constant myocardial inflammation, resulting in arhythmias or heart failure. Information from the earlier SARS pandemic also revealed a long-standing consequence following the SARS coronavirus infection.

Subsequent healing from COVID-19 infection, other significant cardiovascular consequences include the emergence of thromboembolic events, including venous thromboembolism (VTE). Single-center research of 163 patients from the United States of America found VTE in 2.5% of well again patients 30 days after initial diagnosis, all of these individuals underwent a CMR. The majority of these individuals were silent or had slight-to-moderate signs, as well as those with serious cardiac manifestations, were omitted. All this indication alludes to continuing heart inflammation (peri-myocarditis) even during the disease’s convalescent phase.

This persistent myocardial inflammation, edema, and ventricular dysfunction may be one of the causes of symptoms like chest pain also shortness of breath in the post-COVID-19 convalescent phase. Furthermore, persistent inflammation can cause myocardial scarring and also create a breeding ground for lethal ventricular arrhythmias, particularly in the aged and persons with comorbidities.

All of this has far-reaching implications, given the large number of recovered cases, as well as persistent cardiac inflammation or subclinical myocardium dysfunction that may manifest later in life. This necessitates better risk categorization in individuals who are aged or have many comorbidities, as well as the prudent use of CMR in affected individuals with increased biomarkers to find out persistent myocardial inflammation.

This demands better risk categorization in individuals who are elderly or have many comorbidities utilizing biomarkers such as cardiac troponins, as well as the prudent utilization of CMR in affected persons with high biomarkers to identify persistent myocardial inflammation. Furthermore, the application of cardioprotective treatments such as statins or sodium-glucose cotransporter-2 inhibitors has the potential to reduce long-term consequences in these individuals. Previous research has linked worse outcomes to a greater New York Heart Association functional class, immunohistological markers of inflammation, viral genome detection, or CMR characteristics of active inflammation.

**Figs 1A and B:** (A) Direct myocardial damage—occurring because of entry of virus to the cardiac cells by ACE 2 causing inflammatory changes and destruction of myocardial cells; (B) Indirect injury—downregulation of ACE 2 leads to vasoconstriction, endothelial dysfunction, inflammatory changes, and initiation of the coagulation routes associated with microvascular thrombosis; the immune system activation leads to a systemic inflammatory response that finally causes myocardial infarction (created by the mechanism of development.com)
discharge, with most of them being segmental lung embolism, intracoronary thrombus, and ischemic stroke.\textsuperscript{18} Similarly, VTE rates of 4.8 and 7.2\% in individuals with subsequent COVID-19 infection were described in retrospective investigations from the United Kingdom.\textsuperscript{19, 20} The recurrence of lung thromboembolism after remission from COVID-19 illness can be fatal, especially if it is combined with hemodynamic instability. Because COVID-19 infection is linked with a hypercoagulable condition, there is an increased risk of VTE during the disease’s convalescent phase. The recurrence of pulmonary thromboembolism after healing from COVID-19 infection can be fatal, especially if it is combined with hemodynamic instability. Because COVID-19 disease is associated with a hypercoagulable condition, there is an increased risk of VTE during the disease’s convalescent phase. This was noted in a recent study of a 52-year-old lady suffering from acute pulmonary thromboembolism after recovering from COVID-19.\textsuperscript{21}

**Mechanism of Development of CV Consequences in Acute COVID-19: Including Autopsy Studies**

The impact of angiotensin-converting enzyme (ACE) 2 receptors in SARS-CoV-2 heart participation is now well understood. Numerous mechanisms, together with direct cytotoxic injury\textsuperscript{22} dysregulation of the renin-angiotensin-aldosterone system,\textsuperscript{23} endothelitis as well as thrombo-inflammation, and associated alterations in the immune response to cytokine release, have been suggested to cause the myocardial injury.\textsuperscript{24}

The sequence of myocardial damage after SARS-CoV-2 infection obtained from autopsy reviews is biased due to referral bias, although it has specified preliminary pathophysiological clues. Only four affected individuals (5\%) had assumed cardiac damage in an initial autopsy series of 80 back-to-back SARS-CoV-2 polymerase chain reaction (PCR) positive cases.\textsuperscript{25} Two deaths occurred from sudden cardiac arrest due to comorbid conditions. One patient had a serious MI, and the other had right-sided ventricular lymphocytic infiltrates. These preliminary findings implied that wide myocardial impairment as a predominant reason for mortality might be uncommon.

Basso et al.\textsuperscript{26} considered the hearts in 21 chosen autopsies in a subsequent multicenter autopsy study. Myocarditis (characterized as lymphocytic infiltration as well as myocyte necrosis) was seen in 14\% of the cases, infiltration of interstitial macrophage in 86\%, and pericarditis as well as right-sided ventricular damage in 19\%. Halushka and Vander Heide\textsuperscript{27} reviewed 22 publications that described the autopsy outcomes of 277 affected individuals. Lymphocytic myocarditis was mentioned in 7.2\% of cases, but only 1.4\% met the firm histopathological criteria\textsuperscript{28} for myocarditis, implying that exact myocarditis was uncommon. Lindner et al. found COVID-19 viral elements in the cardiac muscles of 24 out of 39 (59\%) back-to-back autopsies; the viral load was medically important in 16/39 (41\%). Notably, viral elements were separated in interstitial cells, such as macrophages and pericytes, rather than cardiomyocytes. The elevated virus load in certain conditions was also not allied with inflammation, which is consistent with autopsy studies showing a low prevalence of myocarditis.\textsuperscript{25}

**Microvascular Injury and Cardiac Complications: Linked with SARS-CoV2**

Cardiac troponin levels in COVID-19 patients are frequently elevated,\textsuperscript{29} suggesting myocardial damage or ischemia. The exploration of Bois et al.\textsuperscript{30} gives the idea to boost the impression of COVID-19-associated microthrombi. In a little group of 15 people, the authors discovered that postmortem fibrin microthrombi were much more usual (80\%) than serious ischaemic damage (13\%) and myocarditis (33\%), implying a part for thrombosis in exacerbating the myocardial impairment.

Fox and Heide\textsuperscript{31} have theorized the wide range of pathophysiological progressions that underpin myocardial impairment. Hypoxia and microvascular harm in the lungs, according to the authors, may result in right heart stress as well as myocyte necrosis. Limited microvascular outcomes, endotheliolysis,\textsuperscript{32} related microthrombi, and varied renin-angiotensin homeostasis may all contribute to this.\textsuperscript{33} Elevated cytokines,\textsuperscript{25} for example, IL-1, IL-16,17,22, JFN-γ, and TNF-α may also make a significant contribution to myocardial damage by triggering dysfunction of endothelium, platelet stimulation, recruitment of neutrophils, and ultimately activating a hypercoagulable situation (Fig. 1).

**Consequences after Acute and Chronic COVID-19 Illness**

The mechanisms underlying persistent cardiac impairment following serious illness are even now unknown. One potential clarification is a long-lasting inflammatory reaction elicited by constant viral reservoirs in the muscles of the heart after the serious infection,\textsuperscript{23} which may be worsened by obesity-accompanying inflammatory signaling driven in part by perivascular adipose tissue through the discharge of adipokines such as monocyte chemoattractant protein-1 as well as adjusted upon initiation, Normal T cell expressed, and presumably discharged, CCL/CXCL that worsen endothelial.\textsuperscript{34} Insidious tissue harm, followed by long-lasting myocardial fibrosis, would be an unintended after-effect of such courses, resulting in worsened ventricular compliance, deficient myocardial perfusion, augmented myocardial stiffness, diminished contractility, and possible arrhythmias.

An autoantibodies reaction to cardiac antigens via molecular mimicry is a second mechanism for late damage.\textsuperscript{35} Wang et al. high-throughput proteome analysis has discovered a variety of autoantibodies to humoral and tissue antigens in COVID-19 patients. Individuals with chronic fatigue syndrome have also been found to have autoantibodies to cholinergic as well as adrenergic receptors.\textsuperscript{35, 36} Several longitudinal cytokine profiling and proteomic studies\textsuperscript{37, 38} has recently revealed an increase in the appearance of prothrombotic factors (e.g., factor VIII, plasminogen activator inhibitor-1, prothrombin) following the serious infection. It is consistent with the growing number of reports of late embolic difficulties.\textsuperscript{25} The elevated prevalence of vascular thrombosis in the lung (5–30\%),\textsuperscript{39, 40} especially in patients with hospitalization, is predictable to increase the threat of pulmonary hypertension with thrombo-embolism in the future.\textsuperscript{40} Dysfunction of the endothelium\textsuperscript{41} and its difficulties may establish in affected individuals, with findings of lasting impairment found in younger people 3–4 weeks later SARS-CoV-2 contamination.\textsuperscript{42}

Countless of these problems are similar to those experienced by survivors of extra epidemics such as SARS, Middle East respiratory syndrome, and H1N1A, emphasizing the importance of recognizing the effect of respiratory viral infections on CV health, formerly highlighted by Xiong et al.\textsuperscript{43} in a previous review.

Explaining cardiac participation in the framework of multisystem health can offer observations into procedures of ongoing damage by identifying distinct patterns of tissue injury (e.g., inflammatory deviations or embolic changes). Raman et al.\textsuperscript{44} performed multi-organ MRI on 58 posthospitalized COVID-19 patients and 30 matched controls and found tissue aberrations in the lungs (60\%), heart (26\%), liver (10\%), kidneys (29\%), and brain (11\%). MRI irregularities in nearly every organ were linked to inflammatory
aggravation may appear even after 30 days following SARS-CoV2 infection; according to the discontinuation of guideline-based medical therapy throughout serious illness is one factor for the increasing epidemic of postdischarge heart failure episodes. Researchers from the TRED-HF study previously established that stopping heart failure therapy had a deleterious impact on individuals with cured dilated cardiomyopathy, leading to recurrence and poor consequences. Successful resumption and optimization of heart failure remedies may thus be critical in preventing heart failure readmissions following an acute COVID-19. COVID-19 has a cardiometabolic profile that is similar to that of cardiac illnesses, suggesting that COVID-19 may have a role in the destabilization of preclinical disorders (e.g., heart failure and coronary artery disease). This could clarify the elevated rate of type 2 MI in people with severe COVID-19, as well as the rise in ‘newly’ diagnosed CV diseases. Alteration of the renin-angiotensin-aldosterone system, endothelial dysfunctions, renal injury, and steroid use are all possible contributors.

**COVID-19 Linked with Chronic CV Disease**

Up to a third of COVID-19 patients have a history of chronic CV disease. Indoor patient mortality, the hazard of thrombo-embolism, and septic shock incidence are all related to the presence of concomitant cardiac illness. Individuals with a history of heart failure have a two to four-fold chance of decompensation and death even in the postacute phase. An increasing incidence of heart failure indicators, implying that long-lasting inflammation could impair healing. Following this, the posthospitalisation-COVID-19 survey found that failure to heal from multi-organ manifestations was linked to symbols of permanent inflammation. Dennis et al. examined the frequency of multi-organ destruction among primarily nonhospitalized affected individuals in another study of 201 affected individuals and discovered that signs of long COVID-19 huddled amongst those with multisystem damage on MRI. Dysfunction of the endothelium, dysfunction microvascularly as well as prothrombotic tendencies may all promote multi-organ impairment. Perfusion imbalances in the heart, as well as lungs (Patelli et al. and Kotecha et al.) of COVID-19 patients, have been observed in preferred studies using advanced imaging modalities such as positron emission tomography, CT, and MRI at 40–60 days after infection.

Multi-organ MRI showed indications of small vessel illnesses (9.3%) and ischemic changes (3.7%) in the brain (9.3%), and 1.9% had a MI 2–3 months after infection in one survey of hospitalized individuals. Some other reports of 104 hospitalized patients found that inducible myocardial perfusion abnormalities were usual in affected individuals with medium to serious disorders but did not fluctuate in burden when contrasted to comorbidity and hazard factor matched controls. Numerous studies are presently being conducted to describe a load of vascular and thrombotic difficulties and also to survey the possible benefits of continuous antithrombotic (extended thromboprophylaxis) as well as vascular protecting treatments (e.g., statins, risk-factor management) in postacute COVID-19 affected individuals, as shown in Table 1 and Figure 2.

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**Fig. 2:** Mechanism of development of cardiac changes due to COVID-19 (created by the mechanism of development.com)
Table 1: After receiving COVID-19 treatment for 4 weeks, prospective clinical trials evaluating CV outcomes are available

<table>
<thead>
<tr>
<th>Category/National clinical trials (NCT) number</th>
<th>Title</th>
<th>Used drugs or intervention</th>
<th>Outcome or result of the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV NCT04324463</td>
<td>Anticoronavirus therapies to prevent progression of COVID-19 trial (ACT COVID-19)</td>
<td>Aspirin Colchicine Rivaroxaban</td>
<td>In the colchicine versus control study, hospitalization for 45 days was associated with mortality, disease progression, and a composite of MACE. Aspirin versus placebo—45-day composite of death and hospitalization, progression of the disease, and MACE composite. Aspirin and rivaroxaban versus the control group—45-day composite of death and hospitalization, disease progression, and MACE composite.</td>
</tr>
<tr>
<td>CV NCT04381936</td>
<td>Randomized evaluation of COVID-19 therapy (RECOVERY)</td>
<td>Aspirin Colchicine Steroid Empagliflozin Anakinra</td>
<td>The primary and secondary consequence measures are death within 28 days, the need for mechanical ventilation, and hospital stay. A second outcome evaluates the risky outcome of a thrombotic event up to 6 months after randomization.</td>
</tr>
<tr>
<td>CV NCT04662684</td>
<td>Medically Ill hospitalized patients for COVID-19 thrombosis extended prophylaxis with rivaroxaban therapy; the MICHELLE trial (MICHELLE)</td>
<td>Rivaroxaban</td>
<td>The main outcome indicators are VTE 35 days later hospital discharge and VTE-related mortality. Secondary outcome measures include bleeding 35 days after hospital discharge and a composite of myocardial ischemia, stroke, arrhythmias, heart failure, and death from any cause.</td>
</tr>
<tr>
<td>CV NCT04406389</td>
<td>Anticoagulation in critically ill patients with COVID-19 (the IMPACT trial) (IMPACT)</td>
<td>Unfractionated heparin Enoxaparin Argatroban Fondaparinux</td>
<td>Death within 30 days is the primary outcome measure; secondary outcomes include the occurrence of VTE at 6 months, length of intensive care unit (ICU) stay, and incidence of serious vascular events.</td>
</tr>
<tr>
<td>CV NCT04486508</td>
<td>Intermediate-dose vs standard prophylactic anticoagulation and statin vs placebo in ICU patients with COVID-19 (INSPIRATION)</td>
<td>Unfractionated heparin Enoxaparin Atorvastatin Matched placebo</td>
<td>The primary outcome measure is the 30-day composite of serious VTE, arterial thrombosis, death, and extracorporeal membrane oxygenation treatment. Secondary outcome measures consist of 30-day major adverse CV events (MACE), arrhythmia, death, major bleeding, decreased platelet count, elevated liver enzymes, and atrial fibrillation; 60, 90-day post-COVID-19 functional status; as well as 30-day MACE, arrhythmia, death, major bleeding, thrombocytopenia, elevated liver enzymes, and atrial fibrillation.</td>
</tr>
<tr>
<td>CV NCT04900155</td>
<td>Evaluation of the effect of long-term lipid-lowering therapy in STEMI patients with coronavirus infection COVID-19 (CONTRAST-3)</td>
<td>Atorvastatin Atorvastatin Ezetimibe</td>
<td>The primary outcome measures are a 96-week lipid profile, electrical instability, ventricular rhythm disturbance, autonomic regulation, myocardial deformation, left ventricular systolic function, and MACE.</td>
</tr>
<tr>
<td>CV NCT04460651</td>
<td>Prevention and treatment of COVID-19 with EPA in subjects at risk-intervention trial (PREPARE-IT)</td>
<td>Icosapent ethyl Placebo</td>
<td>The primary outcome measures are SARS-CoV-2 positivity at 60 days and COVID-19 hospitalization; secondary endpoints include CRP, triglycerides, COVID-19-related hospital stays, nonfatal myocardial infarction, and stroke at 28 days.</td>
</tr>
<tr>
<td>CV NCT04505098</td>
<td>A pragmatic randomized trial of icosapent ethyl for high-CV risk adults (MITIGATE)</td>
<td>Icosapent ethyl</td>
<td>The main outcome indicator is the proportion of individuals with a moderate to severe viral upper airway infection and a worsening clinical status. Mortality at 12 months, MACE, as well as heart failure were secondary outcome measures.</td>
</tr>
<tr>
<td>CV NCT04350593</td>
<td>Dapagliflozin in respiratory failure in patients with COVID-19 (DARE-19)</td>
<td>Dapagliflozin Placebo</td>
<td>30-day organ dysfunction, ventricular tachycardia, respiratory compensation, renal replacement therapy and vasopressor therapy are the primary outcome measures. Upon 30 days in the hospital, days alive without respiratory compensation is a secondary outcome measure.</td>
</tr>
<tr>
<td>Cardiac ISRCTN11721294</td>
<td>Rehabilitation for cardiac arrhythmia</td>
<td>Rehabilitation</td>
<td>Autonomic function was measured with a 12-lead ECG Holter device for 10 minutes and 24 hours at baseline and after the rehabilitation program (6 weeks)</td>
</tr>
</tbody>
</table>
Therapeutic Drug Effects on Heart used in COVID-19

The vast majority of CV problems that persist after COVID-19 are caused by tissue injury acquired during acute sickness. Further research into the influence of critical treatments on long-standing CV health is needed. Anti-inflammatory medicines like dexamethasone and tocilizumab have been known as significant weapons in the COVID-19 therapeutic arsenal. Though, the amount to which they impact long-term cardiopulmonary healing is unknown, and data on heart damage rates are not yet generally available. Further research is needed to see if continued inflammation in long-standing COVID-19 patients reflects a rebound event in dexamethasone- or tocilizumab-treated individuals. Anticoagulation’s intricate role in patients demands considerable thought. In the serious phase, mounting evidence suggests that aspirin has no benefit in dropping mortality between hospitalized patients and nonhospitalized outpatients.

The degree of sickness (noncritical hospitalized affected individuals benefiting the most) is a major factor of medication achievement, according to data in confirmation of therapeutic dosage anticoagulation. A multiplatform adaptive randomized controlled clinical trial combining data from the studies such as REMAP-CAP, ACTIV-4a, and ATTACC found that therapeutic dose heparin enhanced survival until hospital discharge as well as organ support-free days in relatively ill individuals but not in critically ill patients. Other investigations (the ACTION, INPIRATION, and RAPID trials) on the other hand, found no variance in main endpoint measures between ill individuals taking therapeutic vs preventive dosage anticoagulation. The ACTIV-4B242 study found no difference in the 45-day existence between nonhospitalized individuals who received aspirin, minimal dose, or maximum dose apixaban vs placebo. In addition, to comprehend the long-standing advantages of anticoagulation in ill individuals, more research is required.

Possible Investigational Approaches and Management Strategies for Post-COVID-19 CV Consequences

Although the real extent of postacute COVID-19 CV damage is unknown, cardiac symptoms appear to be common in this stage. Proof in favor of cost-effective techniques to rule out substantial CV pathology is urgently needed. Some experts believe this method is reasonable. Some experts believe that screening elevated-risk patients for constant cardiac connection, such as those with irregular cardiac tests during the serious period, newly diagnosed CV changes in post-COVID-19 cases, and sports, is a reasonable method.

A complete history, physical and general examinations, along with a blood test panel (C-reactive protein (CRP), B-type natriuretic peptide (BNP)/ natriuretic pro BNP, troponin I and glycated hemoglobin, and lipids), electrocardiogram (ECG), with transthoracic echocardiography at least 8–12 weeks later infection could be used to screen high-risk people. Additional testing is advised for people who have clinically significant anomalies after the screening. Following screening studies, noninvasive procedures such as stress single positron emission computed tomography, CMR, Holter, and coronary computed tomography angiography may be investigated; invasive coronary angiography or endomyocardial biopsy (EMB) may be directed for elevated-risk people. Where appropriate, referral to specialty clinics [e.g., arrhythmia clinic, postural orthostatic tachycardia syndrome (POTS), or psychiatric assistance] should be measured. Ill individuals with long-lasting CV illnesses should be queried about their past exposure to COVID-19 and the status of vaccination when they come in for a routine follow-up. For particular affected individuals who report persistent symptoms, a short-term evaluation of physical, mental, and cognitive well-being may be mandatory, as this could smooth timely referral to suitable support rehabilitation.

Numerous proposals have been made by consensus societies about athlete return-to-play guidance. Although previous standards were conservative, the latest findings of professional and college sportsmen have directed a change in proposals. As per the 2019 position announcement of the Sports Cardiology Unit of the European Association of Preventive Cardiology, graded resumption of sports and exercise is recently taken into account for minor infections, while a limit of exercises for three months is even now suggested for individuals with assumed myocarditis (Table 2).

The treatment of postexposure COVID-19 with persistent myocarditis is still a hotly debated topic. The European Society of Cardiology (ESC) and American Heart Association (AHA) have proposed EMB for patients with complex (non-COVID-19 individuals) myocarditis (i.e., unexplained dilation of left ventricle associated with significant dysfunction, critical tachy, and bradyarrhythmia, troponin leak continuation) to help guide particular medication options (e.g., antivirals vs immunomodulatory therapy).

There are currently no COVID-19 guidelines on this; however, countless reviews are being conducted to determine the best effective managing technique. The effectiveness of oral nonsteroidal anti-inflammatory medications and also colchicine for COVID-19-associated pericarditis is also being investigated.

Patients with postexposure COVID-19 ACS are usually handled according to the AHA and the ESC recommendations, which were published in 2014 and 2020 separately. Likewise, heart failure medication is focused on making the best use of available medications at the time they are needed, according to recommendations. There are presently no available studies on the effectiveness of long thromboprophylaxis after serious COVID-19; still, several interventional studies (e.g., STIMULATE ICP, HEAL-COVID-19) are presently in progress to fill this void.

The management of protracted COVID-19 is essentially supportive once major CV, as well as other organ pathology, has been ruled out given the substantial link between obesity and extended COVID-19, calorie restriction, nutrition, targeted categorized exercise, decreased stress, and excellent sleep hygiene may be advantageous in the lengthy run. There’s mounting evidence that it can help with vascular dysfunction, systemic inflammation and metabolic syndrome. In addition, a pragmatic, comprehensive approach that is focused on symptom relief may be required. Nonpharmacological treatments for dyspnea include pulmonary rehabilitation, respiratory exercises, and alternative therapies (for example, singing therapy, body rotation, acupuncture, and stretching). Individuals who are sent back to work may advantage from a phased arrival, which allows them to gradually rejoin work after a period of mental and physical rehabilitation. Initial medical appointments for mental well-being assessment behavioral therapy may be advantageous to certain patients, provided that psychosocial issues are a key indicator of partial healing. Dysautonomia and POTS can be debilitating for sufferers. Correcting reversible sources (heat, dehydration), optimizing long-lasting illness management, and educating patients are all important aspects of POTS care. β-blockers may be beneficial in the treatment of palpitations in some patients.
Table 2: Summary of all the relevant cardiac investigations and roles in post-COVID-19 management

<table>
<thead>
<tr>
<th>Mode of investigation</th>
<th>Role of intervention in post-COVID-19 cardiac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography</td>
<td>Evaluation of suspected myopericarditis, right ventricular efficiency in the context of pulmonary emboli, assessment for new onset biventricular dysfunction, and thrombus detection in the atrial appendage diastolic function evaluation.</td>
</tr>
<tr>
<td>MRI</td>
<td>Myopericarditis, myocardial infarction, and cardiomyopathy diagnosis, tracking disease process and recovery of tissue anomalies, biventricular function assessment, micro and macrovascular function assessment, and diastolic function assessment.</td>
</tr>
<tr>
<td>Cardiopulmonary exercise test</td>
<td>Exercise capacity and contributing factors are assessed objectively to determine the primary cause of exercise intolerance (cardiac, pulmonary, skeletal muscle, or anemia). Allows for the evaluation of autonomic response during recuperation.</td>
</tr>
<tr>
<td>CT pulmonary and coronary angiography</td>
<td>Detection of thrombosis in the lungs and the heart, as well as vasculitis, perivascular inflammation, and thrombus burden in major vessels.</td>
</tr>
<tr>
<td>Cardiac single photon emission CT</td>
<td>Provides information on the function and hemodynamic implications of coronary stenosis (micro and macrovascular).</td>
</tr>
<tr>
<td>ECG monitor</td>
<td>Diagnose atrial and ventricular arrhythmias, orthostatic tachycardia syndrome, and ischemic ECG abnormalities during exercise with this tool.</td>
</tr>
<tr>
<td>Tilt table test</td>
<td>POTS, orthostatic hypotension, neurogenic syncope, and vasovagal syncope can all be diagnosed using this test.</td>
</tr>
</tbody>
</table>

Table 3: Examples of vast (n > 400) prospective observational analyses evaluating COVID-19-related cardiovascular effects throughout short and long periods

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Title</th>
<th>CV outcome measures</th>
<th>Age</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04465552</td>
<td>Arrhythmic manifestations and management in hospitalized COVID-19 patients.</td>
<td>In hospitalized COVID-19 patients with arrhythmic symptoms, therapeutic options were used, and long-term outcomes were observed.</td>
<td>18 years and adult (adult, aged).</td>
<td>Observational</td>
</tr>
<tr>
<td>NCT04058712</td>
<td>Long-term outcomes in patients with COVID-19.</td>
<td>Cardiac function</td>
<td>18 years and older (adult, aged).</td>
<td>Observational</td>
</tr>
<tr>
<td>NCT04624503</td>
<td>Prognostic and clinical impact of patients with COVID-19 (CARDIO-COVID-19).</td>
<td>Mortality due to CV disease. NYHA class, left the ventricular systolic performance, all-cause of death, significant adverse CV events (cardiac magnetic resonance, two-dimensional echo).</td>
<td>18–85 years (adult, aged).</td>
<td>Observational</td>
</tr>
<tr>
<td>NCT04724707</td>
<td>Russian Cardiovascular Registry of COVID-19.</td>
<td>Arrhythmias, death, cardiovascular hospitalization, mechanical assistance or transplant of heart, implantable cardioverter-defibrillator or cardiac resynchronization therapy.</td>
<td>18 years and older (adult, aged).</td>
<td>Observational</td>
</tr>
<tr>
<td>NCT04384029</td>
<td>The Geneva COVID-19 CVD Study.</td>
<td>Preexisting clinical outcomes were linked to the former presence of CV risk factors at the time of admission, as well as a new beginning of CVD caused by COVID-19.</td>
<td>18 years and older (adult, aged).</td>
<td>Observational</td>
</tr>
<tr>
<td>NCT04375748</td>
<td>Hospital registry of acute myocarditis—evolution of the proportion of positive SARS-CoV-2 (COVID-19) cases.</td>
<td>Acute myocarditis prognosis and cardiac MRI characteristics.</td>
<td>Adult, child, and aged.</td>
<td>Observational</td>
</tr>
</tbody>
</table>

After prolonged bed rest and graded exercise programs, urging patients to adopt an erect position may help to alleviate postural complaints. Reduced peripheral venous pooling may relieve symptoms of orthostatic hypotension with compression pantyhose-style stockings with a 30–40 mm Hg counter pressure. Pharmacological therapy (such as fludrocortisone, ivabradine, midodrine, ...
methyldopa, and clonidine may be used if symptoms continue despite adherence to the aforementioned procedures.

**Conclusion**

Our existing knowledge of pathophysiologic causes and medications of choice is inadequate, but there is reason to be hopeful. Numerous international and national research endeavors are underway to unravel the disease’s intricacies. The significant prevalence of cardiovascular symptoms, as well as other organ presentations, emphasizes the importance of multispecialty input, a strategy that is expected to benefit other chronic diseases as well. Patients’ fears and anxieties could be alleviated by proactive screening and investigation, if necessary.

Various rehabilitation programs (face-to-face and telemedicine) for the medications for breathing difficulties, fatigue, and cognitive decline, as well as the cognition-targeted therapeutic way (e.g., transcranial stimulation), metabolic modulators (like niagen), immunomodulatory medications (e.g., tocilizumab, steroids, atorvastatin, laranilubmab, colchicine), antifibrotic management (e.g., pirfenidone and apixaban). Further, 730 reports interrelated to COVID-19 are listed on ClinicalTrials.gov and the World Health Organization. Around 80 place a high priority on long-term CV results. Table 3 lists a few research with 400 or more participants as examples.

To ensure long-term service running in these difficult economic periods, significant efforts must be made to obtain the correct balance between patient benefits and cost-effective investigations. Finally, lengthy COVID-19 will amplify the massive inequalities in healthcare facilities shown by COVID-19, a challenge that necessitates worldwide humanitarian labor to boost and fund fair approach to healthcare, social as well as welfare backing, and vaccinations around the world. The devastating impact of COVID-19 on global economies and healthcare has probably been one of humanity’s deadliest calamities in recent decades. COVID-19 survivors are in the hundreds of millions worldwide, with some claiming inadequate recovery months after COVID-19. Chest pain, exhaustion, brain fog, breathlessness, headaches, and palpitations are all continual reminders of the virus’s destruction and the need to be cautious of any long-term effects. Cardiometabolic risk factors should now, more than ever, be a top main concern for medical doctors, as their potent role in exacerbating COVID-19 ailment acuteness has been conclusively demonstrated. The explanation of long COVID-19, the epidemiology of manifestations of cardiopulmonary consequences in the framework of long COVID-19, the pathophysiologic ways for chronic and acute CV injury ancillary to SARS-CoV-2 infection, management, as well as directions for further study are all discussed in this review.

**Statement of Declaration**

Consent to Participate

All the authors mutually agree to participate in this work.

Consent for Publication

All the authors mutually agree to submit the manuscript for publication.

**Authors’ Contributions**

Conceptualization—Debashis Ghosh, Rajdeep Ghosh; Formal analysis and investigation—Ullash Basak, Lakshmi Chakrhadar Yarlagadda, Rajdeep Ghosh; Writing—original draft preparation—Ullash Basak, Lakshmi Chakrhadar Yarlagadda, Debashis Ghosh, Manab Senapati, Rajdeep Ghosh; Writing—review and editing—Ullash Basak, Rajdeep Ghosh; Supervision—Rajdeep Ghosh.

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