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Review Article

Cardiovascular complications of COVID-19 severe acute respiratory syndrome

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Abstract: 603,711,760 confirmed cases of COVID-19 have been reported throughout the world and 6,484,136 individuals have died from complications of COVID-19 as of September 7, 2022. Significantly, the Omicron variant has produced the largest number of COVID-19 associated hospitalizations since the beginning of the pandemic. Cardiac injury occurs in ≥20% of the hospitalized patients with COVID-19 and is associated with cardiac dysrhythmias in 17 to 44%, cardiac injury with increases in blood troponin in 22 to 40%, myocarditis in 2 to 7%, heart failure in 4 to 21%, and thromboembolic events in 15 to 39%. Risk factors for cardiac complications include age >70 years, male sex, BMI ≥30 kg/m^2, diabetes, pre-existing cardiovascular disease, and moderate to severe pneumonia at hospital presentation. Patients with prior cardiovascular disease who contract COVID-19 and experience a significant increase in their blood troponin concentration are at risk for mortality rates as high as 69%. This review focuses on the prevalence, the pathophysiologic mechanisms of CoV-2 injury to the cardiovascular system and the current recommended treatments in hospitalized patients with COVID-19 in order that medical personnel can decrease the morbidity and mortality of patients with COVID-19 and effectively treat patients with Covid and post Covid syndrome.

Keywords: COVID-19 cardiac injury, myocardial infarction, myocarditis, stress-induced cardiomyopathy, cytokine storm, vascular thrombosis, anti-viral drug treatment

Introduction

In December of 2019, an unknown virus caused pneumonia in a cluster of patients in the city of Wuhan, in the Hubei Province of China and brought national then international attention to this viral infection even though similar viral infections in small numbers of patients had been previously reported in multiple countries [1]. The virus spread rapidly within two to three months and resulted in an epidemic of viral infections throughout China and thereafter a pandemic throughout the world. In February of 2020, the World Health Organization officially designated the viral disease as coronavirus disease 2019 (COVID-19) and the RNA virus that causes COVID-19 as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or CoV-2) [2]. The current pandemic has resulted from a rapid transmission of the virus from individual to individual and a general lack of inherent human immunity against the virus. In this regard, viral transmission from human to human begins prior to the development of individual symptoms and transmission is highest three to six days after the initial infection.

Although CoV-2 infection primarily affects the respiratory tract of individuals, cardiac injury occurs in ≥20% of the patients hospitalized with CoV-2 infection and is associated with a 19% increase in the incidence of heart failure, a 3% increase in cardiac arrest, and mortality rates that range from 8 to 69% [1, 3-5]. Patients with prior cardiovascular disease who contract COVID-19 and experience a significant increase in their blood troponin concentration are at risk for mortality rates as high as 69% [3]. These patients can present with cardiac dysrhythmias, acute coronary syndromes, acute heart failure, venous thromboembolic events, cardiogenic shock or cardiac arrest. Consequently, patients with COVID-19 and cardiovascular disease must be quickly identified and prioritized for aggressive monitoring and treatment.

In order to decrease the mortality and improve the longevity of patients with CoV-2 induced

cardiovascular injury, medical personnel should understand the pathophysiology of CoV-2 cardiovascular injury, the patient's immune response to the injury, and the current treatment strategies. This review focuses on the prevalence, the pathophysiologic mechanisms of CoV-2 injury to the cardiovascular system and the current recommended treatments for patients hospitalized with COVID-19. Nevertheless, treatment recommendations are evolving as additional insight is gained into CoV-2 viral structure, function, and replication, as well as evidence from prospective studies, and changes in the COVID-19 pandemic.

COVID-19 prevalence, patient characteristics and mortality

As of September 7, 2022, 603,711,760 confirmed cases of COVID-19 have been reported throughout the world and 6,484,136 individuals have died from complications of CoV-2 infections [6, 7]. The United States is among the countries with the greatest number of CoV-2 infections during the pandemic. Between January 1 and April 13 of 2022, 25,137,807 individuals have had confirmed CoV-2 infections in the United States and more than one million individuals in the United States have died from complications of COVID-19 [6-8]. Moreover, the emergence of the CoV-2 Omicron variant in December of 2021 has substantially increased the number of individuals with CoV-2 infections in the United States and has resulted in the highest number of CoV-2 associated hospitalizations since the beginning of the COVID-19 pandemic [9, 10]. As a consequence, health care systems and medical personnel have been significantly strained. Although the disease severity with the CoV-2 Omicron variant appears to be less than that with the Alpha or Delta variants, elderly patients and patients with cardiovascular disease are at significant risk for morbidity and mortality from Omicron infections. Currently, 2600 individuals die daily from CoV-2 related complications which significantly exceeds the 2,000 daily deaths due to the Delta variant during the viral surge in 2021 [9, 10].

Unfortunately, approximately 85% of the patients hospitalized with CoV-2 infection have not been vaccinated against the virus [11]. In this regard, Black, Hispanic, and Southern Asians currently comprise a disproportionately large number of patients with CoV-2 infections and deaths in the United States. This is due to mistrust by these ethnic groups of the health care system and disparities in access to health care [12, 13]. Consequently, medical personnel must encourage COVID-19 vaccinations and the use of personal protective equipment in all ethnic groups in order to prevent infections, critical cardiopulmonary illness, and death from COVID-19.

The specific risk factors for severe cardiac CoV-2 disease in patients with COVID-19 are listed in Box 1.

Box 1. Patient High Risk Factors for COVID-19 cardiac disease (Adapted from 1, 3-5, 14).

- Age ≥65 years.
- Residence in a long-term care facility, nursing home, or prison.
- Compromised immune system.
- Emphysema or asthma.
- Cardiovascular disease.
- Extreme obesity.
- Diabetes mellitus.
- Cerebrovascular disease.
- Chronic liver or kidney disease.
- Chronic tobacco use.

Based on studies of 1099 patients with COVID-19 who have been hospitalized in China, severe illness can occur in 16% of patients, 5% are admitted to an intensive care unit (ICU), and approximately 2 to 3% are intubated and treated with mechanical ventilation for respiratory failure [15]. Moreover, CoV-2 cardiovascular involvement can occur in as many as 20 to 30% of hospitalized patients and in 38% of all patients who die from CoV-2 infection [1, 16-18].

Box 2 summarizes the specific cardiovascular manifestations of CoV-2 infection and is adapted from [5, 19-21]. See Box 2.

Box 2: Cardiovascular Manifestations of CoV-2 infection.

- Cardiac dysrhythmias.
- LV injury/infarction: type I or type II myocardial infarction.

- RV global longitudinal strain (≤-15.5%) and dysfunction.
- Acute myocarditis or myopericarditis.
- LV failure, cardiogenic shock.
- Takotsubo cardiomyopathy.
- Venous and arterial thrombosis and thromboembolism.

The most significant cardiac complications from CoV-2 infections in hospitalized patients include cardiac dysrhythmias in 17 to 44%, cardiac injury with increases in blood troponin in 22 to 40%, myocarditis in 2 to 7% and heart failure in 4 to 21% [15, 16, 20, 21]. In an investigation of 277 patients who died from COVID-19, autopsy studies identified myocyte ischemia/injury in 14%, non-myocarditis inflammatory infiltrates in 13%, myocarditis in 2 to 7%%, acute myocardial infarction in 5%, and pericardial effusions in 2.5 to 14% [22, 23].

The mortality among patients with CoV-2 infection admitted to the intensive care units (ICU) is dependent on the CoV-2 variant and the severity of the CoV-2 infection, the vaccination status of the patient, the characteristics of the patient and the presence of comorbidities, and the facilities that are available for treatment. In general, the mortality from COVD-19 among hospitalized patients with severe adult respiratory distress syndrome (ARDS) ranges from 25 to 50 percent [24-26]. In hospitalized patients with COVID-19 with cardiovascular disease who develop cardiac injury, with a significant increase in the blood concentrations of troponin, the mortality can increase to as high as 69%, in comparison with a mortality rate of 37.5% among patients without cardiovascular disease (CVD) but an increased troponin, and a 13.3% mortality rate in patients with CVD and normal troponin concentrations [3]. Myocardial infarction and death occur more frequently in unvaccinated patients. The mortality risk in patients with COVID-19 associated with an increase in the blood troponin concentration is greater than the mortality risk from age, diabetes mellitus, or chronic pulmonary disease [4, 18].

In the initial 2020 studies from China, myocardial injury with increased troponin concentrations and heart failure occurred in 24% of hospitalized patients with CoV-2 infection and contributed to patient mortality in ≥49% [27-29]. Troponin increases can also occur in patients with CoV-2-induced myocarditis and these patients can progress to hemodynamic instability, heart failure and cardiogenic shock [30]. In studies of patients with CoV-2 myocarditis and troponin elevation, fulminant myocarditis with cardiogenic shock occurred in as many as 14 to 20% and contributed to patient hospital mortality in in as many as 19% [30-32].

CoV-2 induced venous thrombosis and pulmonary thromboembolic events are additional cardiovascular conditions that contribute to significant risk for patient morbidity and mortality. In hospitalized patients with COVID-19, the incidence of pulmonary thromboembolic events ranges from 3 to approximately 15%. However, in patients who undergo diagnostic CAT pulmonary scans, emboli are present in the lungs of ≥39% of the patients and contribute to death in ≥20% of these patients [33-35].

Arterial thrombi can occur in 4% of patients with COVID-19 infection and are most common in elderly males with comorbidities. Arterial thrombi can involve not only the coronary arteries but also the limb arteries in 39%, cerebral arteries in 24%, the aorta, common iliac, common carotid, and brachiocephalic trunk in 19%, and the superior mesenteric artery in 8% [36, 37]. When arterial thrombi occur in patients with COVID-19, the mortality rate in these patients approaches 20% [35, 37].

Pathophysiologic mechanisms that contribute to cardiac injury

Mechanisms for cardiac injury include ACE receptor downregulation, cytokine storm and catecholamine mediated damage, vascular thrombosis, hypoxia with supply/demand mismatch, and viremia.

ACE receptor downregulation

Coronaviruses contain four major structural proteins: spike (S) proteins, a nucleocapsid protein, a membrane protein, and an envelope protein [38]. The S proteins mediate viral attachment and fusion to the angiotensin-converting enzyme 2 (ACE2) receptors on cardiac cells, vascular endothelial cells, and pulmonary cells [38-40]. This enables CoV-2 entry into the cell, cell infection, and CoV-2 replication. ACE-2 receptors normally serve as regulators of the

renin-angiotensin-aldosterone system by converting the vasoconstricting and proinflammatory angiotensin II into the vasodilating peptide angiotensin 1-7 [39, 40]. However, CoV-2 cell infection results in the down-regulation of the ACE-2 receptor with resultant increased accumulation of angiotensin II. Increased circulating angiotensin II contributes to vasoconstriction, increased vascular permeability, activation of cytokines and chemokines, myocardial oxygen supply-demand mismatch, myocardial fibrosis, and Takotsubo cardiomyopathy [40-43]. Early in the COVID-19 pandemic, a theoretical concern arose that drugs that inhibit ACE enzymes or the ACE receptor system with upregulation of ACE2 receptors might worsen COVID-19 cardiopulmonary disease. However, subsequent studies have demonstrated that discontinuation of ACE inhibitors or angiotensin receptor blockers in patients with COVID-19 who had been previously receiving these medications actually proved detrimental to the patients [41].

Cytokine storm

CoV-2 infects alveolar epithelial cells, vascular endothelial cells, and macrophages, which release the pro-inflammatory cytokines Interleukin (IL)-1, IL-6, IL-12, and Tumor Necrosis Factor alpha (TNFα) which damage the lungs. These inflammatory cytokines recruit monocytes, macrophages, neutrophils, dendritic cells, and natural killer cells and activate CD4+ and CD8+ T cells which contribute to the production of excessive amounts of circulating cytokines. A sustained "cytokine storm" results that involves proinfammatory IL-1, IL-2, IL-6, IL-7, IL-8, granulocyte colony-stimulating factor, interferon gamma-induced protein 10, monocyte chemotactic protein-1, macrophage inflammatory protein 1A and TNF-α [44-46]. The release of IL-6 and TNF-α during the cytokine storm also induces a surge in epinephrine which contributes to myocardial oxygen supply demand imbalance and stress induced cardiomyopathy. The cytokines and catecholamines increase capillary permeability, enhance fibrinogen synthesis, cause disseminated intravascular coagulation, mural and microthrombi, and myocardial edema, ischemia and injury [44-46]. IL-1 and TNFa also impair LV diastolic function by decreasing calcium reuptake by the myocyte sarcoplasmic reticulum through down-regulation of phospholamban and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) [47].

Prothrombotic state/vascular thrombosis

Macro- or microvascular thrombi are present in the lungs and heart in 19 to as many as 78% of the patients who die from CoV-2 infection [22, 36]. These thrombi are due to a CoV-2-induced prothrombotic state that results from vascular endothelial cell inflammation, hypoxic-induced vascular spasm, antiphospholipid antibodies, increased circulating fibrinogen, platelet activation, and patient immobilization with venous stasis [48-50]. In addition, a significant increase of von Willebrand factor also occurs in the blood of COVID-19 patients and predisposes to vascular thrombosis and/or embolism [50]. Systemic Inflammation in patients with COVID-19 also promotes plasminogen activator inhibitor-1 (PAI-1) release from vascular endothelial cells, which suppresses urokinase plasminogen activator and tissue-type plasminogen activator (tPA) and the conversion of plasminogen to plasmin. The action of PAI-1 ultimately leads to the accumulation of fibrin, vascular thrombosis and thrombus propagation [51].

Myocardial oxygen supply demand imbalance

Severe CoV-2 infections cause decreased oxygen delivery to the myocardium due to hypoxemia and vasoconstriction while the hemodynamic effects of viremia increase myocardial oxygen demands due to increases in catecholamines and in heart rate. This supply and demand mismatch leads to myocardial ischemia, injury and Type II infarction, especially in patients with underlying coronary artery disease. Type I myocardial infarction can result from coronary artery spasm, microthrombi or coronary plaque destabilization and rupture due the cytokine storm and vascular endothelial inflammation.

Viremia

CoV-2 induced myocardial injury can also be due to viremia and/or migration of virus laden macrophages from the lungs into the heart that target pericytes, cardiomyocytes, fibroblasts, and myocardial macrophages [22]. In a meta-analysis of autopsy studies of patients who died from COVID-19, CoV-2 RNA was present in 50 of 105 hearts [22]. However, only a minority of hearts at autopsy actually fulfilled strict pathologic criteria for myocarditis with lymphocytic infiltration into the myocardium and myo-

cyte necrosis not due to ischemia [22, 52]. Rather, a macrophage-dominated inflammatory infiltrate predominates in CoV-2 myocardial injury which suggests that CoV-2-induced myocardial inflammation and dysfunction is mediated predominantly by macrophages [22, 23, 48, 53-55].

Box 2 summarizes the pathophysiologic mechanisms by which CoV-2 can cause cardiovascular damage. Box 2 is adapted from [42, 43, 56].

Box 2: CoV-2 Cardiovascular Pathophysiologic Mechanisms.

- Downregulation of ACE2 receptors, angiotensin II accumulation and stimulation.
- Cytokine storm.
- Macro and microvasculature venous and arterial thrombosis.
- Hypoxia.
- Myocardial oxygen supply-demand mismatch.
- Direct myocyte oxidative stress, inflammation, and intracellular acidosis.
- Ventricular diastolic dysfunction.
- Takotsubo catecholamine induced cardiomyopathy.

Symptoms, signs and diagnostic abnormalities of COVID-19

The symptoms and signs of CoV-2 infection are directly dependent on the CoV-2 variant, the age and sex of the patient, and the presence or absence of comorbidities such as heart disease. CoV-2 Alpha and Delta variants are more virulent to the heart than the Omicron variant. Specific patient risk factors for pathologic cardiac events include age >70 years, male sex, BMI ≥30 kg/m^2, diabetes mellitus, pre-existing cardiovascular disease, and moderate to severe pneumonia at hospital presentation [57]. Nevertheless, cardiac complications do occur in younger age patients because 20% of the COVID-19 deaths occur among adults aged 20 to 64 years [58]. In many of these patients, central body obesity provides a reservoir for CoV-2 storage, replication and cytokine amplification, which contributes to severe COVID-19 inflammatory disease [59].

CoV-2 infection symptoms can appear in as few as 2 days or as long as 14 days after initial viral infection. The most common symptoms are fever >99.6°F, cough, shortness of breath and myalgias. Less common symptoms include anorexia, headache, nasal congestion, and sore throat. Loss of smell and/or taste occur in one-third of patients, especially among middle-aged women and appear to be due to neuronal inflammation and downregulation of olfactory gene expression [60]. These symptoms characterize Stage 1 of COVID-19.

CoV-2 infection can progress to Stage II which is characterized by an inflammation that primarily affects the lungs with increased shortness of breath, lower lung infiltrates on chest x-ray, a SpO_2 ≥93% on room air, lymphocytopenia often with reductions in CD3+ and CD8+ T-cells to ≤75 cells/μL and increases in C reactive protein [20, 61]. COVID-19 pulmonary changes on CAT scan in patients can occur prior to the development of a positive reverse transcription polymerase chain reaction laboratory test [62].

Twelve to 30% of patients with Stage II progress to Stage III, which is characterized by a cytokine storm with the development of an adult respiratory distress syndrome with infiltrates involving >50% of the lungs on chest x-ray and requirements for assisted ventilation for treatment of respiratory distress [20]. In these patients, the SpO_2 is <93% on room air and the PaO_2/FiO_2 is <300. In the majority of the ICU patients with severe pneumonia, chest x-rays and computed tomography demonstrate bilateral multiple pulmonary lobular and peripheral sub-segmental areas of ground-glass opacity and consolidation [63]. In addition, microvascular pulmonary thrombi contribute to profound hypoxia. In these patients, hypoxia can contribute to myocardial injury/infarction and blood troponin elevation.

With CoV-2 infection, cardiac dysrhythmias occur in ≥17% of hospitalized patients and in as many as 44% of ICU patients [64, 65]. Hypoxemia, systemic inflammation, sympathetic hyperactivity, myocardial injury, myocarditis, and/or hypokalemia, hypomagnesemia, hypocalcemia, drug side effects or drug interactions contribute to the dysrhythmias. In addition, the inflammatory cytokines IL-6, IL-1 and TNFα modulate the expression and function of myo-

cyte K^+ and Ca^{2+} channels, prolong the myocyte action potential and the ECG QT interval, and thereby predispose patients to recurrent ventricular dysrhythmias.

Diffuse ST segment elevations or depressions and T-wave inversions can occur on the ECG and are associated with supraventricular dysrhythmias or ventricular tachycardia/fibrillation [64]. New-onset atrial fibrillation occurs in 4% to 16% of patients with COVID-19 and is the most common dysrhythmia, followed by frequent premature ventricular contractions in 13%, ventricular tachycardia or ventricular fibrillation in 2.6% and atrioventricular (AV) block in 0.4% [65-68]. The development of atrial premature contractions, atrial fibrillation, an intraventricular conduction defect or localized T-wave inversions on ECG significantly increases the odds ratio of patient mortality by ≥2.65 [67]. Ventricular dysrhythmias occur in as many as 12% of CoV-2 infected patients with increased troponin concentrations and in 5% of patients with normal troponin concentrations and result from cytokine and Angiotensin II storms, activation of the coagulation cascade with vascular thrombosis, endothelial cell injury, and hypoxic myocardial injury [64, 68]. Ventricular dysrhythmias and torsade de pointes can also be precipitated by the administration by medical personnel of ECG QT interval prolonging drugs such as hydroxychloroquine, azithromycin, and quinolone antibiotics.

Twenty-three to 35% of ICU patients with COVID-19 demonstrate signs of cardiac injury with blood troponin concentrations greater than 3 times the upper limit of normal. Echocardiographic abnormalities occur in as many as 60 to 70% of these patients and consist of thickening of the interventricular septum due to myocardial inflammation and edema, increases in LV and RV diastolic diameter, decreases in LV and RV contractility, decreases in global and circumferential longitudinal strain, and reductions in LV diastolic function [69-72]. Global biventricular dysfunction on the echocardiogram associated with diffuse ECG ST segment elevations and depressed PR intervals suggests extensive myocardial inflammation with myocarditis whereas regional wall motion abnormalities on the echocardiogram and localized ECG ST-segment changes indicate focal myocardial ischemic damage due to macro- or microvascular thrombosis [73, 74]. Decreases in LV global longitudinal strain and deformation abnormalities in the LV basal segments can occur prior to reductions in the LV ejection fraction and are early signs of ventricular dysfunction [75]. Moreover, decreases in RV longitudinal strain are better measurements of RV dysfunction and predictors of patient mortality than measurements of RV fractional shortening or tricuspid valve annulus systolic excursion (TAPSE) [76]. The presence of a dilated right ventricle with a hypercontractile RV apex and an akinetic mid-RV wall, which is termed McConnell's sign, suggests the presence of pulmonary embolus [77]. Right ventricular remodeling during COVID-19 is associated with a more than two-fold increase in mortality risk after adjustment for other clinical variables and biomarkers [75, 76].

Echocardiographic signs of pericardial effusion occur in 2.5 to 14% of patients with COVID-19 and is due to impaired lymphatic pericardial drainage from an increase in right-heart pressures, RV dysfunction and significant pulmonary disease [78]. In patients with COVID-19, pericardial effusions are associated with a 2.4 increase in excess mortality [78]. The use of point of care focused ultrasound can significantly facilitate the diagnosis of pericardial effusion and change clinical management in as many as 33% of patients [79, 80].

Cardiac changes on magnetic resonance imaging (MRI) include increases in T1 due to acute myocardial injury or inflammatory cell infiltration with transmural edema and subepicardial or midwall late gadolinium enhancement and also increases in T2 due to myocardial edema [81]. With CoV-2 myocarditis, MRI demonstrates LV wall motion hypokinesis that is in a noncoronary distribution [82-86]. Cardiac MRI is also useful in diagnosing CoV-2 induced Takotsubo cardiomyopathy with diffuse edema in the LV wall that does not correspond to specific coronary arterial distributions and LV wall dyskinesis in the apex with apical ballooning and akinesis in mid LV wall [81]. Pericardial thickening and effusion can also be seen on MRI and can be associated with the symptoms and signs of cardiac pericarditis and tamponade [85-87]. Additional helpful techniques for diagnosing COVID-19 myocarditis include the use of positron emission tomography with myocardial fluorodeoxyglucose uptake in the mid- and/or basal inferolateral walls [88].

Table 1. Factors that contribute to venous thrombosis

Factors	Score
Cancer	3
Prior Venous Thrombosis	3
Reduced/Absent Mobility	3
Factor V Leiden, Prothrombin Gene Mutation, Protein C or S Deficiency, Increased Homocysteine, Increased Factor VIII, IX, XI	3
Trauma or Surgery within previous 1 month	2
Age >70 Years	1
Heart or Respiratory Failure	1
Acute Myocardial Infarction or Stroke	1
Acute Infection or Rheumatologic Disorder	1
BMI ≥30 kg/m^2	1
Active Hormonal Therapy	1

<4 = LOW RISK, >4 = HIGH RISK, BMI = BODY MASS INDEX.

Peripheral venous thrombosis occurs in 3 to as many as 42% of hospitalized patients with COVID-19 especially in overweight, obese, diabetic or pregnant patients [89]. Venous thrombosis is characterized by pain, edema and/or redness that most frequently affects the femoral and popliteal veins of the lower extremities followed in frequency by the brachial-axillary veins in the upper extremities. **Table 1** lists the predisposing factors for venous thrombosis and thromboembolism. Points are assigned to each predisposing factor for thromboembolism. A score of 4 or greater is associated with an increased risk for venous thromboembolism [90].

Laboratory data

Blood counts from COVID-19 patients demonstrate the presence of lymphocytopenia, with reductions in CD4+ and CD8+ T cells in 83% of patients due to the high vulnerability of lymphocytes to CoV-2 cell infection and destruction. The majority of patients with severe COVID-19 have an increase in C-reactive protein and IL-6 whereas increased concentrations of alanine aminotransferase, aspartate aminotransferase, and creatine kinase are less common [15]. An increase in the D-dimer, the prothrombin time, a prolongation of the activated partial thromboplastin time, and a decrease in fibrinogen occur in as many as 50% of patients who do not survive COVID-19 [91, 92]. A D-dimer concentration >2.14 mg/L on hospital admission signifies a hyperfibrinolytic state, an increased inflammatory burden, and can be associated with an in-hospital mortality of 23% [93].

Increases in blood troponin concentrations occur in 23 to 35% of CoV-2 critically ill patients and are due to cardiac dysrhythmias, hypotension, myocardial infarction, right heart strain, or myocarditis [1, 17, 94]. Blood troponin concentrations >5 times the upper limit of normal are associated with the presence of heart failure or cardiogenic shock and are independently linked with increased in-hospital mortality [94].

Box 4 summarizes the Hypoxia, Age, and Troponin (HA_2T_2) Risk Score for 30-day mortality in critically ill patients with COVID-19 with hypoxia and increased troponin determinations on hospital admission. In the HA_2T_2 Risk Score: H = Hypoxia = 1 point; A = Age = 1 point if age = 65 to 74 and 2 if age >75; T = Troponin = 2 points if Troponin >0.34 ng/mL. Box 4 is adapted from [94].

Box 4: HA_2T_2 Risk Score

HA_2T_2 score	30-day mortality %
1	4
2	12
3	35
4	49
5	66

Sustained increases in NT-proBNP to ≥300 pg/mL in patients with COVID-19 are independently associated with patient mortality even after adjusting for heart failure and elevations of blood troponin and D-dimer [95, 96]. In addition, every 2-fold increase in the NT-proBNP concentration above 300 pg/mL is associated with a 21% increase in the odds of fatal patient outcome [96]. The prognostic effect of plasma NT-proBNP concentrations in ICU patients with CoV-2 infection is not completely ascribable to

heart failure or hypoxia induced by the virus but appears to reflect the overall advanced state of the CoV-2 infection [96, 97].

Treatment

All hospital personnel should use personal protective equipment and wherever possible utilize diagnostic equipment that is restricted to the evaluation and treatment of patients with CoV-2 infection. Disinfection procedures for ultrasound probes and scanner equipment should be strictly adhered to after use in each patient with CoV-2 infection.

Daily physical examinations supplemented with handheld ultrasound examinations of LV and RV size and ejection fraction facilitate the prompt diagnosis of cardiac decompensation in patients with COVID-19 [79]. In addition, an electrocardiogram, chest-x-ray, oxygen saturation measurement, and high sensitivity-troponin determination should be measured at the time of initial patient hospitalization and subsequently monitored based on the patient's clinical course. Cardiothoracic CAT scans should be performed if moderate-to-severe respiratory symptoms are present but the RT-PCR is negative and the chest x-ray is indeterminate. Lung CAT scans should also be performed if there is disease progression and clinical deterioration, or if pulmonary embolus, left atrial appendage or intracardiac thrombus are suspected.

New-onset malignant ventricular tachyarrhythmia or severe bradyarrhythmia that are not explained by respiratory insufficiency can be a marker of acute myocardial injury and should trigger diagnostic cardiac evaluation. Myocardial ischemia should be excluded with measurement of serial troponin determinations. High risk patients with symptoms and signs of myocardial ischemia and infarction (STEMI) of <12-hour duration with troponin elevation >99th percentile, and persistent ECG ST-T wave elevations in two contiguous ECG leads should be treated aggressively with medical therapy and coronary primary percutaneous coronary intervention (PCI) [98, 99]. Complete coronary revascularization should be performed if practical and appropriate to avoid multiple catheterization procedures and possible catheterization laboratory CoV-2 contamination. Alternatively, primary fibrinolysis with a fibrin specific agent such as tenecteplase, alteplase or reteplase should be performed in high-risk patients with ST elevation in accordance with AHA/ACC and ESC guideline recommendations [98, 99].

Patients with non-ST segment elevation myocardial infarction (NSTEMI) at high risk due to recurrent chest pain, hemodynamic instability, malignant cardiac dysrhythmias, or heart failure require medical stabilization and coronary angiography, if possible, within 24 hours of hospitalization. Patients at intermediate or low risk for NSTEMI with an increase in blood troponin but no recurrent chest pain or evolving ECG changes should undergo coronary computed tomographic angiography for risk stratification [100]. In intermediate and low risk CoV2 positive patients with NSTEMI and obstructive coronary artery disease, PCI can be deferred until the patient has recovered from the CoV-2 infection with two negative consecutive reverse transcriptase polymerase chain reaction tests for CoV-2 DNA.

Patients with an increase in blood troponin concentration but no acute ECG changes or recurrent chest pain should be carefully evaluated for a Type II MI with myocardial supply/demand imbalance, myocarditis, or stress-induced cardiomyopathy. Cardiac catheterization and endomyocardial biopsy or alternatively cardiac MRI and positron emission tomography should be considered in patients with severe myocarditis with low cardiac output [100-103]. The use of corticosteroids appears to be beneficial in improving the outcome of patients with myocarditis associated with COVID-19 at the possible cost of delay in viral clearance by the patient [102]. Non-steroidal anti-inflammatory drugs must be used cautiously in the treatment of patients with myocarditis because of sodium retention and renal vasoconstrictive effects [103]. Colchicine is an alternative drug that is beneficial in the treatment of myocarditis.

Patients with fulminant myocarditis with cardiogenic shock and advanced atrioventricular block should be treated with vasopressors such as norepinephrine or dobutamine, mechanical circulatory support, the insertion of a transvenous cardiac pacemaker if advanced second or third degree AV heart block is present, and the utilization of mechanical ventilation or veno-arterial extracorporeal membrane oxygenation for treatment of hypoxemia and hypotension [101, 104, 105]. Beta-adrenergic blocking drugs and

Table 2. Drugs for seriously ill patients with COVID-19 pneumonia

Drug	Dosage	Hospital duration	Mechanical ventilation requirement	Mortality	Level of evidence	Reference
Baricitinib	4 mg per nasogastric tube for 14 days if GFR >60 ml/min/ 1.73 m^2	Decreased	Initiation: Decreased. Duration: ?Decreased	Decreased	Low to High	[112-115]
Tocilizumab	8 mg/kg I.V. Second dose in 12-48 hours	Decreased	Initiation: Decrease. Duration: ?Decrease	Decreased	Low to High	[116-118]
Sarilumab (If Baricitinib or Tocilizumab not available)	400 mg I.V. Second dose in 12-48 hours.	Decreased	Initiation: Decreased. Duration: ?Decreased	Decreased	Low to Moderate	[116, 118]
Dexamethasone	6 mg/day for 5 to 14 days	Decreased	Decreased	Decreased	Moderate	[119-121]

renin-angiotensin aldosterone system inhibitors should be utilized when the patient is euvolemic and does not require intravenous vasopressors and inotropes for at least 24 hours provided that the risk of hypotension and hyperkalemia is low, and the patient's renal function has returned nearly to baseline levels [104].

Since critically ill COVID-19 patients are at increased risk for pulmonary embolism, prevention of venous thromboembolism is recommended in patients who do not have contraindications to antithrombotic drugs such as an inherited or active bleeding disorder, a platelet count less than 50,000, a hemoglobin concentration less than 8 g/dL, or a major bleeding episode within the past 30 days [106]. In COVID-19 patients with a high or moderate risk of venous thromboembolism listed in **Table 1**, low molecular weight heparin (LMWH), in a dosage of 4000 IU enoxaparin daily, is recommended [106-108]. The dose should be adjusted in overweight or obese patients to 6,000 IU/d or 4,000 IU twice per day [107]. LMWH has anti-inflammatory properties which is an added benefit in COVID infection where inflammatory cytokines are markedly increased. Patients with severe renal dysfunction should receive subcutaneous injections of unfractionated heparin at a dose of 5,000 U twice daily. At the present time, the routine administration of full therapeutic dose anticoagulation is not recommended in critically ill patients who have a d-dimer serum concentration within normal limits.

In patients with highly suspected or documented pulmonary emboli, anticoagulation is recommended with enoxaparin 100 IU/kg (1 mg/kg), twice daily SQ, or enoxaparin 150 IU/kg (1.5 mg/kg), once daily SQ if there is no contraindication to anticoagulation [106, 107]. In patients with severe renal impairment, unfractionated heparin is recommended initially I.V. and then by subcutaneous injection with regular monitoring of factor Xa inhibition and maintenance of a therapeutic anti factor Xa level of 0.3 to 0.7 IU/mL [108]. Serial platelet counts should be performed to detect the occurrence of heparin-induced thrombocytopenia.

If there are signs of massive pulmonary embolism with hypotension, cardiac arrhythmias or sudden cardiac arrest, and bedside echocardiography indicates new onset right-ventricular strain and pulmonary arterial hypertension, which is not explained by CoV-2 pneumonia, thrombolytic therapy with Alteplase 100 mg infused over 2 hours should be considered. Alternative treatments in critically ill patients include catheter-directed embolectomy or surgical embolectomy [107].

Direct acting oral anticoagulants are not currently recommended in patients treated with the antiviral drugs lopinavir, ritonavir, darunavir, or paxlovid because of increased bleeding risk due to drug-drug interactions via CYP3A4 and/or P-glycoprotein inhibition [107, 109].

Anti-CoV-2 drug treatment

Table 2 summarizes the current recommendations by the WHO, the NIH, and the Infectious Disease Society of America for antiviral drug treatment for critically ill adult patients with myocardial injury who have signs of pneumonia/respiratory distress with oxygen saturations <90% or for seriously ill patients with ARDS, sepsis, who require life sustaining treat-

ment such as mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [110-112]. The drugs listed in **Table 2** are based on best current clinical evidence and the drug recommendations are subject to the results of ongoing clinical trials.

Baricitinib, a Janus kinase inhibitor, should not be given together with the IL-6 receptor inhibitors tocilizumab or sarilumab. An antiviral drug should be administered in combination with systemic corticosteroids such as dexamethasone [110, 111]. See **Table 2**. For adults with refractory septic shock who have completed a course of corticosteroids for COVID-19 pneumonia, the World Health Organization (WHO) recommends continued use of low-dose corticosteroid therapy because corticosteroids reduce the 28 day mortality in patients requiring oxygen therapy or mechanical ventilation [122, 123]. However, corticosteroids are not recommended for treatment of non-severe COVID-19 disease. A dose of 6 mg of dexamethasone is equivalent to 150 mg of hydrocortisone (e.g., 50 mg every 8 hours), or 40 mg of prednisone, or 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours). Serum glucose concentrations should be monitored in patients with severe or critical COVID-19 pneumonia. There are no studies to date that directly compare the use of baricitinib and tocilizumab. Treatment decisions should be based on local drug availability, guidance by infectious disease consultants and hospital pharmacists, and patient comorbidities.

The WHO recommends against the use of remdesivir in patients on supplemental oxygen in the current guideline [110] but adds that this recommendation is under review given new trials, and an update is planned in the next iteration of the guideline. The US National Institutes of Health suggests that remdesivir, 200 mg IV on Day 1, then 100 mg daily for approximately 5 days be considered with or without dexamethasone in patients within the first 10 days of symptom onset who demonstrate respiratory deterioration and require supplemental oxygen [111]. If the patient progresses to requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO, the full course of remdesivir should be completed [111]. Clinical trials have not demonstrated a mortality benefit for remdesivir in COVID-19 patients on mechanical ventilation, but a large, placebo-controlled trial has shown that the administration of remdesivir reduced the time to clinical recovery in hospitalized patients [124, 125].

The WHO recommends against the administration of convalescent plasma to patients with COVID-19, except in the context of a clinical trial [110]. Other drugs that are not recommended include hydroxychloroquine, lopinavir/ritonavir and ivermectin [110, 126]. Sotrovimab is not effective against the Omicron BA.2 subvariant of COVID-19 and is no longer recommended for treatment of COVID-19 caused by this subvariant.

Long-term sequelae of Sars-CoV-2 infection

The World Health Organization and the US Center for Disease Control (CDC) define post-Covid sequelae as symptoms that occur more than one to three months after CoV-2 infection that are not explained by other illnesses and that persist for four or more weeks [6]. Common post-Covid symptoms include recurrent headaches, difficulty thinking, dizziness, changes in smell or taste, cough, shortness of breath, chest pain, palpitations, joint pain, post-exertional malaise, chronic fatigue, and depression.

The incidence of post Covid syndrome progressively increases from non-hospitalized individuals to hospitalized individuals to those hospitalized and treated in the ICU and varies between 16 and 53% of patients with COVID-19 [127-129]. Post Covid syndrome occurs more frequently in patients after infection with the Alpha or Delta variants in comparison with patients infected with the Omicron variant. The clinical risk factors for post Covid syndrome include older patient age, female sex, obesity, asthma, poor general health, lack of COVID-19 vaccination, and poor sociodemographic living conditions [6].

The most common post Covid cardiovascular symptoms are dyspnea and chest pain which can occur in 18 to 21% of patients [129-131]. Sinus bradycardia can occur in 30% of patients but often resolves after 30 to 60 days [132]. Palpitations and/or tachycardia are also common and are present in 9 to 14% of patients between one and six months after COVID-19 [131-135]. A common cause of palpitations/tachycardia is postural orthostatic tachycardia syndrome (POTS), with a >30 beat increase in the heart rate within 10 minutes of assuming

an upright posture without orthostatic hypotension [136]. Dyspnea and chest pain post COVID-19 can occur and can be associated with focal myocardial edema and late gadolinium enhancement on cardiac MRI in 12 to as many as 78% of patients, especially those who experienced an increase in cardiac troponin and NT-proBNP during their initial hospitalization [137-140]. Other manifestations of post Covid syndrome include pericarditis/myocarditis, heart failure, and arterial and venous thromboembolism. Notably, the risk of new onset cardiovascular disease increases two to eightfold 30 or more days after acute pneumonia due to residual infection, chronic inflammation, hypercoagulation, and physical debilitation and deconditioning [6, 127]. In a study of 139 health care workers who were 10 or more weeks post COVID-19, Isolated pericarditis was present in 3% of the individuals, myopericarditis in 11%, and isolated myocarditis was present in 26% individuals as determined by cardiac magnetic resonance imaging (MRI) and high sensitivity cardiac troponin [141]. Consequently, cardiac MRI should be considered in patients with unexplained, persistent, or recurring cardiovascular symptoms possibly due to myocarditis post COVID-19.

Post Covid syndrome treatment that is useful include inhaled corticosteroids and bronchodilators for persistent cough and shortness of breath, statins for reduction in inflammation and oxidative stress, and selective serotonin reuptake inhibitors, such as fluvoxamine or fluoxetine, for symptoms of anxiety, difficulty thinking, and depression. Treatment options for control of postural orthostatic tachycardia include high salt diet or salt tablets, fludrocortisone, beta-adrenergic receptor blockers, verapamil or diltiazem, ivabradine, or midodrine, and compression garments with 30-40 mmHg counter pressure that cover the abdomen and lower extremities [136, 142]. Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and/or prednisone are useful in the treatment of patients with pericarditis/myocarditis. In patients with ventricular dysfunction and heart failure, which can occur in 8% of patients who recover from myocarditis [142, 143], medical therapy with ACE inhibitors or sacubitral/valsartan, beta-adrenergic receptor antagonists, mineralocorticorticoid receptor blockers, SGLT2 inhibitors and diuretics should be initiated and optimized as tolerated. Patients with post-Covid cardiac symptoms also benefit from cardiopulmonary rehabilitation. Nevertheless, as many as 12% of patients readmitted to the hospital with a post Covid syndrome can experience a fatal outcome [127].

In high-risk patients with a history of venous thromboembolism, cancer, and limited mobility (see **Table 1**), prophylactic anticoagulation can reduce the risk of venous thromboembolism at the risk of increased bleeding events [111, 144]. In these patients, rivaroxaban 10 mg daily for 31 to 39 days has been approved by the Food and Drug Administration [109]. Currently, the HEAL-COVID trial and the COVID-19 Post-hospital Thrombosis Prevention Trial are studying the effects of apixaban on hospital readmission, morbidity and mortality in patients with prior COVID-19 [145, 146].

In patients with prior hospitalization for COVID-19, and in post Covid patients >70 years of age, the risk of emergent or urgent surgery and postoperative mortality is increased from 2% to 15% [147, 148]. In these patients, the risks of proceeding with surgery must be weighed against the risks of delaying surgery especially in patients with ischemic heart disease, critical neurological disease, or cancer. If the decision is made to delay surgery, surgery should be deferred for ≥7 weeks [144, 148].

In athletes who have COVID-19 antibodies from recent infection and seek medical clearance prior to returning to competitive sports that require moderate to high levels of physical exertion, a comprehensive examination of the cardiovascular, pulmonary, neurological and muscular systems should be performed [139, 142, 149]. This should include an ECG, echocardiogram, pulmonary function test or spiroergometry, and determinations of systemic oxygen saturation. In competitive athletes after recovery from severe COVID-19, CMR should be considered: (1) prior to resumption of training especially in those athletes with high-pretest probability of myocardial injury; or (2) in those athletes who have returned to play and have new cardiovascular symptoms possibly due to myocardial injury [139, 142, 150]. Cardiac MRIs should be evaluated by physicians familiar with MRIs of athlete hearts because focal late gadolinium enhancement of the inferoseptal right ventricle is common due to athletic training and ventricular remodeling and should not be confused with focal myocarditis [151].

If the patient examination is within normal limits, a managed exercise program tailored to the individual regarding exercise duration and intensity should be pursued and if tolerated the athlete allowed to return to supervised sports participation. In athletes with a history of CoV-2 myocarditis, sports eligibility should be evaluated during cardiopulmonary rehabilitation because serious adverse outcomes, including sudden death, myocardial scarring and LV dysfunction, can result from resuming exercise too quickly after viral myocarditis in athletes. In a long-term follow-up study of 1142 patients who recovered from acute myocarditis with a mean age of 40.2 years, heart failure hospitalizations occurred in 6% to 8% [152].

If there are no further COVID-19 symptoms, no structural cardiac damage on echocardiogram or cardiac MRI, and the individual is able to carry out activities of daily living and participate in supervised activity without excessive fatigue, breathlessness, or cardiac dysrhythmias then the athlete can undertake a gradual resumption of physical activity in competitive sports with monitoring by the patient's coach and a medical practitioner. Athletes with uncomplicated acute myocarditis and complete recovery have a good prognosis. If a detailed cardiopulmonary evaluation and/or participation in an exercise program is abnormal, a supervised cardiopulmonary rehabilitation program for three to six months should be pursued and sports eligibility restricted [142]. These athletes should be re-evaluated at regular intervals during the rehabilitation program for the absence of cardiopulmonary symptoms, the resolution of laboratory evidence of myocardial injury, the normalization of LV systolic function and the absence of spontaneous/inducible cardiac arrhythmias in order to consider resumption of competitive sports [139, 140]. As the long-term manifestations of COVID-19 are unclear, cardiopulmonary re-evaluation in competitive athletes, should occur one and two years after the initial CoV-2 infection [139].

Summary

603,711,760 confirmed cases of COVID-19 have been reported throughout the world and 6,484,136 individuals have died from complications of CoV-2 infections. Significantly, the Omicron variant has produced the largest number of CoV-2 associated hospitalizations since the beginning of the pandemic.

Individuals suffering from COVID-19 infection with underlying CVD have an extremely poor prognosis and a high risk of mortality. Cardiac injury can occur in ≥20% of the hospitalized patients and is associated with a 19% increase in incidence of heart failure, a 3% increase in cardiac arrest, and mortality rates that range from 8 to 69%. Risk factors for cardiac complications include age >70 years, male sex, BMI ≥30 kg/m^2, pre-existing cardiovascular disease, diabetes, and moderate to severe pneumonia at hospital presentation. Cardiac complications are more frequent with the Alpha and Delta CoV-2 variants than with the Omicron variant.

Extensive myocardial inflammation is characterized by global biventricular dysfunction on echocardiogram with diffuse ECG ST elevations and depressed PR intervals whereas regional wall motion abnormalities and localized ECG ST-segment changes indicate focal ischemic damage due to macro- or microvascular thrombosis. Cardiac MRI changes include increases in T1 due to acute injury or inflammatory cell infiltration with transmural edema, subepicardial or midwall late gadolinium enhancement and increases in T2 due to edema. Diffuse edema in the LV wall on MRI that does not correspond to specific coronary arterial distributions and LV wall dyskinesis at the apex and akinesis in mid LV wall suggests CoV-2-induced stress-induced cardiomyopathy.

CoV-2 induced STEMI <12-hour duration with troponin elevation and persistent ECG ST-T wave elevations should be treated with aggressive medical and reperfusion therapy. Patients with an increase in blood troponin but no acute ECG changes or recurrent chest pain should be evaluated with echocardiography, cardiac MRI, or PET for myocardial supply/demand imbalance, myocarditis, or stress-induced cardiomyopathy.

Long-term sequelae of CoV-2 infection, which can occur in 18 to 53% of patients, consist of dyspnea, chest pain, and palpitations/tachycardia, which is often due to postural orthostatic tachycardia. Competitive athletes who seek medical clearance prior to returning to competitive sports, should undergo a comprehensive

physical examination. If a detailed examination and participation in an exercise program is abnormal, a supervised cardiopulmonary rehabilitation program for three to six months should be pursued and sports eligibility restricted.

Future directions

Studies are needed to clearly elucidate the host/COVID-19 pathogen interactions, the host immune response, and the methods used by the virus to evade the host immune response.

The benefits of combined drug therapy, such as baricitinib and tocilizumab, must be determined in limiting and resolving cardiopulmonary injury. Moreover, the long-term safety and side-effects of anti-viral therapies are not known and must be determined.

Determinations must be made whether acute delivery of antifibrotic therapy, anti-inflammatory therapy, or antiviral therapy significantly affects long-term patient outcomes.

The impact that CoV-2 hypercoagulability, microvascular thrombosis, and myocardial inflammation and injury will have on long-term patient functional status, quality of life, and mortality are not known and require extensive research on longitudinal follow-up studies. The role that imaging can play in guiding these determinations must be clarified.

The lessons that are currently being learned during the COVID-19 pandemic must guide the assessment and therapeutics of future hyper-inflammation syndromes that significantly affect the heart, lungs, and vasculature. Toward this end, the global medical community must closely interact because in this age of world travel emerging pathogens do not respect geopolitical boundaries.

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The drugs and drug dosages cited in this article are taken from the recommendations of the WHO, the NIH, and the Infectious Disease Society of America and are general guidelines. Specific drugs and drug dosages must be tailored by medical practioners to each patient with COVID-19.

Disclosure of conflict of interest

None.

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