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"When," "Where," and "How" of SARS-CoV-2 Infection Affects the Human Cardiovascular System: A Narrative Review

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Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory coronavirus-2 (SARS-CoV-2). Several explanations for the development of cardiovascular complications during and after acute COVID-19 infection have been hypothesized. The COVID-19 pandemic, caused by SARS-CoV-2, has emerged as one of the deadliest pandemics in modern history. The myocardial injury in COVID-19 patients has been associated with coronary spasm, microthrombi formation, plaque rupture, hypoxic injury, or cytokine storm, which have the same pathophysiology as the three clinical variants of Kounis syndrome. The angiotensin-converting enzyme 2 (ACE2), renin-aldosterone system (RAAS), and kinin-kallikrein system are the main proposed mechanisms contributing to cardiovascular complications with the COVID-19 infection. ACE receptors can be found in the heart, blood vessels, endothelium, lungs, intestines, testes, neurons, and other human body parts. SARS-CoV-2 directly invades the endothelial cells with ACE2 receptors and constitutes the main pathway through which the virus enters the endothelial cells. This causes angiotensin II accumulation downregulation of the ACE2 receptors, resulting in prothrombotic effects, such as hemostatic imbalance via activation of the coagulation cascade, impaired fibrinolysis, thrombin generation, vasoconstriction, endothelial and platelet activation, and pro-inflammatory cytokine release. The KKS system typically causes vasodilation and regulates tissue repair, inflammation, cell proliferation, and platelet aggregation, but SARS-CoV-2 infection impairs such counterbalancing effects. This cascade results in cardiac arrhythmias, cardiac arrest, cardiomyopathy, cytokine storm, heart

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failure, ischemic myocardial injuries, microvascular disease, Kounis syndrome, prolonged COVID, myocardial fibrosis, myocarditis, new-onset hypertension, pericarditis, postural orthostatic tachycardia syndrome, pulmonary hypertension, stroke, Takotsubo syndrome, venous thromboembolism, and thrombocytopenia. In this narrative review, we describe and elucidate when, where, and how COVID-19 affects the human cardiovascular system in various parts of the human body that are vulnerable in every patient category, including children and athletes.

Severe acute respiratory coronavirus-2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has infected around 670 million people worldwide since January 2023. According to the May 2, 2023, report, the COVID-19 outbreak has spread to almost every country in the world, with more than 6.86 million deaths (Table 1 Supplementary), reaching 6,961,001 (updated October 15, 2023),[1] attributed to COVID-19, with increasing evidence supporting the existence of long-term COVID-19 syndrome. COVID-19, which is caused by SARS-CoV-2, often manifests as a pulmonary illness but can potentially affect extrapulmonary organs, such as the heart.[2] Several studies have found a higher risk of adverse cardiovascular outcomes after COVID-19 exposure, even after recovering from the acute infection.[3] The myocardial injury in COVID-19 patients has been associated with coronary spasm, microthrombi formation, plaque rupture, hypoxic injury, or cytokine storm, which have the same pathophysiology as the three clinical variants of Kounis syndrome.[4] ACE2 and its interactions with RAAS and KKS are one of the main proposed mechanisms for the development of cardiovascular complications and new-onset hypertension.[5] ACE2 receptors are found all over the human body, most notably in the heart, blood vessel endothelium, lungs, intestines, testes, and neurons. SARS-CoV-2 directly invades endothelial cells with ACE2 receptors and constitutes the main pathway through which the virus enters the cardiovascular system.[6] The S1 subunit of the SARS-CoV-2 spike protein binds to the ACE2 receptors on the cell surface, allowing the virus to enter the cell membrane. This causes ACE2 receptor downregulation and angiotensin II accumulation, resulting in prothrombotic effects, such as hemostatic imbalance through activation of the coagulation cascade, impaired fibrinolysis, thrombin generation, vasoconstriction and hypertension, endothelial and platelet activation, and proinflammatory cytokine release.[7] Angiotensin I has no direct biological effect other than to stimulate catecholamine production when levels are high. Angiotensin I has distinct and opposing effects to angiotensin II, including vasodilation induction, inflammation, and thrombosis inhibition. However, angiotensin I is metabolized to its biologically active byproduct, angiotensin II, a potent vasoconstrictor, via cleavage of the two terminal amino acids. Moreover, SARS-CoV-2 infection inhibits the counterbalancing function of the KKS system, which commonly causes vasodilation and regulates tissue repair, inflammation, cell proliferation, and platelet aggregation.[8]

Because cardiovascular complications are a significant risk factor for COVID-19 mortality, this narrative review aims to search the published literature up to June 2023 to elucidate the risk factors, putative causes, diagnosis, and pathophysiology of COVID-19 cardiovascular complications (Figure 1).

A literature search was conducted and updated on June 30, 2023, on the PubMed, MedLine, and Embase databases, as well as Google, using the keywords "COVID-19," "cytokine storm," "SARS-CoV-2," "SARS-CoV," "COVID-19 and the heart," "cardiovascular complications of COVID-19 infection," "ischemic myocardial injury," "coronaviruses," "mast cells," and "Kounis syndrome." A bibliographic search was also conducted. Articles in this review were to be published before the end of June 2023, be full text in English, and be classified as original research, reviews, meta-analyses, or letters to the editor. The database screening period ended on June 30, 2023. These criteria were validated by reviewing titles and abstracts. The articles were thoroughly examined to determine if all inclusion requirements were met. An additional literature screening method was searching for references included in the manuscripts. The abstracts were scanned to determine their suitability for inclusion in this narrative review.

Arrhythmias and COVID-19

Arrhythmias in COVID-19 may be caused by hypoxia due to direct viral lung tissue injury, myocarditis, or secondary causes, such as myocardial ischemia, myocardial strain, electrolyte abnormalities, changes in intravascular volume, drug adverse effects, and the context of systemic illness.[9]

In one retrospective study of COVID-19-admitted patients, atrial arrhythmias were found in 7.1% of the patients, whereas

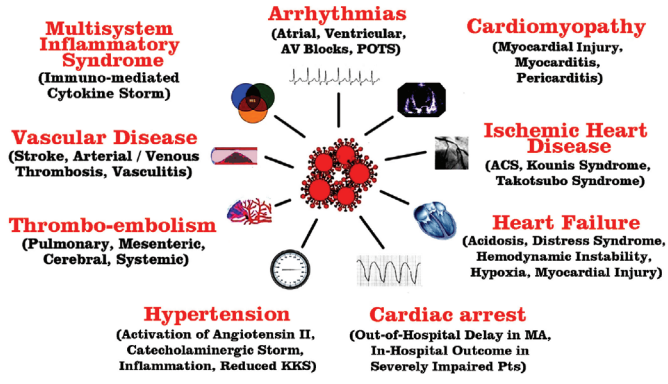

FIG. 1. Synopsis of cardiovascular diseases caused by COVID-19 infection.

ACS, Acute coronary syndrome; AV, atrioventricular; KKS, kinin-kallikrein system; MA, medical assistance; POTS, postural orthostatic tachycardia syndrome, Pts, patients; COVID-19, coronavirus disease 2019.

ventricular arrhythmias were found in 0.3% of mechanically ventilated patients.[10] Another study found atrial arrhythmias in 16.5% of intensive care unit (ICU) patients.[11] On the other hand, He et al.[12] revealed one of two COVID-19 patients with transient complete heart block accompanied by transient S wave in the lead 1, Q wave in the lead 3, and inverted T wave in the lead 3 (*S1Q3T3*), supporting the diagnosis of temporary pulmonary artery hypertension secondary to acute respiratory distress syndrome (ARDS). Beyond complete heart block and bradyarrhythmias, COVID-19 patients have shown supraventricular tachyarrhythmias, atrial fibrillation, atrial flutter, and ventricular arrhythmias, such as polymorphic ventricular tachycardia (VT), monomorphic VT, and multifocal VT, indicating various mechanisms for arrhythmogenesis.

Hypoxia is important in arrhythmogenesis because hypoxia-induced cellular damage can activate anaerobic glycolysis and increase cytosolic calcium levels, enabling early and late depolarizations and causing changes in action potential duration.[13] Furthermore, hypoxia can increase extracellular potassium levels, improving electrical conduction while decreasing electrical coupling and tissue anisotropy through connexin dephosphorylation in gap junctions.[14]

The pathophysiology of SARS-CoV-2 myocarditis can be attributed to direct viral myocardial tissue injury, alveolar macrophage migration/accumulation, or lymphocyte cell-mediated cytotoxicity, resulting in myocardial inflammation and further injury.[15] Consequently, myocarditis can cause arrhythmias due to direct myocardial cell damage and altered expression of myocardial connexins. This causes gap junction impairment or ion channel dysfunction, particularly in those with coexisting channelopathies. Viral myocarditis causes structural and electrophysiological remodeling, resulting in inefficient calcium handling and potassium channel downregulation, leading to prolonged repolarization and conduction abnormalities, such as decreased conduction velocity and reduced refractoriness. Prolonged repolarization may trigger activity, whereas conduction abnormalities may result in circus-type or phase 2 re-entry.[16] Arrhythmias can be observed during the post-myocardial inflammation phase due to re-entry in the case of myocardial scar.[17] Finally, inflammatory cytokines, including interleukin-6 (IL-6) and IL-1, as well as tumor necrosis factor-α, may affect the expression and function of calcium and potassium channels, contributing to inflammatory cardiac channelopathies and ventricular action potential alterations.[18] Consequently, inflammatory cytokines due to increased sympathetic system activation can cause QT prolongation and arrhythmias in patients with long QT syndrome.

Another factor contributing to arrhythmogenesis in COVID-19 is myocardial ischemia caused by microvascular dysfunction in conjunction with an enhanced inflammatory state, where activation of inflammatory cells can induce vasoconstriction due to impaired vascular endothelial function in individuals with pre-existing atherosclerotic lesions. IL-6 and tumor necrosis factor-α have been shown to significantly impair coagulation and fibrinolysis, causing bleeding and thrombosis.[19] Microvascular dysfunction and myocardial ischemia can also be induced via viral-mediated vasculitis due to SARS-CoV-2 attachment to ACE receptors in arterial endothelial cells.[20] COVID patients have been shown to have a myocardial injury with ST-segment elevation, whereas cytokine storms can cause acute coronary syndromes in cases of pre-existing atherosclerotic plaque due to inflammatory cell activation and impaired endothelial vascular function.[21]

Arrhythmias can be caused by right ventricular myocardial strain in the context of pulmonary embolism, a common thrombotic complication in COVID-19, or by pulmonary hypertension, which can be caused by increased right heart pressures due to ARDS, sepsis, or co-existing heart failure.[22] Atrial arrhythmias are the most common in patients with increased atrial pressures and increased sympathetic activity in individuals with pulmonary hypertension.[23]

Finally, fluid imbalance and electrolyte abnormalities can cause various arrhythmias. Intravascular volume alterations in critically ill patients, whether caused by ARDS-induced sepsis or secondary due to heart failure, can lead to atrial fibrillation.[24] Electrolyte abnormalities can trigger de novo or potentiate pre-existing arrhythmias. According to previous retrospective studies, electrolyte abnormalities can be caused by either acute or chronic renal dysfunction or COVID-associated diarrhea.[25] Atrial arrhythmias are the most commonly reported electrolyte abnormalities.

Moreover, drugs, such as hydroxychloroquine and azithromycin, used as "off-label" therapies in COVID-19 patients, can cause QT prolongation, increasing the risk of Torsades de Pointes.[26] These agents, in particular, can induce action potential prolongation and trigger early after depolarizations due to increased inward Na^+ and Ca^{2+} currents, which can lead to Torsades de Pointes by inhibiting the human ether-à-go-go-related gene $(hERG\text{-}K)^+$ channel.

Cardiac Arrest

Cardiac arrest (CA) is a primarily fatal condition, and its annual incidence, before the COVID-19 pandemic, ranged from 40 to 80 per 100,000, with an average survival rate of 9%.[27] During the COVID-19 pandemic, there was an increase in the incidence of out-of-hospital CA (OHCA) and in-hospital CA (IHCA), as well as a decline in survival. During the first weeks of the COVID-19 pandemic, the OHCA was worst, followed by areas with high and decreased case fatality rates. According to a recent study from the United States, the age-standardized annual CA incidence increased during the pandemic from 39 per 100,000 prepandemic to 54 per 100,000. The incidence increased by 77% among Hispanics, from 38 per 100,000 to 68 per 100,000, with disproportionate increases in total cardiovascular mortality.[28]

This increase was attributed to malignant tachyarrhythmias, delays in seeking care among individuals with cardiac symptoms, and delayed emergency medical service activation/response during COVID-19 waves. In a retrospective study[29] of 136 patients with COVID-19, the respiratory causes of CA impacted 119 (87.5%) patients. The initial rhythm was asystole in 89.7%, pulseless electrical activity in 4.4%, and shockable rhythm in 5.9%. In this study,[30] the return-of-spontaneous-circulation rate was 13.2%, and

the 30-day survival rate was only 2.9%. In a multicenter study[31] of more than 5,000 critically ill COVID-19 patients, 14% developed IHCA. After cardiopulmonary resuscitation, the mortality rate in another study of 54 COVID-19 patients was even higher (100%). Although 52 patients (96.3%) had non-shockable initial rhythms, pulseless electrical activity was the most common clinical result (81.5%). The return-of-spontaneous-circulation rate was achieved in 29 patients (53.7%); however, none survived to be discharged to homes.[32] The presence of the underlying illness during the CA, mechanical ventilation, kidney replacement therapy, vasopressor support, a high percentage of non-shockable rhythms, a lack of treatments to treat the underlying disease process, and potential delays in response time due to isolation procedures, the need to use personal protective equipment, and restricted access to COVID-19 units appear to be some of the causes of the low survival rates of IHCA. Moreover, the incidence of OHCA significantly increased during the COVID-19 pandemic[33,34] in different cities by 21% (Los Angeles County, California) and 62% (Detroit, Michigan) and various geographic regions worldwide with similar trends. According to a meta-analysis[35] of 10 studies with more than 35,000 OHCA episodes from multiple geographic regions, the increase in OHCA was 120%. The common and rare causes and mechanisms of COVID-19-associated CA are shown in Table 1.

COVID-19 Multisystem Inflammatory Syndrome-Induced Cardiac Manifestations in Children and Adults

The multisystem inflammatory syndrome (MIS) is a severe symptom of SARS-CoV-2 infection. The true incidence of MIS is unknown; however, it appears to be an underdiagnosed condition. The syndrome often occurs within 1-6 weeks following COVID-19 infection, affecting children (MIS-C) and adults (MIS-A).

Primary classical syndrome symptoms include fever, mucocutaneous manifestations (e.g., strawberry tongue, malar rash, periorbital erythema, and conjunctivitis), lymphadenopathy, peripheral edema, elevated inflammatory biomarkers, and multiorgan involvement (Figure 2).

The involvement of cardiovascular, gastrointestinal, neurological, and hematological systems in MIS varies. The cardiovascular system is the most commonly affected. The predominant cardiac symptoms of MIS include left ventricular systolic dysfunction, coronary artery aneurysms (CAAs), arrhythmias, conduction abnormalities, and pericardial involvement (Table 2).

Patients with MIS-C may have some symptoms consistent with toxic shock syndrome and Kawasaki disease. MIS patients are typically more critically ill than those with Kawasaki disease, and ventricular dysfunction is more common. Nevertheless, CAAs are less common in MIS patients.

The exact pathophysiology remains unclear. However, MIS appears to be characterized by a post-infectious cytokine storm triggered by a dysfunctional immune response, resulting in systemic inflammation, endothelial dysfunction, and a procoagulant state.

Supportive care, immunomodulatory therapy, glucocorticoids and intravenous immunoglobulin, anakinra or tocilizumab, and a low dose of aspirin are used to treat MIS. The treatment aims to include patient stabilization, CAAs, and myocardial fibrosis prevention. Anticoagulation may be indicated in patients with a coronary artery *z* score[36] (coronary arterial diameter) > 10.0 and/or an EF < 35%.

Capone et al.[37] investigated the early and midterm outcomes of 50 MIS-C patients. Although some of them developed myocardial fibrosis, coronary aneurysm, and myocardial dysfunction on magnetic resonance imaging (MRI), the majority of them recovered completely. In a study of 95 MIS-C patients, troponin was found in 71%, myocarditis in 53%, 80% were admitted to the ICU, and two died.[38] Another cohort from 55 centers showed a high incidence of myocardial injury (93%), shock (40%), and arrhythmia (35%). In this cohort,[39] 24% had coronary artery involvement, and 15.3% required mechanical ventilation.

Cardiomyopathy

Cardiomyopathy is a Greek word ("cardio" means heart, "myo" means muscle, and "pathy" means disease) that refers to a group of diseases that affect the structure of the heart muscle. According to large database studies, cardiomyopathy is a serious complication of SARS-CoV-2-induced acute COVID-19 infection.[40]

Other studies have found that the risk of ischemic and non-ischemic cardiomyopathy in vaccinated and unvaccinated patients who tested positive for COVID-19 was higher in SARS-CoV-2-positive individuals than in non-infected control participants.[40,41] In these studies, ischemic cardiomyopathy was classified as one of the two most significant risks following COVID-19 infection for all ages, preferably in the female gender. Ischemic cardiomyopathy develops 1-12 months after a positive COVID-19 test. Several mechanisms

TABLE 1. Causes and Mechanisms Predisposing for Cardiac Arrest During COVID-2019.

Common causes
Acute coronary syndrome
- Arrhythmias
- Cytokine storm
- Drug inducing arrhythmias
- Endothelial inflammation
- Increased immune response
- Myocarditis
- Pericarditis
- Prothrombotic state triggers
- Pulmonary embolism
- Respiratory hypoxia
- Vascular thrombosis
Uncommon causes
- Delay in patient care
- Lonely patients
- Neglected hygiene
- Over tired *medical service staff* and hospital systems
- Reduced hospital work force
- Reduced prevention
- Reduced emergency tests and procedures
- Reorganization order to stay-at-home
- Strict lockdown measures
- Use of personal protective equipment

have been proposed to explain how COVID-19 infection can lead to cardiomyopathy. COVID-19 has been proposed to cause myocardial injury as a result of LV systolic dysfunction; however, the exact pathophysiology is unknown.

Cytokine storm-induced inflammatory cascade is the most commonly proposed hypothesis for the resulting myocardial injury. The growth in cardiac troponins coincides with increased inflammatory mediators, such as IL-1, C-reactive protein, and other inflammatory biomarkers. Other suggested mechanisms include acute inflammatory triggering of atheromatous plaque destabilization leading to acute coronary syndrome, microvascular injury secondary to disseminated intravascular coagulation, and thrombosis. Moreover, a mismatch in oxygen supply and demand can cause myocardial injury similar to type 1 and type 2 myocardial infarctions. Another mechanism that has been proposed is the virus' direct invasion of the myocardium, resulting in acute cardiomyopathy. Endomyocardial biopsy is the only diagnostic method for determining the etiology of myocarditis or inflammatory cardiomyopathy. However, autopsy series have failed to show myocardial necrosis[42] caused by COVID-19. Furthermore, this technique is problematic considering the risk of infectious transmission, the required expertise, and the false negative rates in endomyocardial biopsies in all suspected cases.[43] Although myocardial damage caused by COVID-19 infection is most likely due to an excessive inflammatory response, direct myocardial invasion cannot be ruled out.

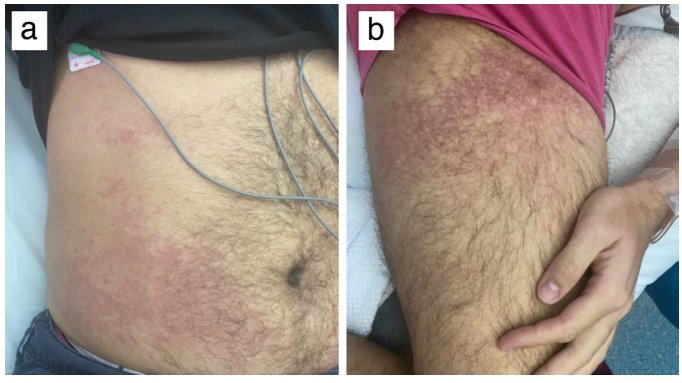

FIG. 2. Skin rash mainly located in the abdominal (a) and femoral area (b) in a 24 year-old male with COVID-19 induced MIS-A. The patient presented with acute heart failure, peripheral edema, pyrexia and neurological manifestations.

TABLE 2. Cardiovascular Manifestations of Multisystem Inflammatory Syndrome in Children (MIS-C) and Adults (MIS-A).

Pericardial involvement (pericardial effusion, pericarditis, cardiac tamponade)
Coronary involvement (dilation, aneurysms, thrombosis)
Myocarditis
Shock (vasodilatory, cardiogenic)
Left ventricular myocardial dysfunction (systolic, diastolic)
Valve regurgitation (mitral, tricuspid)
Left ventricular apical thrombus
Pulmonary embolism
Arterial and venous thrombosis
Conduction disturbances ($1^{nd}/2^{nd}/3^{rd}$ degree A-V block, LBBB, RBBB, sinus bradycardia)
Brugada pattern
Prolonged QTc interval
ST-T wave segment abnormalities
Elevated cardiovascular biomarkers (BNP, NT-pro-BNP, troponin, D-dimers)
Arrhythmias (ventricular, supraventricular)

Cytokine Storm

Severe COVID-19 is characterized by an overactive immune system and a hyper-inflammatory condition. Cytokines are considered the "lingua franca" of the immune system, facilitating effective communication between immune and non-immune cells. Cytokine storms are a defining feature of critical COVID-19 and a significant determinant of adverse outcomes. In particular, SARS-CoV-2 infection is associated with an exaggerated production of cytokines and chemoattractant molecules, including IL-1β, IL-2, IL-6, IL-8, IL-10, IL-18, IL-33, tumor necrosis factor-α, interferon (IFN)-γ, monocyte chemoattractant protein 1 (MIP-1), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage CSF (GM-CSF). Notably, cytokine levels strongly correlate with disease severity, often serving as valuable prognostic indicators or potential therapeutic targets.[44]

The underlying mechanisms that cause the cytokine storm during SARS-CoV-2 infection are not fully understood; however, several hypotheses contribute to our present understanding. SARS-CoV-2 causes direct cytopathic damage to alveolar epithelial cells and resident macrophages that express ACE2. Subsequently, tissue injury and the subsequent release of damage-associated molecular patterns stimulate the production of pro-inflammatory mediators, which attract and activate additional innate and adaptive immune cells, thereby accelerating the inflammatory cascade.[45] SARS-CoV-2 can hijack the normal immune system in the early stages of infection, notably by interfering with IFN responses. This inhibits the clearance of the virus, resulting in paradoxical hyper-inflammation.[46] SARS-CoV-2 also manipulates programmed cell death mechanisms to facilitate replication and promote pyroptosis (programmed necrotic cell death derived from the Greek words "pyro," which means fire, and "ptosis," which means falling)-mediated inflammation.[46] Defective adaptive immune responses are also linked to developing the COVID-19 cytokine storm. Antibody-dependent enhancement occurs when pre-existing antibodies bind to SARS-CoV-2, but instead of neutralizing the virus, they can facilitate its propagation by interacting with fragment crystalizable (Fc) receptors on immune cells.[47] In addition, the virus can cause direct injury to intestinal epithelial cells that express the ACE-2 receptor or impair gut barrier integrity by changing tight junction protein production. Furthermore, COVID-19 is associated with significant changes in intestinal microflora, resulting in dysbiosis and dysregulation of mucosal immune responses. This multifaceted disruption of gut barrier integrity allows an aberrant influx of microbes, fungi, and other pathogen-associated molecular patterns into the systemic circulation and, to some extent, leads to immune

system overactivation[48] during COVID-19. Finally, hypoxia and oxidative stress act as additional driving mechanisms for the cytokine storm, further fueling the vicious cycle.[49]

Cytokine storms are complex and dynamic inflammatory processes that cause detrimental complications, such as capillary leaks, thrombo-inflammation, ARDS, and multiorgan failure, contributing to higher mortality during COVID-19. Systemic inflammation is important in the development of cardiovascular complications, and hyper-cytokine-mia has been linked to various heart-related conditions, including myocarditis, unstable plaque rupture, acute myocardial injury, stress-induced cardiomyopathy, arrhythmias, and heart failure.[50] Patients with a pre-existing inflammatory state or impaired gut barrier function, such as obesity, diabetes mellitus, or chronic coronary syndromes, are predisposed to more intense inflammatory responses and deteriorating disease progression.[51] The cardiovascular complications of cytokine storm in general, and viral infections in particular, have been described as arrhythmias, myocarditis, myocardial ischemia, pericarditis, and type 1 (atherosclerotic plaque rupture) and type 2 (secondary to an ischemic imbalance) myocardial infarction and heart failure.[52]

Heart Failure

COVID-19 myocardial injury leading to heart failure (HF) is not rare. In a retrospective study of 191 COVID-19 patients in Wuhan, China, HF was found to be the fourth most common outcome of the disease.[53] Moreover, in another study including 131 patients who have died of COVID-19, 49% of all deaths were due to HF, although these patients had no previous history of cardiovascular diseases.[54]

After sepsis, it appears that the most common COVID-19 complications are respiratory failure, including ARDS, cardiac injury, and HF.

The risk of HF in patients infected with SARS-CoV-2 has been observed to be increased after the first 30 days. The risks and burdens were evident even among non-hospitalized individuals and increased in a graded fashion depending on the treatment setting during the acute phase, such as non-hospitalized, hospitalized, and admitted to intensive care.

Predisposing factors of HF include worsening of previous cardiovascular disease, long-term effects of SARS-CoV-2 on cardiac function, and adverse effects of cardiac injury during the acute phase of COVID-19 infection.

Other studies have found no difference in long-term mortality between patients with ST-elevation myocardial infarction and COVID-19 infection.[55] However, patients who tested positive for COVID-19 had higher rates of major cardiovascular and cerebrovascular events and hospitalization with HF than those who did not.[55] However, later changes in cardiac function, such as diastolic dysfunction, may occur. Indeed, echocardiography changes often appear within 3-6 months.[56] After acute COVID-19 infection, left and right ventricular dysfunction (RVD) have been reported.

a. Left ventricular dysfunction: Several studies have found statistically significant reductions in LVEF 2-9 months after acute COVID-19 infection compared with controls. These studies included patients with acute disease ranging from asymptomatic to severe illness.[57] Congestive heart failure and a prominent reduction in LVEF (mean LVEF 28%) were found in patients with biopsy-proven post-COVID-19 myocarditis 5.5 months after COVID-19 infection. Moreover, subclinical low-voltage direct LVDs have been reported following COVID-19 infection in asymptomatic patients with low cardiac risk who recovered from acute symptoms at home.

On admission, patients with COVID-19 with higher cardiovascular biomarkers had an equivalent echocardiographic LVEF, LV diameter, LV mass, or left atrial volumes at a median of 4.3 months after discharge than those without high markers.

Some authors suggest that this method may not be sensitive enough to detect cases of minor LV impairment.[58] However, it has been suggested that LV longitudinal strain (LVLS) has a greater sensitivity than LVEF measurement in detecting minor LV myocardial function impairment. Concomitant diseases, such as peripartum cardiomyopathy, may affect left ventricular systolic function with a 10-15% decrease in ejection fraction (EF) in patients with COVID-19 infection.

Both LV systolic and diastolic dysfunction can complicate COVID-19 infection. However, 6 months after hospitalization, there were severe cardiac diastolic abnormalities without systolic involvement.

b. Right ventricular dysfunction: The majority of SARS-CoV-2-related deaths have been associated with cardiovascular events and ARDS. Indeed, COVID-19 cases with myocardial injury[59] had a significantly higher mortality rate than those without (59.6% vs. 8.9%). RVD can be evident in nearly one out of every five patients, and the severity of COVID-19 disease is crucial. RVD may be a vital marker for prognostic stratification in COVID-19 patients.

A recent study found that a decrease in RV global longitudinal strain and RV free wall longitudinal strain at 3 months was negatively correlated with C-reactive protein levels, neutrophil-to-lymphocyte ratio, D-dimer, ferritin, and platelet-to-lymphocyte ratio. Because these markers are signs of inflammation and thrombosis, the possible pathology underlying RVD is the combination of reduced contractility due to myocardial injury and increased right ventricular afterload. Indeed, this study found increased RV diameter and systolic pulmonary artery pressure at 3 months after COVID-19 infection, implying the same mechanism.[60] However, other studies have found that subclinical RV dysfunction caused by abnormal RV longitudinal strain was associated with PH or increased RV afterload in 42% of patients 2 to 3 months after COVID infection.[61]

According to Parhizgar et al.,[40] RV dysfunction without increased afterload may suggest reduced contractility as the primary potential mechanism.

Ischemic Myocardial Injury and Coronary Thrombosis

There is a relationship between the incidence of acute myocardial infarction (AMI) and respiratory infections. For example,

patients with influenza virus or other respiratory diseases are at a higher risk of AMI.[62] Respiratory illness can lead to prothrombotic conditions, myocardial supply-demand mismatch, platelet activation, coronary vasoconstriction, and endothelial cell dysfunction.[63] Indeed, platelet surface expresses particular low-affinity FcγRIIa receptors, additional high affinity for immunglobulin (Ig)E FcεRI, and low affinity for IgE FcεRII/CD32 receptors, which are potential targets for various antigens and can contribute to thrombosis. These factors can cause plaque rupture and thrombosis, resulting in myocardial injury. Recent reports suggest that ST-segment-elevation myocardial infarction (STEMI) may be the first clinical manifestation of COVID-19. Indeed, STEMI was the first clinical manifestation of COVID-19 in 85.7% of patients who did not have a COVID-19 test result at the time of coronary angiography. Therefore, further understanding of the myocardial injury pathophysiology in COVID-19 patients appears paramount.

A multicenter observational study assessing clinical and prognosis differences in patients with COVID-19 STEMI found a significant increase in in-hospital mortality, stent thrombosis, and cardiogenic shock after percutaneous coronary intervention in patients with STEMI and COVID-19 compared with contemporaneous non-COVID-19 STEMI patients.[64] The North American COVID-19 STEMI registry[65] compared 230 patients with confirmed COVID-19 infection with 995 controls. Patients with COVID-19 and STEMI had a higher rate of cardiogenic shock or CA and had less primary PCI than age and sex-matched control patients. On invasive angiography, COVID-19-infected patients had a longer door-to-balloon time and no culprit lesions. COVID-19-positive patients had longer stays in intensive care units, and the primary outcome of in-hospital death, stroke, recurrent MI, or unplanned revascularization occurred in 36% of them than only 4% of the control patients.

COVID-19-positive STEMI patients had greater infarct size, reduced left ventricular function, greater intracoronary thrombus, and more life-threatening arrhythmias.[66] A meta-analysis of these studies[67] found that mortality in COVID-19 patients with STEMI was just over 25%. Although patients can develop myocardial infarction during the acute phase of COVID-19 infection, studies on myocardial ischemic disease in the post-COVID-19 period are few.[40] Indeed, around 20-30% of patients with COVID-19 infection experience chest pain and angina-like chest discomfort as post-COVID-19 symptoms. However, non-cardiac causes of post-COVID-19 chest pain, such as anxiety, physical and emotional stress, and musculoskeletal and pulmonary factors, should be considered, and physicians should be careful with the accurate diagnosis.[68] In a study of patients hospitalized with severe SARS-CoV-2 infection and increased troponin on admission, cardiac MRI revealed ischemic heart disease in 26% of them 2 months later.[69] Six months after ICU admission, 19% of COVID-19 patients who had mechanical ventilation had newly diagnosed coronary artery disease.[70] In another study, after 8 months of SARS-CoV-2 infection, the cardiac MRI showed a significant circumferential subendocardial perfusion defect in 50% of patients with no history of cardiovascular disease who reported chest pain during their COVID-19 illness.[71] Therefore, patients with post-COVID-19 atypical chest pain require close monitoring and treatment.

Kounis Syndrome and COVID-19

Kounis syndrome is a condition that causes coronary spasms, myocardial infarction, and stent thrombosis. It is related to mast cell activation and inflammatory cell interactions, including T-lymphocytes and macrophages, and is associated with allergic, hypersensitive, or anaphylactic insults.[72] Mast cells are a significant source of proinflammatory cytokines during COVID-19 infection.[73] Mast cell-derived proteases and eosinophil-associated mediators also increase in COVID-19 patient sera and lung tissues.[74] Mast cells are typically activated by allergens, but they can also be triggered by virus-associated molecular patterns.[74] This is achieved by activating toll-like receptors, particularly SARS-CoV-2, which produces proinflammatory mediators, such as IL-6 and IL-1β, thus potentially contributing to COVID-19 pathology.[75] These cells enter the circulation from the bone marrow as mononuclear cell progenitors and circulate as mast cell precursors, disposing in their surface KIT receptors (cytokine receptors) for stem cell factor (SCF). SCF is essential for mast cell growth, survival, differentiation, proliferation, adhesion, and homing. Mast cells can attach to all human tissues, even tissue without allergic reactions, because IgE antibodies cannot pass the blood-brain barrier. Mast cells develop and mature in these tissues for several days or weeks. Mast cells form in the coronary arteries under local microenvironmental factors, resulting in different phenotypes.[75]

The following evidence suggests and supports an association between COVID-19 and Kounis syndrome:

- COVID-19 affects the coronary and peripheral arterial vasculature. It can cause coronary spasm, direct endothelial or vascular injury, plaque rupture and microthrombi, hypoxic injury, cytokine storm, and an increased risk of stent thrombosis. This is due to the underlying hypercoagulable condition, which clinically corresponds with the three main types of Kounis syndrome, namely, coronary spasm, AMI, and stent thrombosis.[76,77]

- Antihistamines (famotidine, rupatadine, and ebastine), which block histamine receptors, and corticosteroids (dexamethasone), which are potent anti-inflammatory and immunomodulating agents, are the drugs of choice for treating COVID-19 and Kounis syndrome.[78]

- COVID-19-induced immune system activation in asymptomatic patients may increase the risk of transitioning from asymptomatic, subclinical, or atherosclerotic disease to an unstable condition with vulnerable plaques prone to thrombosis, as in Kounis syndrome.[79]

- As a result of the increased risk of fatal arterial thrombosis caused by COVID-19-induced cytokine storm and hypercoagulopathy, large cerebral vessel occlusion and Kounis syndrome might occur.[80]

- Recently, a COVID-19 CA caused by Prinzmetal's angina mimicking Kounis syndrome in a previously normal heart was described.[81]

- COVID-19 is associated with an increase in effector cells, such as eosinophils and IgEs.[82]
- After eating canned tuna, a female patient developed erythematous lesions, mild itching, nausea, diaphoresis, and weakness, indicating scombroid syndrome. She tested positive for SARS-CoV-2 infection and had acute coronary syndrome[83] of Kounis type 1. This case demonstrated a relationship between Kounis syndrome with SARS-CoV-2 disease and histamine fish poisoning.[83]

Long COVID-19 and the Heart

Prolonged COVID-19 is defined as symptoms that have lasted 4 weeks or longer following the follow-up index date, including symptom onset, hospitalization, and discharge. This condition is attributed to numerous risk factors that include ethnic minority, chronic obstructive pulmonary disease, female gender, obesity, psychiatric conditions, smoking, and socioeconomic deprivation. General symptoms of prolonged COVID include general pain, muscle or joint pain, mobility dysfunction, fatigue, fever, hair fall, skin rash, and weight loss. Cardiopulmonary symptoms, such as chest pain (5%), palpitations (9%), sore throat, dyspnea, dyspnea, and cough, have been reported 6 months after recovery. In a study of 534 patients who underwent cardiac MRI at baseline, 6 months, and 12 months after the onset of prolonged COVID symptoms, findings such as ventricular dilatation, systolic dysfunction, reduced global strain, and elevated native T1 signals were found in approximately 20% of patients.[84] One in 20 children with post-COVID-19 condition at 3 months have persistent symptoms 18 months after SARS-CoV-2 infection.[85] A new onset of atrial fibrillation (AF) has been reported in patients with acute COVID-19 and patients with any other systemic diseases.[86] These patients may not develop recurrent AF after recovery, eliminating the need for rate, rhythm, and antithrombotic therapy. However, if the AF lasts more than 48 h, treatment and prevention should be continued. The intensity and timespan of prolonged COVID-19 cardiac symptoms vary from patient to patient. It should be noted that detecting long COVID-19 risk factors is an important and active area of research.

Myocardial Fibrosis

Acute myocardial injury, including ischemic myocardial involvement and myocarditis after recovery from acute SARS-CoV-2 infection, may lead to myocardial fibrosis.[40] After recovering from an acute COVID-19 infection, roughly 20-30% of patients develop myocardial fibrosis. A prospective study of 159 COVID-19 patients indicated that one in every five patients had indications of myocardial fibrosis 28-60 days after discharge.[70] Moreover, 21% of patients in another study using late gadolinium enhancement imaging had myocardial fibrosis 6 months after ICU admission.[87] One-third of the patients needed to be hospitalized, and 19% required ventilatory support. According to two additional cardiac MRI studies, the incidence of myocardial fibrosis was 31% and 32%, respectively, with a similar distribution of injury.[88,89] All patients reported cardiac symptoms at the follow-up and had been hospitalized with COVID-19 infection. Myocardial fibrosis is a potentially fatal condition that may lead to severe and chronic congestive cardiac failure.

Myocarditis Related to SARS-CoV-2 Infection

Myocarditis is an inflammatory disease of the myocardium that causes myocardial injury but does not have an underlying ischemic etiology. Viral infections are common causes of myocarditis, which can lead to hospitalizations, heart failure, and sudden cardiac death. The exact definition and differentiation of myocarditis caused by vaccines, drugs, or substances remain unclear. The types of myocarditis[90] based on causative, histological, and clinicopathological criteria were classified (Table 3).

The gold standard for diagnosing myocarditis is histological evidence of an inflammatory cell infiltration with or without myocardial damage. However, the pathogenesis of COVID-19-associated myocarditis is poorly understood because of its mild initial clinical history, and myocardial biopsies are not commonly performed. Although myocarditis is considered a rare cardiovascular complication of COVID-19, several cases of acute myocarditis in COVID-19 patients have been described. According to a recent consensus statement, the average prevalence of definitive/probable myocarditis in COVID-19 patients admitted to the hospital was estimated to be 2.4 cases/1,000 hospitalized patients, with a possible higher mortality rate (20.4%). Moreover, the risk of myocarditis increased by roughly 10-fold in the month after a positive SARS-CoV-2 test, and it was more common in males.[91] Several hypotheses on the pathophysiological mechanisms

TABLE 3. Classification Criteria of Myocarditis.

CAUSATIVE
- Viral: enteroviruses (e.g., Coxsackie B), erythroviruses (e.g., Parvovirus B19), adenoviruses, and herpes viruses
- Bacterial: *Corynebacterium diphtheriae, Staphylococcus aureus, Borrelia burgdorferi, Ehrlichia species*
- Drug induced or hypersensitivity
- Protozoal: Babesia
- Toxic: alcohol, radiation, chemicals (hydrocarbons and arsenic), drugs, e.g., doxorubicine
- Trypanosomal: *Trypanosoma cruzi*
HISTOLOGICAL
- Eosinophilic: Hypersensitivity or drug induced
- Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
- Giant cell myocarditis (cell mass formed by histiocytes and eosinophils).
- Histiocytic myocarditis (histiocytes have eosinophilic cytoplasm)
- Hypereosinophilic syndrome Malignancies
- Parasitic infections
- Idiopathic acute necrotizing eosinophilic myocarditis
- Granulomatous myocarditis
- Lymphohistiocytic (histiocytes have eosinophilic cytoplasm)
- Lymphocytic
CLINICOPATHOLOGICAL
- Fulminant
- Acute chronic
- Active chronic
- Persistent
- Myopericarditis

of COVID-19-associated myocarditis have been proposed. They include cytotoxicity mediated by a hyperimmune response triggered by mRNA molecules, excessive release of inflammatory mediators causing lymphocyte dysregulation resulting in T-lymphocyte–mediated necrosis, direct myocardial injury, and autoimmune disorders mediated by molecular mimicry. In Germany,[92] the incidence of myocarditis in COVID-19 hospitalized patients was found to be 1.28 cases per 1,000 hospitalizations in 2020. The primary risk factors for myocarditis in COVID-19 were young age, male sex, pneumonia, and multisystemic inflammatory COVID-19 infection. Another study using cardiac MRI in COVID-19 patients with increased troponin levels found that 50% of patients had pathological signs of myocarditis (27%), ischemic heart disease (22%), and the rest non-specific.[93] According to a propensity-matched analysis of a National Inpatient Sample in the United States, myocarditis as part of long-term COVID-19 treatment has also been reported in several studies.[94] In a large study of people 16 yr and older, an additional 40 myocarditis occurrences per million were observed 1-28 days after a positive SARS-CoV-2 test.[95] Moreover, another study found that males aged 12-17 yr had 450 cases per million infections within 3 months after being infected with COVID-19.[95,96] Clinically, in the absence of myocardial injury, the possibility of myocarditis should always be considered in patients with persistent chest pain, exertional dyspnea or asthenia, palpitations, or syncope. The treatment of COVID-19-related myocarditis is primarily supportive while treating the underlying COVID-19 infection. COVID-19 patients are often given drugs, such as steroids, antivirals, and pain relievers. Further management may include the treatment of complications and tertiary comorbidities, such as heart failure, which should be treated using goal-directed medical therapy based on current standards of care.

New-onset Hypertension and COVID-19

Arterial hypertension is one of the most common complications of COVID-19 illness, which is an independent predictor of short-term mortality and severe disease. In a recent analysis of 19,293,346 patients (mean age: 54.6 yr, 54.6% males), including all studies published at any time up to February 11, 2023, and reporting the long-term risk of new-onset hypertension in COVID-19 survivors, the following results were found:[97] in a mean follow-up of 6.8 months, new-onset hypertension was observed to 12.7 [95% confidence interval (CI), 11.4-13.5] out of 1,000 patients survived from COVID-19 infection compared with 8.17 (95% CI, 7.34-8.53) out of 1,000 control patients. Moreover, 12 (2.2%) of 543 patients hospitalized or discharged from an emergency room with COVID-19 developed high blood pressure the following year.[98] This study had no control group, and the authors suspected that this finding was due to pandemic stress rather than COVID-19 infection. Another study found that 1.3% of 538 COVID-19 patients developed hypertension after 3 months of being discharged from the hospital.[99] Even in young and previously healthy patients, new-onset hypertension has been observed. One study of young adults [mean age: 21 (standard deviation, 20-22) yr] found that acute COVID-19 infection had a long-term effect on systolic and mean arterial blood pressure, with gradual improvement 6 months later.[100] Several months after mild COVID-19 infection, healthy adolescents developed new-onset hypertension.[40] The activity of ACE2 receptors might explain the new-onset hypertension. When the SARS-CoV-2 binds to ACE2, it inhibits ACE2 from performing its normal function to regulate angiotensin II (ANG II) signaling. Thus, ACE2 activity is inhibited, allowing more ANG II to reach injured tissues. This increase in ANG II is most likely causing vasoconstriction and new-onset hypertension in COVID-19 patients.[101]

Pericarditis and Pericardial Involvement

The association between pericardial diseases and infections was first reported by Bing[102] in 1933. The most common infecting agents are parvovirus B19, echovirus, coxsackie, and herpes viruses. Coronaviruses, like other infections, have the potential to cause pericardial involvement. Other coronavirus family members have also been implicated. Pericardial involvement is a frequently underdiagnosed condition associated with significantly higher all-cause mortality in COVID-19 patients. Clinically, it manifests as pericardial effusion, acute pericarditis, constrictive pericarditis, or life-threatening cardiac tamponade. Pericarditis is typically associated with myocarditis, and the frequency of pericardial involvement alone is estimated to be much lower.

Although the primary pathophysiology mechanism of pericardial diseases in COVID-19 is unknown, it is thought to develop after a cytokine storm. The pro-inflammatory cytokines IL-6, transforming growth factor-β, and vascular endothelial growth factor, released via the associated angiotensin II pathway, may cause inflammation and pericardial fibrosis. In addition, the viral presence was found in the pericardial fluid of a patient with cardiac tamponade. This finding provides new evidence in the complex puzzle of pathophysiology mechanisms.[103] Many epidemiological studies have found an increase in the incidence of pericarditis in COVID-19-infected patients. COVID-19-induced pericarditis is similar to other forms of viral pericarditis. There is no particular medical management strategy for pericarditis in patients with COVID-19 and pre-COVID pericarditis. Pericardial involvement is often seen as an asymptomatic pericardial effusion. Nevertheless, despite several studies, the prevalence of pericardial effusion in COVID-19 patients remains unclear. A systematic review and meta-analysis found pericardial effusion on chest computed tomography in approximately 5% of COVID-19 patients.[104] In contrast, Liu et al.[105] found pericardial effusion in almost 90% of critically ill patients. In a retrospective cohort study of 718,365 COVID-19 patients, 5% developed new-onset pericarditis. The 6-month all-cause mortality for pericarditis was 15.5% compared with 6.7% in matched controls. Furthermore, patients with pericarditis appeared to be associated with more new-onset cardiovascular sequelae than those with myocarditis. In an observational cohort study on 100 patients with severe COVID-19, pericardial effusion had a high prevalence (27%), and only 30% of them developed pericarditis. Additionally, patients with pericardial effusion had a higher overall mortality rate.[106] In a large prospective cohort of 530 COVID-19 hospitalized patients, pericardial effusion was found in

75 (14%), although only 17 patients (3.2%) met the criteria for acute pericarditis. Furthermore, pericardial effusion was associated with COVID-19 severity, myocardial dysfunction, and increased mortality.[107] Hence, these studies suggest that pericardial fluid may be a marker for several diseases and poor outcomes.

Cardiac magnetic resonance (CMR) is the most sensitive imaging modality for identifying pericardial involvement and may be useful in some cases. It has been used in several studies to evaluate symptomatic and asymptomatic COVID-19 patients. In a cohort study of 100 patients who had recently recovered from COVID-19 infection, CMR revealed pericardial involvement (22%), even without cardiac symptoms.[108] Although cardiac tamponade is regarded to be a rare manifestation of pericardial diseases, a systematic review found a higher proportion (35%) of cardiac tamponade in COVID-19 patients than those with other viral infections. After reviewing the literature, we found several case reports and case series of cardiac tamponade[109] secondary to COVID-19. Although this could be overestimated as the information is based on case reports, the significant inflammatory response presented in COVID-19 patients may contribute to developing this complication. Constrictive pericarditis rarely occurs in these patients, with only a few cases reported in the literature. In conclusion, pericardial involvement in COVID-19 patients is a commonly underdiagnosed condition associated with significantly higher all-cause mortality.

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome is a heterogeneous multidisciplinary and multisystem disorder characterized by orthostatic intolerance and tachycardia, which have a significant impact on quality of life.

The syndrome is regarded to be the most prevalent cardiovascular dysautonomia and a primary phenotype/subsyndrome in the post-acute COVID-19 syndrome that can develop after SARS-CoV-2 infection. The vast majority of patients are female (4:1) and relatively young. Patients typically present with varied symptoms, such as chest discomfort, fatigue, muscle weakness, gastrointestinal symptoms, sleep disturbances, dyspnea, palpitations, and pre-syncope. Diagnostic criteria are chronic symptoms of orthostatic intolerance accompanied by an increased heart rate $\geq$ 30 bpm within 10 min of establishing an upright position without significant hypotension. Additionally, orthostatic tachycardia must occur without other apparent causes of orthostatic symptoms or tachycardia, such as hypovolemia, hyperthyroidism, or medications. There is strong evidence that SARS-CoV-2 may trigger POTS in patients with prolonged COVID-19 syndrome. Although the exact pathophysiology mechanism is unclear, it is thought that the combination of autoimmunity, relative central hypovolemia, small fiber neuropathy, hyperadrenergic stimulation, and pro-inflammatory cytokine production (i.e., cytokine storm) is a critical factor in POTS and COVID-19 infection. The fact that sympathetic and parasympathetic nervous system receptors are immune-mediated targets is particularly interesting. According to Gunning et al.,[110] POTS is associated with increased G-protein coupled receptor autoantibodies. Other proposed mechanisms included those against ACE-2 and muscarinic receptors.[111] There are also related polymorphisms in other potential genes.[112] Several case reports and case series have recently been published detailing patients who developed POTS after SARS-CoV-2 infection.[113] Due to the heterogeneity of examined populations and the lack of rigorous diagnostic criteria, the prevalence of POTS among COVID-19 survivors differs in the present study. In a retrospective analysis from Mayo Clinic, when autonomic testing was conducted 119 days after an acute COVID-19 infection, 22% of patients met the criteria for POTS.[114] In a prospective study, a tilt table test with cerebral blood flow measurement was performed on 29 patients with long-term COVID-19 symptoms to evaluate their orthostatic intolerance. Seventy-one percent of them developed POTS within the first 12 months of infection and none after 24 months of follow-up. The authors concluded that the incidence of POTS decreased over time after the onset of the prolonged COVID-19 disease, with no cases after 24 months.[115] An online survey from 56 countries analyzed 3,672 participants with long-term COVID-19 symptoms. Of the 2,308 patients who reported tachycardia, 72.8% reported being able to measure their heart rate in standing versus sitting posture. Of those, 30.65% reported an increase in heart rate, indicating the possibility of POTS.[116] In contrast with other studies, Monaghan et al. found that POTS was not associated with orthostatic intolerance in 85 patients with long-term COVID-19 symptoms, with only one presenting. However, this study had several significant limitations, including a median delay in testing of 302 days.[117] Because the knowledge about managing POTS caused by COVID-19 is limited, further controlled studies are warranted. Thus, the present guidelines for POTS should be used for patients presenting with post-COVID-19 POTS. As a first-line treatment, it includes increasing fluid and salt intake, physical counter-pressure maneuvers, and aerobic exercise. When non-pharmacological therapy is insufficient, various medications, such as beta-blockers, fludrocortisone, midodrine, and ivabradine, can be used. Intravenous immunoglobulin can be used in several cases with promising results. A small Indian study found that ivabradine was more effective than carvedilol in controlling symptomatic tachycardia in post-COVID-19 survivors.[118] In a prospective observational study, 55 young patients with post-COVID-19 POTS were treated with ivabradine. They reported improvement in symptoms (78%) after 7 days of ivabradine treatment, with a significant reduction in 24-h average heart rate and improvement in heart rate variability time domains.[119] In conclusion, recent literature highlights the importance of detecting POTS as a potential complication caused by SARS-CoV-2. Further prospective studies are necessary to understand the possible mechanisms, therapies, and future directions.

Pulmonary Hypertension

Pulmonary hypertension (PH) is a pulmonary vascular disease characterized by vasoconstriction and pulmonary arterial remodeling, resulting in high pulmonary artery pressure and, eventually, right heart failure. Some recent studies have reported PH after acute COVID-19 illness, although evidence remains

limited. Indeed, only a few cases of COVID-19 disease in PH patients have been reported. A recent retrospective cohort study of elderly critically ill patients with severe COVID-19 pneumonia without a history of heart failure found increased pulmonary artery systolic pressure. Increased pulmonary artery systolic pressure predicted ICU admission and hospital mortality.[120] Another recent cross-sectional study for PH patients conducted at a large tertiary center found that COVID-19 infection in patients with increased PH was associated with high mortality and morbidity. The authors concluded that more scientific evidence is needed to elucidate many aspects of COVID-19 infection in this population.[121] Some other studies have shown that COVID-19-infected patients developed PH after their illness. Tudoran et al.[40,122] reported that seven (7.69%) of 91 patients hospitalized with moderate COVID-19 were diagnosed with PH 2 months after discharge. These patients were under the age of 55 yr, did not require mechanical ventilation during hospitalization, and had no history of cardiovascular pathology. Other studies have shown that the PH develops 6-12 weeks after a relatively severe COVID-19 illness.[40,123] A survey of 58 PH centers in the United States found 2.9 cases of COVID-19 infection per 1,000 patients.[124,125] Hospitalization was markedly higher than in the general population at 30%, and mortality occurred in 12% of cases.[125,126] This study included seven pediatric centers, and there was no breakdown of the pediatric patients with PH and COVID-19. PH has been identified as an underlying condition that increases the risk of severe SARS-CoV-2 infection. There are several mechanisms by which COVID-19 can worsen underlying PH as follows:[122,125,126] (a) hypoxia due to pneumonia and hypercapnic vasoconstriction is a potential mechanism for worsening PH; (b) cytokine release due to accumulation of inflammatory cells in the endothelium results in further cell death and inflammation, potentially worsening underlying PH; it has been proposed that the endothelin upregulation could promote PH development; (c) histological examination of patients who died with COVID-19 revealed thickening of the pulmonary arterial walls; and (d) pulmonary damage and vascular remodeling have also been associated with post-COVID PH and PH due to endothelial and mitochondrial dysfunction.

Stroke and Cerebrovascular Disease

COVID-19 patients and other comorbidities are at risk for cerebrovascular complications and stroke. Several studies have shown that stroke and cerebrovascular diseases do not occur in these patients. In a retrospective study of 214 hospitalized patients in Wuhan, China, 78 (36.4%) showed symptoms associated with the nervous system, such as stroke, dizziness, consciousness-level alterations, ataxia, and convulsions.[127] In a study of 125 COVID-19 patients conducted in the United Kingdom, stroke was reported in younger patients aged 33-49 yr. In this study, cerebrovascular events were present in 77 (62%), with stroke being the most common related complication, accounting for 57 (74%) cases.[128] Cerebrovascular disease was more common in deceased patients than in recovered patients,[127] and it was more common in non-survivors than in survivors.[129] Another study found cerebrovascular disease in 6.8% of the patients.[130] This study found a statistically significant difference between COVID-19 severe and non-severe forms. Moreover, it was statistically different in patients with cardiac injury than patients without cardiac injury. There was a statistically significant difference in the groups of non-survivors and survivors in chronic cardiac failure.

Takotsubo Syndrome and COVID-19

Due to increased stress and anxiety during the pandemic, one would predict an increase in the incidence of potentially life-threatening Takotsubo syndrome (TTS). However, this remains to be proven, as the current literature on COVID-19-related cardiac effects typically does not even introduce TTS. Nevertheless, the incidence of TTS during the pandemic ranged from 4% to 8%, which is higher than the expected 1.7-2.0% in patients with acute coronary syndrome before the pandemic.[131] Clinical diagnosis is based mainly on precordial chest pain (in 80-90% of cases), electrocardiographic ST and T wave critical ischemic changes (95%), and pathognomonic large symmetrical areas of apical and/or midventricular akinesia or dyskinesia on echocardiography, which is reversible within 30 days. While serum testing in COVID-19 patients was not regularly conducted, the catecholamine surge alone is widely claimed to cause TTS without definite evidence; however, if this is the case, using catecholamines to control cardiogenic shock would be contraindicated. As a result, the surge is more likely secondary to the TTS event, demonstrating the complex pathophysiology of TTS. TTS has been associated with COVID-19 as either a direct infectious complication or an indirect psychological effect of quarantined social isolation. Because some COVID-19 patients showed cutaneous microvascular changes and pulmonary vascular endothelialitis in histological studies of the lungs, similar changes could be systemic or cardiac, resulting in luminal thrombosis due to endothelial dysfunction in the lungs and other organs. Therefore, the relationship between COVID-19 and TTS has been predicted to involve coronary endothelial dysfunction, septic state, inflammatory storm, hypercoagulability, endothelial necrosis, and small-vessel clotting. Angelini and Uribe[132] postulated a theory of "coronary endothelial dysfunction-coronary artery spasm (CAS)-myocardial stunning." According to this theory, a patient becomes infected with COVID-19, and approximately 1 week later, the coronary endothelium develops a hyperactive immune or inflammatory response, resulting in acute TTS in the presence of stress and/or a catecholamine surge (either naturally produced or administered for shock). The initial CAS can be suppressed by nitroglycerin administration within a few minutes of onset in spontaneous TTS or at CAS provocative testing. Because the increased CAS caused by endothelial dysfunction gradually dissolves, TTS spontaneously disappears in survivors within a few days.[133] TTS is typically not reproduced by CAS-provoking testing after about 1 week, and recurrent TTS is rare. When recurrent CAS can be produced by provocative testing, a delayed spontaneous recurrence of TTS may appear in more than a week.[132] While coronary endothelial dysfunction is reportedly necessary for developing CAS and CAS-related TTS in COVID-19 patients, microvascular dysfunction has not been demonstrated. The initial treatment of TTS includes anticoagulants, angiotensin-converting

enzyme inhibitors or aldosterone receptor blockers, beta-blockers, dual antiplatelet therapy, diuretics, and levosimendan. While beta-blockers and alpha-blockers have been proven protective in animal immobilization stress-induced TTS models, their combined effects in humans at the acute stage of TTS do not last long. The use of sublingual or intravenous nitroglycerin could provide further symptomatic relief. Although the pathophysiology of TTS is complex and not fully understood, early TTS diagnosis within 15 min of onset is potentially life-saving and may be confirmed by CAS provocative testing. Therefore, physicians must be aware of COVID-19-related TTS.

Thromboembolism

According to 35 observational studies from around the world, the incidence of thromboembolism complications in COVID-19 patients[62,135] ranged from 1.7% to 16.5%. When adjusted for age, sex, and region, the hazard ratio) for developing deep vein thrombosis in England and Wales among 1.4 million patients who tested positive for COVID-19 was 12 in the first week and 2.6 at 27-49 weeks. The same results were observed in cases of pulmonary embolism and arterial thrombosis. COVID-19-induced thromboembolism has been associated with cytokine storm, complement activation, and endotheliosis. Several risk factors associated with higher severity of COVID-19 and higher mortality, such as inflammatory markers, including IL-6, D-dimer, ferritin, and lactate dehydrogenase, have also been proposed for these thrombotic episodes. Moreover, an autopsy of patients who died of COVID-19 disease revealed microthrombi. In addition, elevated circulating prothrombotic factors, such as von Willebrand factor, factor VIII, D-dimer, fibrinogen, neutrophil extracellular traps, prothrombotic microparticles, and anionic phospholipids, have been associated with disease severity and mortality in COVID-19 cases. Virchow's triad thrombosis is characterized by hypercoagulation, abnormal blood flow, and endothelial injury; there is a medical paradox about COVID-19 associated with thrombosis and hormonal contraception. While increased estrogen levels may be protective against severe COVID-19 disease,[136] using hormonal contraception during the COVID-19 pandemic is an independent risk factor for thrombosis, particularly when the patient is taking estrogen-containing drugs.[137] Myocardial injury manifests clinically as arterial and venous thromboembolism.

Venous thromboembolism: Deep-vein thrombosis (DVT) generally affects the venous system of the lower extremities, with clot formation originating in the deep veins of the femur and spreading to proximal veins. The incidence of DVT in patients infected with COVID-19[138] is 14.8%. A history of previous or current cancer, increased D-dimers, length of hospital stay, and the need for a high-flow nasal cannula or non-invasive ventilation were significantly associated with the development of DVT. On days 7, 14, and 21, the prevalence of DVT was 16%, 33%, and 42%, respectively.[138] Moreover, an increased incidence of DVT has been observed in critically ill COVID-19 patients with high D-dimer.[139] The thrombus formation during DVT may extend to the general circulation and induce pulmonary embolism. When D-dimer levels are more than 1,600 ng/ml, pulmonary embolism may be predicted with a sensitivity of 100% and a specificity of 62%.[140] During COVID-19 infection, thrombus formation can affect the cerebral venous vasculature and induce cerebral venous thrombosis (CVT). CVT accounts for approximately 4% of all cardiovascular events associated with COVID-19. COVID-19-associated CVT affects the transverse sinus (65%), the sigmoid sinus, and the superior sagittal sinus (45%). Similar to COVID-19-associated PE and DVT, D-dimer and C-reactive protein levels increased in most COVID-19-associated CVT cases.[141] Lymphopenia was another commonly reported laboratory finding.

Arterial thromboembolism (ATE): In addition to the coronary arteries, COVID-19 infection can affect the mesenteric, splenic, and renal arteries. However, ATE of these arteries is rare, with only case reports and short case series reported thus far. The reported rates of COVID-19-associated mesenteric ischemia range from 15% to 38%, indicating a predominant small vessel affection.[139] During the physical examination, common signs and symptoms include abdominal pain, vomiting, nausea, and abdominal distention. COVID-19-associated mesenteric ischemia has a high mortality rate, ranging from 34% to 54%. The diagnostic biomarkers are the same in arterial and venous mesenteric ischemia.[139]

In conclusion, this narrative review summarizes the potential cardiovascular complications that might occur during and after acute COVID-19 infection and hypotheses on the underlying mechanisms. Indeed, a variety of cardiovascular complications appear to be common in COVID-19, potentially worsening the clinical outcome. Cardiovascular complications might be caused by damage associated with the acute COVID-19 illness, inflammation-inducing injury, and exacerbation of preexisting conditions.[40] COVID-19 disease is typically related to vascular ischemia, which causes myocardial injury, cardiac dysfunction, arrhythmias, myocarditis, POTS, and dysautonomia. Some of these complications have been observed in mild cases and are facts that must be monitored, particularly in young, healthy patients. In athletes recovering from COVID-19, for example, a recommended 2-week convalescence period is followed by no diagnostic cardiac tests if asymptomatic and an electrocardiogram and transthoracic echocardiogram in mildly symptomatic patients. Despite this, some studies have shown improvement over time. Long-term COVID complications will require ongoing monitoring for years to better characterize long-term outcomes. We must not forget that myocarditis can lead to dilated cardiomyopathy, resulting in end-stage heart failure requiring advanced therapies, such as orthotopic heart transplantation.[141] Therefore, more clinical research is needed for specific diagnostic and therapeutic activities showing the results and long-term sequelae of COVID-19-associated myocarditis.

Because the present data are limited in quantity and quality, we expect that such reviews will help clinicians be aware of possible cardiovascular risks, prompting future studies.

Supplementary Materials: The following are available online at (Supplementary Table S1).

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REFERENCES

1. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Gavrilov D, Giattino C, Hasell J, Macdonald B, Dattani S, Beltekian D, Ortiz-Ospina E, Roser M (2020–2022). «Coronavirus Pandemic (COVID-19)». Our World in Data. Retrieved 15 October 2023. **[CrossRef]**
2. Condurache DG, Shanmuganathan M, Raisi-Estabragh Z, Raman B. Editorial: Post-COVID-19 cardiovascular sequelae. *Front Cardiovasc Med*. 2023;10:1191953. **[CrossRef]**
3. Wan EYF, Mathur S, Zhang R, et al. Association of COVID-19 with short- and long-term risk of cardiovascular disease and mortality: a prospective cohort in UK Biobank. *Cardiovasc Res*. 2023;119:1718-1727. **[CrossRef]**
4. Kounis NG, Koniari I, de Gregorio C, et al. COVID-19 Disease, Women's Predominant Non-Heparin Vaccine-Induced Thrombotic Thrombocytopenia and Kounis Syndrome: A Passepartout Cytokine Storm Interplay. *Biomedicines*. 2021;9:959. **[CrossRef]**
5. Cooper SL, Boyle E, Jefferson SR, et al. Role of the Renin-Angiotensin-Aldosterone and Kinin-Kallikrein Systems in the Cardiovascular Complications of COVID-19 and Long COVID. *Int J Mol Sci*. 2021;22:8255. **[CrossRef]**
6. Barthe M, Hertereau L, Lamghari N, Osman-Ponchet H, Braud VM. Receptors and Cofactors That Contribute to SARS-CoV-2 Entry: Can Skin Be an Alternative Route of Entry? *Int J Mol Sci.* 2023;24:6253. **[CrossRef]**
7. Bellavite P, Ferraresi A, Isidoro C. Immune Response and Molecular Mechanisms of Cardiovascular Adverse Effects of Spike Proteins from SARS-CoV-2 and mRNA Vaccines. *Biomedicines*. 2023;11:451. **[CrossRef]**
8. Cooper SL, Boyle E, Jefferson SR, et al. Role of the Renin-Angiotensin-Aldosterone and Kinin-Kallikrein Systems in the Cardiovascular Complications of COVID-19 and Long COVID. *Int J Mol Sci*. 2021;22:8255. **[CrossRef]**
9. Dherange P, Lang J, Qian P, et al. Arrhythmias and COVID-19: A Review. *JACC Clin Electrophysiol*. 2020;6:1193-1204. **[CrossRef]**
10. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med.* 2020;382:2372-2374. **[CrossRef]**
11. Colon CM, Barrios JG, Chiles JW, et al. Atrial Arrhythmias in COVID-19 Patients. *JACC Clin Electrophysiol*. 2020;6:1189-1190. **[CrossRef]**
12. He J, Wu B, Chen Y, et al. Characteristic Electrocardiographic Manifestations in Patients With COVID-19. *Can J Cardiol.* 2020;36:966.e1-966.e4. **[CrossRef]**
13. Lazzerini PE, Boutjdir M, Capecchi PL. COVID-19, Arrhythmic Risk, and Inflammation: Mind the Gap! *Circulation*. 2020;142:7-9. **[CrossRef]**
14. Kolettis TM. Coronary artery disease and ventricular tachyarrhythmia: pathophysiology and treatment. *Curr Opin Pharmacol*. 2013;13:210-217. **[CrossRef]**
15. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17:1463-1471. **[CrossRef]**
16. Tse G, Yeo JM, Chan YW, Lai ET, Yan BP. What Is the Arrhythmic Substrate in Viral Myocarditis? Insights from Clinical and Animal Studies. *Front Physiol*. 2016;7:308. **[CrossRef]**
17. Peretto G, Sala S, Rizzo S, et al. Arrhythmias in myocarditis: State of the art. *Heart Rhythm*. 2019;16:793-801. **[CrossRef]**
18. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. *Nat Rev Immunol*. 2019;19:63-64. **[CrossRef]**
19. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370:847-859. **[CrossRef]**
20. Huertas A, Montani D, Savale L, et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Respir J. 2020;56:2001634. **[CrossRef]**
21. Musher DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial Infarction. *N Engl J Med*. 2019;380:171-176. **[CrossRef]**
22. Ñamendys-Silva SA, Santos-Martínez LE, Pulido T, et al. Pulmonary hypertension due to acute respiratory distress syndrome. *Braz J Med Biol Res*. 2014;47:904-910. **[CrossRef]**
23. Wanamaker B, Cascino T, McLaughlin V, Oral H, Latchamsetty R, Siontis KC. Atrial Arrhythmias in Pulmonary Hypertension: Pathogenesis, Prognosis and Management. *Arrhythm Electrophysiol Rev*. 2018;7:43-48. **[CrossRef]**
24. Bosch NA, Cimini J, Walkey AJ. Atrial Fibrillation in the ICU. *Chest*. 2018;154:1424-1434. **[CrossRef]**
25. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5:802-810. **[CrossRef]**
26. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). *Mayo Clin Proc.* 2020;95:1213-1221. **[CrossRef]**
27. Bharmal M, DiGrande K, Patel A, Shavelle DM, Bosson N. Impact of Coronavirus Disease 2019 Pandemic on Cardiac Arrest and Emergency Care. *Heart Fail Clin*. 2023;19:231-240. **[CrossRef]**
28. Chan PS, Girotra S, Tang Y, et al. Outcomes for Out-of-Hospital Cardiac Arrest in the United States During the Coronavirus Disease 2019 Pandemic. *JAMA Cardiol*. 2021;6:296-303. **[CrossRef]**
29. Chugh HS, Sargsyan A, Nakamura K, et al. Sudden cardiac arrest during the COVID-19 pandemic: A two-year prospective evaluation in a North American community. *Heart Rhythm*. 2023;20:947-955. **[CrossRef]**
30. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-Segment Elevation Cardiac Catheterization Laboratory Activations in the United States During COVID-19 Pandemic. *J Am Coll Cardiol*. 2020;75:2871-2872. **[CrossRef]**
31. Uy-Evanado A, Chugh HS, Sargsyan A, et al. Out-of-Hospital Cardiac Arrest Response and Outcomes During the COVID-19 Pandemic. *JACC Clin Electrophysiol*. 2021;7:6-11. **[CrossRef]**
32. Thapa SB, Kakar TS, Mayer C, Khanal D. Clinical Outcomes of In-Hospital Cardiac Arrest in COVID-19. *JAMA Intern Med*. 2021;181:279-281. **[CrossRef]**
33. Rollman JE, Kloner RA, Bosson N, et al. Emergency Medical Services Responses to Out-of-Hospital Cardiac Arrest and Suspected ST-Segment-Elevation Myocardial Infarction During the COVID-19 Pandemic in Los Angeles County. *J Am Heart Assoc*. 2021;10:e019635. **[CrossRef]**
34. Mathew S, Harrison N, Chalek AD,et al. Effects of the COVID-19 pandemic on out-of-hospital cardiac arrest care in Detroit. *Am J Emerg Med*. 2021;46:90-96. **[CrossRef]**
35. Bharmal M, DiGrande K, Patel A, Shavelle DM, Bosson N. Impact of Coronavirus Disease 2019 Pandemic on Cardiac Arrest and Emergency Care. *Heart Fail Clin*. 2023;19:231-240. **[CrossRef]**
36. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. *Arthritis Rheumatol*. 2022;74:e1-e20. **[CrossRef]**
37. Capone CA, Misra N, Ganigara M, et al. Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children. *Pediatrics*. 2021;148:e2021050973. **[CrossRef]**
38. Dufort EM, Koumans EH, Chow EJ, et al. New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem Inflammatory Syndrome in Children in New York State. *N Engl J Med*. 2020;383:347-358. **[CrossRef]**
39. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. *Circulation*. 2021;143:21-32. **[CrossRef]**

40. Parhizgar P, Yazdankhah N, Rzepka AM, et al. Beyond Acute COVID-19: A Review of Long-term Cardiovascular Outcomes. *Can J Cardiol*. 2023;39:726-740. **[CrossRef]**
41. Wang W, Wang CY, Wang SI, Wei JC. Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks. *EClinicalMedicine*. 2022;53:101619. **[CrossRef]**
42. Pilati M, Rebonato M, Formigari R, Butera G. Endomyocardial Biopsy in Pediatric Myocarditis and Dilated Cardiomyopathy: A Tool in Search for a Role. *J Cardiovasc Dev Dis*. 2022;9:24. **[CrossRef]**
43. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17:1463-1471. **[CrossRef]**
44. Hsu RJ, Yu WC, Peng GR, et al. The Role of Cytokines and Chemokines in Severe Acute Respiratory Syndrome Coronavirus 2 Infections. *Front Immunol*. 2022;13:832394. **[CrossRef]**
45. Yang L, Xie X, Tu Z, et al. The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct Target Ther*. 2021;6:255. **[CrossRef]**
46. Wang M, Chang W, Zhang L, Zhang Y. Pyroptotic cell death in SARS-CoV-2 infection: revealing its roles during the immunopathogenesis of COVID-19. *Int J Biol Sci*. 2022;18:5827-5848. **[CrossRef]**
47. Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. *Clin Chim Acta*. 2020;509:280-287. **[CrossRef]**
48. Tsounis EP, Triantos C, Konstantakis C, Marangos M, Assimakopoulos SF. Intestinal barrier dysfunction as a key driver of severe COVID-19. *World J Virol*. 2023;12:68-90. **[CrossRef]**
49. Petrushevska M, Zendelovska D, Atanasovska E, Eftimov A, Spasovska K. Presentation of cytokine profile in relation to oxidative stress parameters in patients with severe COVID-19: a case-control pilot study. *F1000Res*. 2021;10:719. **[CrossRef]**
50. Buicu AL, Cernea S, Benedek I, Buicu CF, Benedek T. Systemic Inflammation and COVID-19 Mortality in Patients with Major Noncommunicable Diseases: Chronic Coronary Syndromes, Diabetes and Obesity. *J Clin Med*. 2021;10:1545. **[CrossRef]**
51. Assimakopoulos SF, Triantos C, Maroulis I, Gogos C. The Role of the Gut Barrier Function in Health and Disease. *Gastroenterology Res*. 2018;11:261-263. **[CrossRef]**
52. Kounis NG, Koniari I, de Gregorio C, et al. COVID-19 Disease, Women's Predominant Non-Heparin Vaccine-Induced Thrombotic Thrombocytopenia and Kounis Syndrome: A Passepartout Cytokine Storm Interplay. *Biomedicines*. 2021;9:959. **[CrossRef]**
53. Zhou F, Yu T, Du R, et al Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062. **[CrossRef]**
54. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. **[CrossRef]**
55. Sechi LA, Colussi G, Bulfone L, et al. Short-term cardiac outcome in survivors of COVID-19: a systematic study after hospital discharge. *Clin Res Cardiol*. 2021;110:1063-1072. **[CrossRef]**
56. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1265-1273. **[CrossRef]**
57. Petersen EL, Goßling A, Adam G, et al. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme. *Eur Heart J*. 2022;43:1124-1137. **[CrossRef]**
58. Ródenas-Alesina E, Rodríguez-Palomares J, Bach-Oller M et al. Echocardiographic assessment of COVID19 sequelae in survivors with elevated cardiac biomarkers. *Int J Cardiol*. 2022;360:104-110. **[CrossRef]**
59. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:811-818. **[CrossRef]**
60. Akkaya F, Yenerçağ FNT, Kaya A, Şener YZ, Bağcı A. Long term effects of mild severity COVID19 on right ventricular functions. *Int J Cardiovasc Imaging*. 2021;37:3451-3457. **[CrossRef]**
61. Nuzzi V, Castrichini M, Collini V, et al. Impaired Right Ventricular Longitudinal Strain Without Pulmonary Hypertension in Patients Who Have Recovered From COVID-19. *Circ Cardiovasc Imaging*. 2021;14:e012166. **[CrossRef]**
62. Randhawa S, Alsamarrai AJ, Lee S, Somaratne JB. Cardiac complications of COVID-19 infection. *N Z Med J*. 2023;136:73-82. **[CrossRef]**
63. Kounis NG, Koniari I, Soufras GD, et al. Respiratory Infections as Predictors of Hospital Admission for Myocardial Infarction and Stroke: Pathophysiologic and Therapeutic Considerations. *Clin Infect Dis*. 2019;68:533. **[CrossRef]**
64. Rodriguez-Leor O, Cid Alvarez AB, Pérez de Prado A, et al. In-hospital outcomes of COVID-19 ST-elevation myocardial infarction patients. *EuroIntervention*. 2021;16:1426-1433. **[CrossRef]**
65. Garcia S, Dehghani P, Grines C, et al. Society for Cardiac Angiography and Interventions, the Canadian Association of Interventional Cardiology, and the American College of Cardiology Interventional Council. Initial Findings From the North American COVID-19 Myocardial Infarction Registry. *J Am Coll Cardiol*. 2021;77:1994-2003. **[CrossRef]**
66. Toscano O, Cosentino N, Campodonico J, Bartorelli AL, Marenzi G. Acute Myocardial Infarction During the COVID-19 Pandemic: An Update on Clinical Characteristics and Outcomes. *Front Cardiovasc Med*. 2021;8:648290. **[CrossRef]**
67. Gharibzadeh A, Shahsanaei F, Rahimi Petrudi N. Clinical and Cardiovascular Characteristics of Patients Suffering ST-Segment Elevation Myocardial Infarction After Covid-19: A Systematic Review and Meta-Analysis. *Curr Probl Cardiol*. 2023;48:101045. **[CrossRef]**
68. Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 2021;27:258-263. **[CrossRef]**
69. Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J*. 2021;42:1866-1878. **[CrossRef]**
70. Raafs AG, Ghossein MA, Brandt Y, et al. Cardiovascular outcome 6 months after severe coronavirus disease 2019 infection. *J Hypertens*. 2022;40:1278-1287. **[CrossRef]**
71. Vallejo Camazón N, Teis A, Martínez Membrive MJ, et al. Long COVID-19 and microvascular disease-related angina. *Rev Esp Cardiol (Engl Ed)*. 2022;75:444-446. **[CrossRef]**
72. Kounis NG, Koniari I, Velissaris D, Tzanis G, Hahalis G. Kounis Syndrome—not a Single-organ Arterial Disorder but a Multisystem and Multidisciplinary Disease. *Balkan Med J*. 2019;36:212-221. **[CrossRef]**
73. Gebremeskel S, Schanin J, Coyle KM, et al. Mast Cell and Eosinophil Activation Are Associated With COVID-19 and TLR-Mediated Viral Inflammation: Implications for an Anti-Siglec-8 Antibody. *Front Immunol*. 2021;12:650331. **[CrossRef]**
74. Kounis NG, Koniari I, de Gregorio C. COVID-19 and Kounis Syndrome: Deciphering Their Relationship. *Balkan Med J*. 2021;38:145-149. **[CrossRef]**
75. Theoharides TC. Potential association of mast cells with coronavirus disease 2019. *Ann Allergy Asthma Immunol*. 2021;126:217-218. **[CrossRef]**
76. Prieto-Lobato A, Ramos-Martínez R, Vallejo-Calcerrada N, Corbí-Pascual M, Córdoba-Soriano JG. A Case Series of Stent Thrombosis During the COVID-19 Pandemic. *JACC Case Rep*. 2020;2:1291-1296. **[CrossRef]**
77. Kounis NG, Mplani V, de Gregorio C, Koniari I. Attack the ATAK; A Challenging Contemporary Complex: Pathophysiologic, Therapeutic, and Preventive Considerations. *Balkan Med J*. 2023;40:308-311. **[CrossRef]**
78. Kounis NG, Koniari I, de Gregorio C, et al. Allergic Reactions to Current Available COVID-19 Vaccinations: Pathophysiology, Causality, and Therapeutic Considerations. *Vaccines (Basel)*. 2021;9:221. **[CrossRef]**
79. Ertekin A. Triggered by Covid-19? Large vascular occlusion resulting in cytokine Storm syndrome and Kounis syndrome: A case report. *J Biomed Res Environ Sci*. 2021;2:030-033. **[CrossRef]**
80. Wang M, Talon A, Saririan M. COVID-19 cardiac arrest due to Prinzmetal's angina in a previously normal heart. *Clin Case Rep*. 2021;9:e04205. **[CrossRef]**
81. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med*. 2021;384:2092-2101. **[CrossRef]**
82. Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature*. 2020;584:463-469. **[CrossRef]**
83. Orlando L, Trapani G, Vatrano M, Giovanni Versace A, Imbalzanoa E. Kounis syndrome associated with COVID-19 infection: cause or coincidence? *Cor Vasa*. 2021;63:592-596. **[CrossRef]**
84. Roca-Fernandez A, Wamil M, Telford A, et al. Cardiac abnormalities in Long COVID 1-year post-SARS-CoV-2 infection. *Open Heart*. 2023;10:e002241. **[CrossRef]**

85. Morello R, Mariani F, Mastrantoni L, et al. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. *EClinicalMedicine*. 2023;59:101961. [CrossRef]
86. Siripanthong B, Asatryan B, Hanff TC, et al. The Pathogenesis and Long-Term Consequences of COVID-19 Cardiac Injury. *JACC Basic Transl Sci*. 2022;7:294-308. [CrossRef]
87. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1265-1273. [CrossRef]
88. Huang L, Zhao P, Tang D, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging*. 2020;13:2330-2339. [CrossRef]
89. Krishnan A, Ellenberger KA, Phetsouphanh C, et al. Myocardial fibrosis occurs in non-hospitalised patients with chronic symptoms after COVID-19. *Int J Cardiol Heart Vasc*. 2022;39:100964. [CrossRef]
90. Kounis NG, Koniari I, Mplani V, Plotas P, Velissaris D. Hypersensitivity Myocarditis and the Pathogenetic Conundrum of COVID-19 Vaccine-Related Myocarditis. *Cardiology*. 2022;147:413-415. [CrossRef]
91. Barreiro-Pérez M, Pastor Pueyo P, Raposeiras-Roubín S, et al. Myocarditis related SARS-CoV-2 infection or vaccination: an expert consensus statement on its diagnosis and management. *Rev Esp Cardiol (Engl Ed)*. 2023;76:555-563. [CrossRef]
92. Keller K, Sagoschen I, Konstantinides S, et al. Incidence and risk factors of myocarditis in hospitalized patients with COVID-19. *J Med Virol*. 2023;95:e28646. [CrossRef]
93. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med*. 2022;28:410-422. [CrossRef]
94. Wilson C. Myocarditis more likely after infection than vaccination. *New Sci*. 2021;251:14. [CrossRef]
95. Singer ME, Taub IB, Kaelber DC. Risk of Myocarditis from COVID-19 Infection in People Under Age 20: A Population-Based Analysis. *medRxiv*. 2022:2021.07.23.21260998. https://www.medrxiv.org/content/10.1101/2021.07.23.21260998.abstract [CrossRef]
96. Zuin M, Rigatelli G, Bilato C, Pasquetto G, Mazza A. Risk of Incident New-Onset Arterial Hypertension After COVID-19 Recovery: A Systematic Review and Meta-analysis. *High Blood Press Cardiovasc Prev*. 2023;30:227-233. [CrossRef]
97. Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, et al. Long-Term Outcomes of Patients with Coronavirus Disease 2019 at One Year after Hospital Discharge. *J Clin Med*. 2021;10:2945. [CrossRef]
98. Xiong Q, Xu M, Li J, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin Microbiol Infect*. 2021;27:89-95. [CrossRef]
99. Szeghy RE, Stute NL, Province VM, et al. Six-month longitudinal tracking of arterial stiffness and blood pressure in young adults following SARS-CoV-2 infection. *J Appl Physiol (1985)*. 2022;132:1297-1309. [CrossRef]
100. Uysal B, Akça T, Akacı O, Uysal F. The Prevalence of Post-COVID-19 Hypertension in Children. *Clin Pediatr (Phila)*. 2022;61:453-460. [CrossRef]
101. Vicenzi M, Di Cosola R, Ruscica M,. The liaison between respiratory failure and high blood pressure: evidence from COVID-19 patients. *Eur Respir J*. 2020;56:2001157. [CrossRef]
102. Bing HI. Epidemical pericarditis. *Acta Medica Scandinavica*. 1933;80:29-33. [CrossRef]
103. Farina A, Uccello G, Spreafico M, Bassanelli G, Savonitto S. SARS-CoV-2 detection in the pericardial fluid of a patient with cardiac tamponade. *Eur J Intern Med*. 2020;76:100-101. [CrossRef]
104. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. *J Am Coll Radiol*. 2020;17:701-709. [CrossRef]
105. Liu Y, Xie J, Gao P, et al. Swollen heart in COVID-19 patients who progress to critical illness: a perspective from echo-cardiologists. *ESC Heart Fail*. 2020;7:3621-3632. [CrossRef]
106. Lazar M, Barbu EC, Chitu CE, et al. Pericardial Involvement in Severe COVID-19 Patients. *Medicina (Kaunas)*. 2022;58:1093. [CrossRef]
107. Ghantous E, Szekely Y, Lichter Y, et al. Pericardial Involvement in Patients Hospitalized With COVID-19: Prevalence, Associates, and Clinical Implications. *J Am Heart Assoc*. 2022;11:e024363. [CrossRef]
108. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5:1265-1273. [CrossRef]
109. Diaz-Arocutipa C, Saucedo-Chinchay J, Imazio M. Pericarditis in patients with COVID-19: a systematic review. *J Cardiovasc Med (Hagerstown)*. 2021;22:693-700. [CrossRef]
110. Gunning WT 3rd, Kvale H, Kramer PM, Karabin BL, Grubb BP. Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. J Am Heart Assoc. 2019;8:e013602. [CrossRef]
111. Narasimhan B, Calambur A, Moras E, Wu L, Aronow W. Postural Orthostatic Tachycardia Syndrome in COVID-19: A Contemporary Review of Mechanisms, Clinical Course and Management. *Vasc Health Risk Manag*. 2023;19:303-316. [CrossRef]
112. Jacob G, Garland EM, Costa F, et al. Beta2-adrenoceptor genotype and function affect hemodynamic profile heterogeneity in postural tachycardia syndrome. *Hypertension*. 2006;47:421-427. [CrossRef]
113. Gall NP, James S, Kavi L. Observational case series of postural tachycardia syndrome (PoTS) in post-COVID-19 patients. *Br J Cardiol*. 2022;29:3. [CrossRef]
114. Shouman K, Vanichkachorn G, Cheshire WP, et al. Autonomic dysfunction following COVID-19 infection: an early experience. *Clin Auton Res*. 2021;31:385-394. [CrossRef]
115. Campen CLMCV, Visser FC. Long-Haul COVID Patients: Prevalence of POTS Are Reduced but Cerebral Blood Flow Abnormalities Remain Abnormal with Longer Disease Duration. *Healthcare (Basel)*. 2022;10:2105. [CrossRef]
116. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019. [CrossRef]
117. Monaghan A, Jennings G, Xue F, et al. Orthostatic Intolerance in Adults Reporting Long COVID Symptoms Was Not Associated With Postural Orthostatic Tachycardia Syndrome. *Front Physiol*. 2022;13:833650. [CrossRef]
118. Jadhav K, Jariwala P. 'Ivabradin' versus 'Carvedilol' in the management of Post-COVID-19 palpitation with sinus tachycardia. *Indian Heart J*. 2020;72:S33. [CrossRef]
119. Abdelnabi M, Saleh Y, Ahmed A, et al. Ivabradine effects on COVID-19-associated postural orthostatic tachycardia syndrome: a single center prospective study. *Am J Cardiovasc Dis*. 2023;13:162-167. [CrossRef]
120. Kurnik M, Božič H, Vindišar A, Kolar P, Podbregar M. Pulmonary hypertension at admission predicts ICU mortality in elderly critically ill with severe COVID-19 pneumonia: retrospective cohort study. *Cardiovasc Ultrasound*. 2023;21:1. [CrossRef]
121. Serati A, Keshmiri MS, Shafaghi S, et al. The Outcome of Patients with Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension during the COVID-19 Pandemic. *Crit Pathw Cardiol*. 2023;22:60-64. [CrossRef]
122. Tudoran C, Tudoran M, Lazureanu VE, et al. Evidence of Pulmonary Hypertension after SARS-CoV-2 Infection in Subjects without Previous Significant Cardiovascular Pathology. *J Clin Med*. 2021;10:199. [CrossRef]
123. Khan AW, Ullah I, Khan KS, et al. Pulmonary arterial hypertension post COVID-19: A sequala of SARS-CoV-2 infection? *Respir Med Case Rep*. 2021;33:101429. [CrossRef]
124. Jone PN, John A, Oster ME, et al. American Heart Association Leadership Committee and Congenital Cardiac Defects Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Hypertension, and Council on Peripheral Vascular Disease. SARS-CoV-2 Infection and Associated Cardiovascular Manifestations and Complications in Children and Young Adults: A Scientific Statement From the American Heart Association. *Circulation*. 2022;145:e1037-e1052. [CrossRef]
125. Lee JD, Burger CD, Delossantos GB, et al. A Survey-based Estimate of COVID-19 Incidence and Outcomes among Patients with Pulmonary Arterial Hypertension or Chronic Thromboembolic Pulmonary Hypertension and Impact on the Process of Care. *Ann Am Thorac Soc*. 2020;17:1576-1582. [CrossRef]
126. Das BB. COVID-19 and Pulmonary Hypertension in Children: What Do We Know So Far? *Medicina (Kaunas)*. 2020;56:716. [CrossRef]
127. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol*. 2020;5:279-284. [CrossRef]

128. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. 2020;382:e60. **[CrossRef]**

129. Sousa Rêgo LO, Alves Braga LL, Vilas-Boas GS, Oliveira Cardoso MS, Duraes AR. Cardiovascular and Neurological Complications of COVID-19: A Narrative Review. *J Clin Med*. 2023;12:2819. **[CrossRef]**

130. Tu WJ, Xu Y, Chen H, Li J, Du J. Impact of the COVID-19 pandemic lockdown on hospitalizations for cerebrovascular disease and related in-hospital mortality in China: A nationwide observational study. *Arch Gerontol Geriatr*. 2023;104:104832. **[CrossRef]**

131. Jabri A, Kalra A, Kumar A, et al. Incidence of Stress Cardiomyopathy During the Coronavirus Disease 2019 Pandemic. *JAMA Netw Open*. 2020;3:e2014780. **[CrossRef]**

132. Angelini P, Uribe C. Is Transient Takotsubo Syndrome Associated With Cancer? Why, and With What Implications for Oncocardiology? *J Am Heart Assoc*. 2019;8:e013201. **[CrossRef]**

133. Hegde S, Khan R, Zordok M, Maysky M. Characteristics and outcome of patients with COVID-19 complicated by Takotsubo cardiomyopathy: case series with literature review. *Open Heart*. 2020;7:e001360. **[CrossRef]**

134. Jin Y, Li Q, Guo X. Alternate recurrent coronary artery spasm and stress cardiomyopathy: a case report. *BMC Cardiovasc Disord*. 2020;20:476. **[CrossRef]**

135. Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis. *Thromb Res*. 2020;196:27-30. **[CrossRef]**

136. Ramanadhan S, Hansen K, Henderson JT, et al. Risk of thromboembolism in patients with COVID-19 who are using hormonal contraception. *Cochrane Database Syst Rev*. 2023;5:CD014908. **[CrossRef]**

137. Sutanto H, Soegiarto G. Risk of Thrombosis during and after a SARS-CoV-2 Infection: Pathogenesis, Diagnostic Approach, and Management. *Hematol Rep*. 2023;15:225-243. **[CrossRef]**

138. Goswami J, MacArthur TA, Sridharan M, et al. A Review of Pathophysiology, Clinical Features, and Management Options of COVID-19 Associated Coagulopathy. *Shock*. 2021;55:700-716. **[CrossRef]**

139. Greistorfer T, Jud P. Clinical characteristics of COVID-19 associated vasculopathic diseases. *Thromb J*. 2023;21:61. **[CrossRef]**

140. Riyahi S, Dev H, Behzadi A, et al. Pulmonary Embolism in Hospitalized Patients with COVID-19: A Multicenter Study. *Radiology*. 2021;301:E426-E433. **[CrossRef]**

141. ElAmm CA, Al-Kindi SG, Oliveira GH. Characteristics and Outcomes of Patients With Myocarditis Listed for Heart Transplantation. *Circ Heart Fail*. 2016;9:e003259. **[CrossRef]**