Acute and Post-Acute COVID-19 Cardiovascular Complications: A Comprehensive Review

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Abstract

Purpose of Review The risk of cardiovascular complications due to SARS-CoV-2 are significantly increased within the first 6 months of the infection. Patients with COVID-19 have an increased risk of death, and there is evidence that many may experience a wide range of post-acute cardiovascular complications. Our work aims to provide an update on current clinical aspects of diagnosis and treatment of cardiovascular manifestations during acute and long-term COVID-19.

Recent Findings SARS-CoV-2 has been shown to be associated with increased incidence of cardiovascular complications such as myocardial injury, heart failure, and dysrhythmias, as well as coagulation abnormalities not only during the acute phase but also beyond the first 30 days of the infection, associated with high mortality and poor outcomes. Cardiovascular complications during long-COVID-19 were found regardless of comorbidities such as age, hypertension, and diabetes; nevertheless, these populations remain at high risk for the worst outcomes during post-acute COVID-19. Emphasis should be given to the management of these patients. Treatment with low-dose oral propranolol, a beta blocker, for heart rate management may be considered, since it was found to significantly attenuate tachycardia and improve symptoms in postural tachycardia syndrome, while for patients on ACE inhibitors or angiotensin-receptor blockers (ARBs), under no circumstances should these medications be withdrawn. In addition, in patients at high risk after hospitalization due to COVID-19, thromboprophylaxis with rivaroxaban 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis.

Summary In this work we provide a comprehensive review on acute and post-acute COVID-19 cardiovascular complications, symptomatology, and pathophysiology mechanisms. We also discuss therapeutic strategies for these patients during acute and long-term care and highlight populations at risk. Our findings suggest that older patients with risk factors such as hypertension, diabetes, and medical history of vascular disease have worse outcomes during acute SARS-CoV-2 infection and are more likely to develop cardiovascular complications during long-COVID-19.

Keywords Acute-COVID-19 · Post-COVID-19 · Cardiovascular manifestations · Myocardial injury · Heart failure · Dysrhythmias

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Introduction

Since late December 2019, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide, becoming a global pandemic [1–3] accounting for more than 753,823,259 reported cases and more than 6.8 million deaths worldwide as of February 2, 2023 [4]. SARS-CoV-2 frequently causes a respiratory infection manifesting a range of clinical presentations, from asymptomatic subclinical infection to severe viral pneumonia, acute respiratory distress syndrome (ARDS), a life-threatening form of respiratory failure that requires mechanical ventilation and admission to the intensive care unit (ICU) [5], as well as septic shock and specific organ dysfunction [1]. In addition, uncontrolled SARS-CoV-2 infection can trigger a cytokine storm resulting in multi-organ failure [6], while coagulation abnormalities have been reported in patients with COVID-19 leading to thromboembolic events [7]. For the purpose of this review, and according to the Royal College of General Practitioners, COVID-19 infection is divided into three phases: acute COVID-19, including patients with symptoms of COVID-19 infection for up to 4 weeks; subacute or ongoing symptomatic COVID-19 if symptoms persist 4–12 weeks and post-COVID-19 syndrome if symptoms persist after 12 weeks; and long COVID-19 including both ongoing symptomatic COVID-19 and post-COVID-19 syndrome [8, 9].

Given the significant association of COVID-19 with severe cardiovascular damage during the acute phase of the infection and a related increased risk of death [10, 11], there is increasing evidence that many patients with COVID-19 may experience a wide range of post-acute sequelae of cardiovascular complications. We provide herein a comprehensive review of the current literature on acute and post-acute COVID-19 cardiovascular sequelae and their pathophysiological mechanisms. Finally, we discuss therapeutic strategies for these patients during acute and long-term care and highlight populations at high risk.

Clinical Manifestation of SARS-CoV-2 During Acute and Post-COVID-19 Syndrome

Patients with acute SARS-CoV-2 infection may present with a broad spectrum of clinical manifestations, from no clinical evidence of heart disease or asymptomatic cardiac arrhythmias or dysrhythmias, to symptomatic heart disease [12]. Most patients with acute SARS-CoV-2 infection have typical symptoms of COVID-19 including dry cough, sore throat, fever, dyspnea, myalgias, headache, fatigue, diarrhea, and smell or taste abnormalities, as well

as lymphopenia, neutrophilia, and bilateral ground-glass opacities on chest computed tomography (CT) scans [10, 13–15]. Even symptoms such as dyspnea are nonspecific and are evaluated as they are more likely caused by a noncardiac condition (e.g., pneumonia) or cardiac disease. Only a small percentage of patients present with symptoms that may suggest heart disease including palpitations (9%) at 6-month follow-up [16–18] and chest pain at ~20% and 5% at 60-day and 6-month follow-up in the post-acute COVID-19 period, respectively [19]. Therefore, clinical evaluation by different diagnostic modalities such as electrocardiography (ECG), echocardiography, and cardiac magnetic resonance imaging (CMR), serum cardiac troponin, natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro-BNP) levels, and initial laboratory tests to assess for symptoms and signs of heart failure (HF) in addition to history and physical examination are necessary. According to guidelines [20], BNP/NT-proBNP biomarkers in COVID-19 patients should be examined as the combination of the presence or extent of pre-existing cardiac disease and the acute hemodynamic stress related to COVID-19. ECG abnormalities including ST-segment elevation or depression, T-wave depression/inversion, and Q-waves, as well as laboratory tests including troponin, BNP, and D-dimer level elevation, have been commonly reported in patients with COVID-19 [10, 21–24]. Moreover, increased levels of cardiac troponin I (cTnI), BNP, and D-dimer are related to more severe clinical outcomes and higher mortality rates [25–36].

Post-COVID-19 syndrome is poorly understood, as it affects COVID-19 survivors at all levels of disease severity and across all age ranges. Associated cardiovascular events included chest tightness, cardiac arrhythmias, palpitations, and hypotension, as well as increased heart rate, venous thromboembolic diseases, myocarditis, and acute/decompensated HF [37, 38]. The most common prevalent long-term symptom in COVID-19 is chest pain, reported in up to 20% of COVID-19 survivors at 60 days of follow-up [16, 17], while 9% and 5% reported palpitations and chest pain, respectively, at 6 months post-acute COVID-19 [39]. Cardiac damage can manifest as myocarditis, pericarditis, and rhythm abnormalities.

Myocardial Injury As shown in meta-analyses [40, 41], the most common cardiovascular complications in COVID-19 patients was myocardial injury, at 21.2% (95% CI: 12.3–30.0%), associated with higher mortality rates (51.2% vs. 4.55%, $P < 0.001$) [42], poor outcomes [1, 43, 44], and ICU admissions (risk ratio [RR] = 3.78, 95% CI: 2.07–6.89) (Table 1) [45]. Moreover, myocardial injury was reported as an independent predictor of death (hazard ratio [HR] = 2.25, 95% CI: 1.27–3.96, $P = 0.005$) [28]. SARS-CoV-2 infection

Table 1 Characteristics of cardiovascular complications associated with SARS-CoV2 infection during acute and post-acute phase

Cardiovascular Complications	Acute incidence	ICU admissions (RR)	Post-acute risk (HR)	References
Myocardial injury	21.2% (95% CI: 12.3–30.0)	3.78 (95% CI: 2.07–6.89)	NA	[42, 45, 49–54]
Myocarditis	1.4%	7.94	5.38 (95% CI: 3.80–7.59)	
Type I or II MI	16% (95% CI: 9.0–27.0)		1.66 (95% CI: 1.52–1.80)	
Dysrhythmias	10.11–15.3%	13.09 (95% CI: 7.00–24.47)	1.69 (95% CI: 1.64–1.75)	[1, 40, 41, 53–57]
Atrial arrhythmia	9.2% (95% CI: 6.5–12.7%)	NA	1.71 (95% CI: 1.64–1.79)	
AV block	12%	NA	NA	
Sinus tachycardia	NA	NA	1.84 (95% CI: 1.74–1.95)	
Sinus bradycardia	NA	NA	1.53 (95% CI: 1.45–1.62)	
Heart failure	22.34% (95% CI: 14.05–33.60)	8.9% ICU admissions OR = 1.70 (95% CI: 1.12–2.56)	2.29 (95% CI: 2.20–2.39)	[40, 41, 48, 54, 58, 59]
RVD	20.4% (95% CI: 17.1–24.3)			
Coagulation abnormalities	NA			
DVT	27% (95% CI: 21–34%)	NA	2.39 (95% CI: 2.27–2.51)	[54, 60, 61]
PE	21% (95% CI: 18–24%)	2.25 (95% CI: 1.64–3.08)	2.55 (95% CI: 2.09–3.11	
VTE	21.0–42.0%	NA	3.16 (95% CI: 2.63–3.79)	
			1.95 (95% CI: 1.80–2.12)	
Other complications				[25, 53, 54, 62, 63]
Pericarditis	3.2%	NA	1.85 (95% CI: 1.61–2.13)	
Pericardial effusion	7.2–14%	NA	NA	
Takotsubo syndrome	2–5.6%	NA	NA	

MI: myocardial infarction; **AV**: atrial ventricular; **RVD**: right ventricular dysfunction; **DVT**: deep vein thrombosis; **PE**: pulmonary embolism; **VTE**: venous thromboembolism; **RR**: risk ratio; **HR**: hazard ratio; **ICU**: intensive care unit

includes direct infection and damage to the myocardium causing myocarditis [46], and indirect cardiac damage by type I and type II (secondary to hypoxemia) myocardial infarction (MI) [47]. A prospective observational cohort study in 100 patients who had recently recovered from COVID-19 illness reported that 78 patients (78%) had cardiovascular involvement as a consequence of acute infection as detected by standardized CMR, irrespective of pre-existing conditions. The most prevalent abnormality was myocardial inflammation (defined as abnormal native T1 and T2 measures), detected in 60 patients who had recently recovered from COVID-19 (60%), followed by regional scar and pericardial enhancement. In addition, patients recently recovered from COVID-19 had lower left ventricular ejection fraction (LVEF), higher left ventricle volumes, and elevated native T1 and T2 compared with healthy controls and risk factor-matched controls [48].

Myocarditis directly caused by SARS-CoV-2 infection as diagnosed by endomyocardial biopsy, which is the gold standard method according to the European Society of Cardiology [64], is very rare [65, 66]. Although lymphocytic myocarditis was reported in 7.2% of 277 autopsies, only 1.4% met the well-established histological criteria for myocarditis [67]. On the other hand, in a cohort study, 14 out of 112 COVID-19 patients presented with symptoms related to myocardial injury, including elevated cTnI and abnormalities on echocardiography and ECG, whereas none of them met the full criteria for true myocarditis [49]. In

addition, SARS–CoV-2 RNA was detected in the heart tissue of postmortem patients (5 out of 12) [68], while in another cohort study, 24 out of 39 autopsy cases (61.5%) supported the presence of SARS-CoV-2 in cardiac tissue; however, none of these tissue samples showed evidence of an influx of inflammatory cells consistent with clinical myocarditis [69]. Nevertheless, this low sensitivity could be attributed to secondary sampling error [70]. In addition, during post-acute COVID-19, only 10–20% of myocarditis is diagnosed with endomyocardial biopsy [70].

On the other hand, the frequency of type I or type II myocardial injury, as defined by elevated cTn levels > 99th percentile, in acute SARS-CoV-2 infection was 16% (95% CI: 9–27%) [50] and 24.4% during hospitalization due to COVID-19 (Table 1) [51]. Thus it is possible that myocardial injury due to SARS-CoV-2 infection is attributable to myocardial oxygen supply–demand imbalance in MI type II rather than MI type I [71, 72]. Nevertheless, this type of myocardial injury has been associated with higher mortality (RR = 7.95, $P < 0.001$; I^2: 65%) and higher rates of ICU admissions (RR = 7.94, $P = 0.01$; I^2: 79%) [52]. Myocardial injury was also significantly associated with a higher incidence of complications, including ARDS (58.5% vs. 14.7%, $P < 0.001$), acute kidney injury (8.5% vs. 0.3%, $P < 0.001$), electrolyte disturbance (15.9% vs. 5.1%, $P = 0.003$), hypoproteinemia (13.4% vs. 4.8%, P = 0.01), and coagulation disorders (7.3% vs. 1.8%, P = 0.02), compared with those without cardiac injury [43].

As reported by Xie et al. and Wang et al., survivors of COVID-19 exhibit higher risk of myocarditis (HR = 5.38, 95% CI: 3.80–7.59) 30 days after discharge and ischemic heart disease (IHD) (HR = 1.66, 95% CI: 1.52–1.80) such as acute coronary disease (HR = 2.048, 95% CI: 1.752−2.393), MI (HR = 1.979, 95% CI: 1.831−2.138), ischemic cardiomyopathy (HR = 2.811, 95% CI: 2.477−3.190), and angina (HR = 1.707, 95% CI: 1.545−1.885) (Table 1) [53, 54].

Dysrhythmias Cardiac dysrhythmias may be the initial clinical presentation of cardiovascular manifestation of COVID-19 during acute SARS-CoV-2 infection [73], with incidence ranging from 10.11% to 15.3% as shown in meta-analyses [40, 41], and atrial arrhythmia reported at 9.2% (95% CI: 6.5–12.7%) [55]. In addition, patients with newly occurring arrhythmias were at higher risk of developing severe disease or requiring ICU admission (RR = 13.09, 95% CI: 7.00–24.47, $P < 0.001$) [56]. Atrioventricular (AV) block may account for up to 12% of arrhythmias seen in patients with COVID-19 [57]. In addition, the incidence of cardiac arrhythmia in patients admitted to the ICU was 44.4% [1]. Among hospitalized patients and patients admitted to the ICU, atrial fibrillation, significant bradyarrhythmias, non-sustained ventricular tachycardia (NSVT), and cardiac arrest were common findings [74] in ICU patients, with atrial arrhythmia showing a higher prevalence among patients with poor outcomes [55]. Moreover, patients with elevated troponin T (TnT) levels were associated with malignant arrhythmias, ventricular tachycardia, and fibrillation [30, 75].

Cardiac arrhythmias such as atrial fibrillation, supraventricular tachycardia, complete heart block, and ventricular tachycardia occur in patients infected with, recovering from, and after recovery from COVID-19 [76]. COVID-19 survivors were associated with increased risk of arrhythmia-related disorders as post-COVID conditions, such as atrial fibrillation and flutter (HR 1.71–2.407). Other dysrhythmias reported were tachycardia (HR = 1.682–1.84); bradycardia (HR = 1.53–1.599), and ventricular arrhythmias (HR = 1.600–1.84) (Table 1) [48, 54].

Heart Failure (HF) Acute HF is reported as the most common complication in COVID-19 patients, with incidence of HF ranging from 14.4% (95% CI: 5.7–23.1) to 22.34% (95% CI: 14.05–33.60) [40, 41], and a high mortality rate, at 47.8% (95% CI: 41.4–54.2) (Table 1) [40]. Another study reported that among 901 admissions to an ICU due to COVID-19, 80 (8.9%) had acute HF, including 18 (2.0%) with classic cardiogenic shock (CS) and 37 (4.1%) with vasodilatory CS. The majority ($n = 45$) were de novo HF presentations [58], with LVEF ranging from 7.5% to 11% [49, 77]. In addition, HF is one of the most important comorbidities significantly affecting prognosis [54], with a high overall mortality rate

ranging between 20% and 40% among patients with previously diagnosed HF and acute SARS-CoV-2 infection [78].

Echocardiographic evaluation in patients diagnosed with SARS-CoV-2 infection reporting a cardiac pathology within 24 hours of admission demonstrated that right ventricular (RV) dilatation and dysfunction was the most common cardiac pathology (observed in 39% of patients), followed by left ventricular (LV) diastolic dysfunction (16%) and LV systolic dysfunction (10%) [25, 79]. A systematic review and meta-analysis in 29 studies including a total of 3813 patients reported a pooled prevalence of right ventricular dysfunction (RVD) of 20.4% (95% CI: 17.1–24.3), with a high grade of heterogeneity (Table 1) [80]. In addition, RVD was associated with worse prognosis [81] and complications such as increased severity (odds ratio [OR] = 3.61, 95% CI: 2.05−6.35, $P < 0.001$), ICU admission (OR = 1.70, 95% CI: 1.12−2.56, $P = 0.01$), mechanical ventilation (MV) (OR = 1.60, 95% CI: 1.14−2.25, $P = 0.007$) [59], and increased all-cause death (OR = 3.32, 95% CI: 1.94–5.70) [80].

In addition, patients who recovered from COVID-19, regardless of pre-existing conditions, had lower left and right ventricular ejection fraction and higher left ventricular volume than healthy controls and risk factor–matched controls [48]. HF-related causes at 30-day readmission were significantly higher in patients with HF with reduced ejection fraction (HFrEF) (47.1%) compared with those with HF with midrange ejection fraction (HFmrEF) (0%) or those with HF with preserved ejection fraction (HFpEF) (8.6%) [82]. Moreover, patients who had recovered from COVID-19 ware associated with an increased risk of HF (HR = 2.29, 95% CI: 2.20−2.39), cardiomyopathy (HR = 1.62–2.413), cardiac arrest (HR = 1.751–2.45), and cardiogenic shock (HR = 1.988–2.43) [48, 54].

Coagulation Abnormalities Acute SARS-CoV-2 infection has been associated with increased risk of disseminated intravascular coagulation (DIC) and thromboembolic events such as superficial vein thrombosis or so-called venous thromboembolism (VTE) and pulmonary embolism (PE) [10, 19, 83–86], even though there were no other risk factors for thrombosis in these patients [87, 88]. Meta-analysis studies reported that the prevalence of deep vein thrombosis (DVT) in patients with COVID-19 was 27% (95% CI: 21, 34%) [89], while the incidence of pulmonary embolism was 21% (95% CI: 18−24%; $P < 0.001$) and the incidence of pulmonary embolism in ICU and non-ICU patients was 26% (95% CI: 22−31%; $P < 0.001$) and 17% (95% CI: 14−20%; $P < 0.001$), respectively (Table 1). In addition, the predictive role of pulmonary embolism in ICU admission was reported at a diagnostic odds ratio (DOR) of 2.25 (95% CI: 1.64−3.08) [60]. The prevalence of VTE was found to be 21–42%, with VTE more common among older individuals

with COVID-19 [83]. In addition, a systematic review and meta-analysis reported that the cumulative incidence of PE and DVT in patients who had recovered from COVID-19 was 1.2% (95% CI:0.9–1.4, I^2: 99.8%) and 2.3% (95% CI:1.7–3.0, I^2: 99.7%), respectively. Recovered COVID-19 patients presented a higher risk of PE (HR = 3.16, 95% CI: 2.63–3.79, I^2: 90.1%) and DVT (HR = 2.55, 95% CI: 2.09–3.11, I^2: 92.6%) compared with non-infected patients from the general population over the same follow-up period [61]. Meta-regression showed a higher risk of PE and DVT with age and with female gender, and lower risk with longer follow-up. Recovered COVID-19 patients had a higher risk of VTE (HR = 1.95, 95% CI: 1.80−2.12), which increased with aging and among females [54, 61].

Other Complications Although limited to case reports, other complications include endocarditis, pericarditis, and Takotsubo syndrome (TTS) [90–95]. In a study of 530 hospitalized patients with COVID-19, pericardial effusion was found in 75 (7.2–14%), but only 17 patients (3.2%) fulfilled the criteria for acute pericarditis (Table 1) [62, 96]. A systematic review of a total of 33 studies (32 case reports and one case series) involving clinical data on patients with COVID-19 and pericarditis reported that pericarditis was found in 8/13 (62%) concurrently with COVID-19 and 5/13 (38%) after COVID-19 with a range from 5 to 56 days [94]. Thirteen patients (38%) were diagnosed with acute pericarditis, whereas the remainder (62%) were diagnosed with myopericarditis [94, 97]. Pericarditis, pericardial effusion, and consequent cardiac tamponade as a complication of myocarditis was also reported in a case study [92]. The most common symptoms were chest pain (68%), fever (65%), and dyspnea (56%). Pericardial friction rub was reported in four cases (two with acute pericarditis and two with myopericarditis) [94]. Diffuse ST-elevation and PR depression ECG pattern was also the most frequent among patients diagnosed with myopericarditis, while pericardial effusion and cardiac tamponade were reported in 76% and 35% of cases, respectively [94]. Although acute pericarditis is the inflammatory condition that affects the pericardium, which is most often due to viral infections, in COVID-19 patients it may be an under-diagnosed pathology. Post-acute sequelae with increased risk of pericarditis was also reported (HR = 1.85, 95% CI: 1.61–2.13) [53, 54]. On the other hand, Takotsubo syndrome (TTS), also referred to as stress-induced cardiomyopathy mimicking acute coronary syndrome [98], is a diagnosis of exclusion. During the COVID-19 pandemic, 2–5.6% (Table 1) [25, 63] were diagnosed with stress-induced cardiomyopathy, whereas before the pandemic, only 1.5–1.8% of patients in this population were diagnosed with TTS [95, 99]. While echocardiograms demonstrate segmental left ventricular dysfunction and patients present with symptoms such as shortness of breath, hypotension, and chest pain,

angiography does not reveal significant coronary blockage [100–102]. Several findings, some of them very heterogeneous case reports [95], have shown an increased incidence of TTS that was significantly higher in female COVID-19 patients [95, 103, 104]. However, coronary CT is recommended rather than coronary angiography to rule out the presence of coronary artery disease and TTS [105].

Mechanisms of Cardiac Damage

Coronaviruses are a positive-sense single-stranded RNA (ssRNA) genome, 27–32 kilobases in size, enveloped by the nucleocapsid (N) protein in crown-like morphology; viral particles are 100–160 nm in diameter and present a great capacity for fast mutation and recombination (Fig. 1A) [106, 107], while the viral envelope contains the spike (S), membrane (M) and envelope (E) proteins (Fig. 1A). Infection of target cells by SARS-CoV-2 occurs when the spike (S) protein on the surface of the virus binds to a membrane-bound aminopeptidase, angiotensin-converting enzyme 2 (ACE2) [108], a protein which plays a critical role in the regulation of blood pressure and cardiovascular system homeostasis [109, 110] (Fig. 1B). Spike has a receptor-binding domain (RBD) that mediates direct contact with a cellular receptor and an S1/S2 polybasic cleavage site that is cleaved by cellular cathepsin L and the transmembrane protease serine 2 (TMPRSS2) [111]. After binding on the surface of the cell, TMPRSS2 facilitates the entry of the virus by cleaving the spike protein and promoting the fusion of the viral membrane with the membrane of the host cell [112]. Once the RNA genome of the virus is released, replication-assisting proteins are translated followed by replication of the virus in virus-induced double-membrane vesicles derived from the endoplasmic reticulum (ER) that facilitate viral replication of genomic and subgenomic RNAs translated to form the structural proteins and accessory proteins [113]. RNA replication starts with the synthesis of full-length negative-strand copies of the viral genome. These serve as templates for the production of new positive-strand genomes, which are translated to form more non-structural proteins or are packaged into newly formed virions and released [114, 115]. ACE2 protein and TMPRSS2 are mostly present in respiratory tract epithelial cells, making the lungs the main gateway for the virus [116]. Besides the lung, ACE2 expression is also found in many extrapulmonary tissues including cardiomyocytes and pericytes, leading to cardiovascular complications and partially explaining the extrapulmonary manifestation of SARS-CoV-2 infection [117, 118].

The proposed mechanisms of myocardial injury by SARS-CoV-2 include both direct and indirect mechanisms (Fig. 1C, D). Briefly, direct mechanisms (Fig. 1C) include viral infiltration of cardiomyocytes which can lead to viral direct cell lysis and inflammatory response, consequently
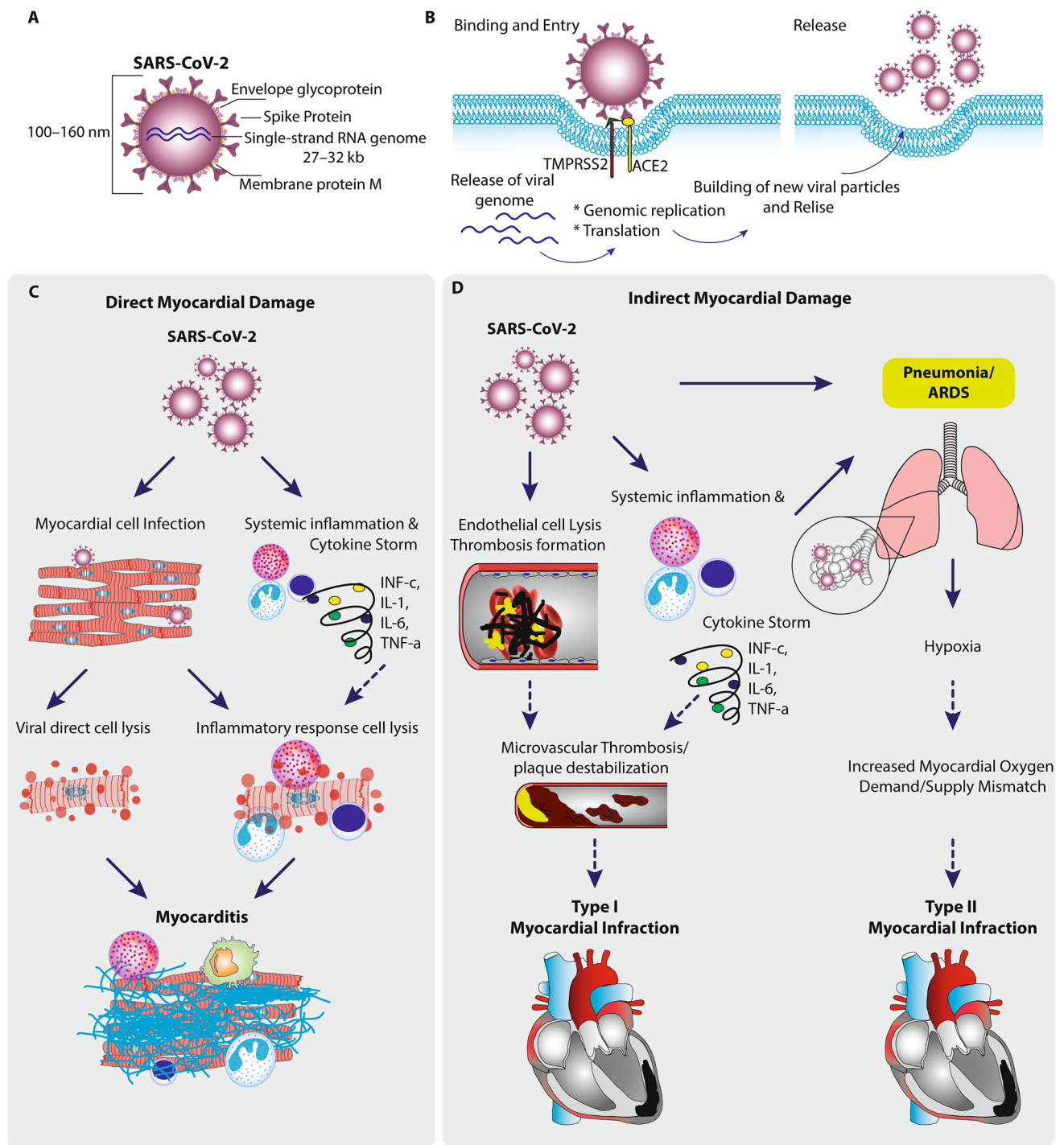
leading to myocardial inflammation—myocarditis. Indirect myocardial damage includes SARS-CoV-2 interaction with ACE2 , increased inflammation, cytokine storm release, and endothelial dysfunction which consequently increases hypercoagulability and thrombosis formation, leading to microvascular thrombosis, plaque destabilization, and type I MI (Fig. 1D). In addition, pneumonia and ARDS caused by SARS-CoV-2 and aggravated by cytokine storm exacerbate

myocardial oxygen demand/supply mismatch, leading to type II MI. Systemic inflammation seems to be the most prominent mechanism underlying cardiovascular complications of COVID-19. Infection with SARS-CoV-2 is followed by intrinsic immune response and activation of pattern recognition receptors which will lead to the secretion of antiviral cytokines and chemokine levels [10] including interferon-c (INF-c) and pro-inflammatory cytokines including

◄**Fig. 1** Mechanisms of myocardial damage by SARS-CoV2. **A** SARS-CoV-2 is a spherical viral particle consisting of three structural proteins—envelope glycoprotein, spike, and nucleocapsid protein—and a positive-sense, single-stranded RNA genome. **B** Infection occurs when spike protein binds to angiotensin-converting enzyme 2 (ACE2), while the transmembrane protease serine 2 (TMPRSS2) facilitates entry of the virus and the viral genome is released into the cytoplasm, followed by genomic replication/transcription and translation of viral proteins. Viral nucleocapsids are assembled in the cytoplasm, followed by budding of new particles at the membrane of the endoplasmic reticulum–Golgi intermediate compartment. Finally, viral genome and structural proteins are assembled into new viral particles and released via exocytosis. **C** Direct myocardial damage. Direct injury (bold arrows), through direct viral myocardial invasion and activation of inflammatory response activation. Inflammatory cells induced by SARS-CoV-2 or pro-inflammatory cytokines can cause necrosis and death of the myocardium. **D** Indirect injury, through interaction with ACE2, increases inflammation and endothelial dysfunction. Endothelial cell damage by SARS-CoV-2 increases the hypercoagulability state, thrombosis formation, and inflammatory response activation. Consequently, this may lead to plaque destabilization and atherothrombotic event causing type I MI. In addition, pneumonia and ARDS caused by SARS-CoV-2 and aggravated by cytokine storm exacerbate myocardial oxygen demand/supply mismatch, consequently leading to type II MI

interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α) [119]. Inflammatory cells induced by SARS-CoV-2 or pro-inflammatory cytokines can cause necrosis and death of the myocardium (Fig. 1C) and fibro-fatty displacement of desmosomal proteins important for cell-to-cell adherence [120], in addition to endothelial injury and micro-thrombosis, and hypoxia due to ARDS and respiratory failure and coagulopathy activation that can lead to cardiovascular complications (Fig. 1D) [121–123]. IL-1 levels are associated with HF and death [124]. IL-1 is reported to impair cardiac contraction due to suppression of β-adrenergic receptor signaling [125, 126] and nitric oxide production, which in turn inhibits anaerobic glycolysis in cardiac myocytes [127], playing an important role in cardiovascular disease (CVD) [128]. IL-1 also induces the expression of TNF-α [129], which in turn increases concentrations of TNF-α that can impair Keap1/Nrf2 response and result in cardiomyocyte death due to severe oxidative stress [130]. In addition, IL-6 binds to the soluble IL-6 receptor and initiates subsequent signaling through engagement with 130-kDa glycoprotein [131]. Excessive synthesis of IL-6 [132] and activation of the trans-signaling pathway of IL-6 causes inflammation and oxidative stress, which further results in cardiac and cerebral injury [133]. In addition, it is likely that cytokines also increase myocardial electrical instability as a result of direct cell injury (Fig. 1C). TNF, IL-1, and IL-6 are shown to directly and indirectly promote cardiac arrhythmias by modulating cardiomyocyte ion channel expression (Fig. 2) [134, 135]. Increased levels of IL-6 and IL-10 are associated with increased risk of atrial and ventricular arrhythmias in hospitalized COVID-19 patients [136]. Moreover, IL-6

levels and infection status were directly correlated with QTc prolongation [137] and new-onset atrial fibrillation or atrial flutter regardless of patient baseline characteristics [138]. In addition, inflammatory cytokines can induce cardiac fibrosis by activating myofibroblast-driven extracellular matrix synthesis, further impairing the velocity and homogeneity of cardiac conduction (Fig. 2) [135]. Myocardial fibrosis or scarring and the resultant cardiomyopathy from viral infection can lead to re-entrant arrhythmias in post-acute COVID-19 (Fig. 2) [139]. In addition, SARS-CoV-2 may perpetuate arrhythmias due to a heightened catecholaminergic state and autonomic dysfunction after viral illness, resulting in postural orthostatic tachycardia syndrome (POTS) and inappropriate sinus tachycardia (Fig. 2), as was previously reported as a result of adrenergic modulation [140–142], while electrolyte imbalance during COVID-19 illness may increase vulnerability to various tachyarrhythmias [143].

In addition, endothelial cell injury induced by SARS-CoV-2, cytokine storm, platelets, and inflammatory cells and underlying comorbidities are considered to play a central role in immunothrombosis [7]. In general, endothelial injury is caused by aging, reactive oxygen species, an increased ratio of circulating endothelium microparticles to progenitor cells, a pro-inflammatory state, and/or a decrease in sex hormones [144, 145]. Endothelial dysfunction is also a frequent characteristic in major comorbidities which enhance the risk of SARS-CoV-2 infection and mortality, such as obesity, hypertension, diabetes, coronary artery disease, and HF [146]. The presence of viral inclusions in endothelial cells induces direct damage [147] and attraction of immune cells, resulting in widespread endothelial dysfunction and death [148]. Histological analysis revealed significant changes in endothelial morphology, including cell swelling, disruption of intercellular junctions, and cell death, in post-mortem lung tissues from patients who died from SARS-CoV-2 infection [118]. IL-1, IL-6, and tumor necrosis factor are associated with acute endothelial cell activation, while creating an amplification loop that perpetuates the cytokine storm [149, 150]. Pro-inflammatory cells, cytokines, and chemokines can activate the coagulation system and downregulate crucial physiological anticoagulant mechanisms [149]. The vascular response to hypoxia is controlled primarily by the hypoxia-inducible transcription factors (HIFs), whose target genes include several factors that regulate thrombus formation, which will all be progressively aggravated by the development of local hypoxia [151]. This in turn will establish a deleterious positive thrombo-inflammatory feedback loop [151]. The potential pathophysiological mechanisms that underlie the association between COVID-19 and development of CVD in the post-acute phase are not entirely clear [152, 153]; however, the previously discussed mechanisms in the acute phase, namely inflammatory cytokines, hypoxia induced due to respiratory changes,
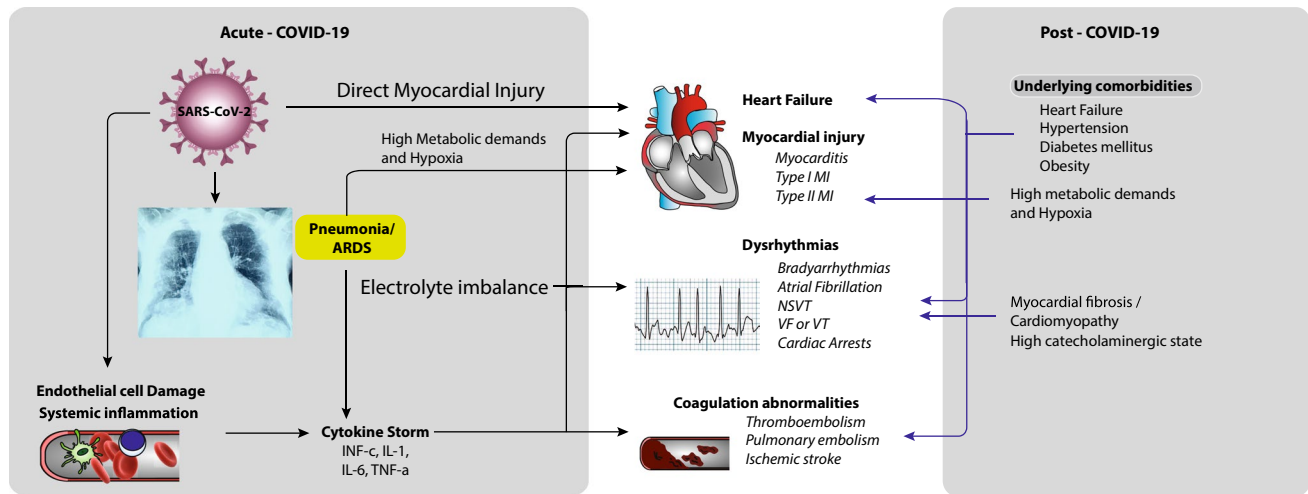
Fig. 2 Cardiovascular manifestations of SARS-CoV-2 during acute and post-acute phase. During the acute phase (black arrows), SARS-CoV-2 infects host cells of the respiratory tract, endothelial cells, pericytes, and cardiomyocytes, leading to cardiovascular manifestations. Infection of the respiratory tract, particularly type 2 pneumocytes, leads to the development of pneumonia and ARDS, which promote the progression of systemic inflammation and immune system overreaction, leading to cytokine storm. In addition, systemic inflammation increases oxidative stress, electrolyte imbalance, and systemic endothelial dysfunction, resulting in increased incidence of coagulation abnormalities and dysrhythmias. Direct viral infection and cytokine storm may cause myocyte damage and contribute to the development of myocardial fibrosis and cardiomyopathy (black arrows), which in turn can lead to heart failure and dysrhythmias during post-acute manifestation (blue arrows). High catecholamine levels can cause autonomic dysfunction after viral illness, resulting in postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia (blue arrows). In addition, underlying comorbidities in a patient after recovery from COVID-19 can increase the risk of recurrence of cardiovascular manifestations

endothelial damage and damage to the structural integrity of the myocardium, pericardium, and conduction system due to previous infection, may also take place in the post-acute phase (Fig. 2). Moreover, as observed during long-term evaluation, survivors of SARS-CoV-2 infection have persistently increased cardiometabolic demand [154].
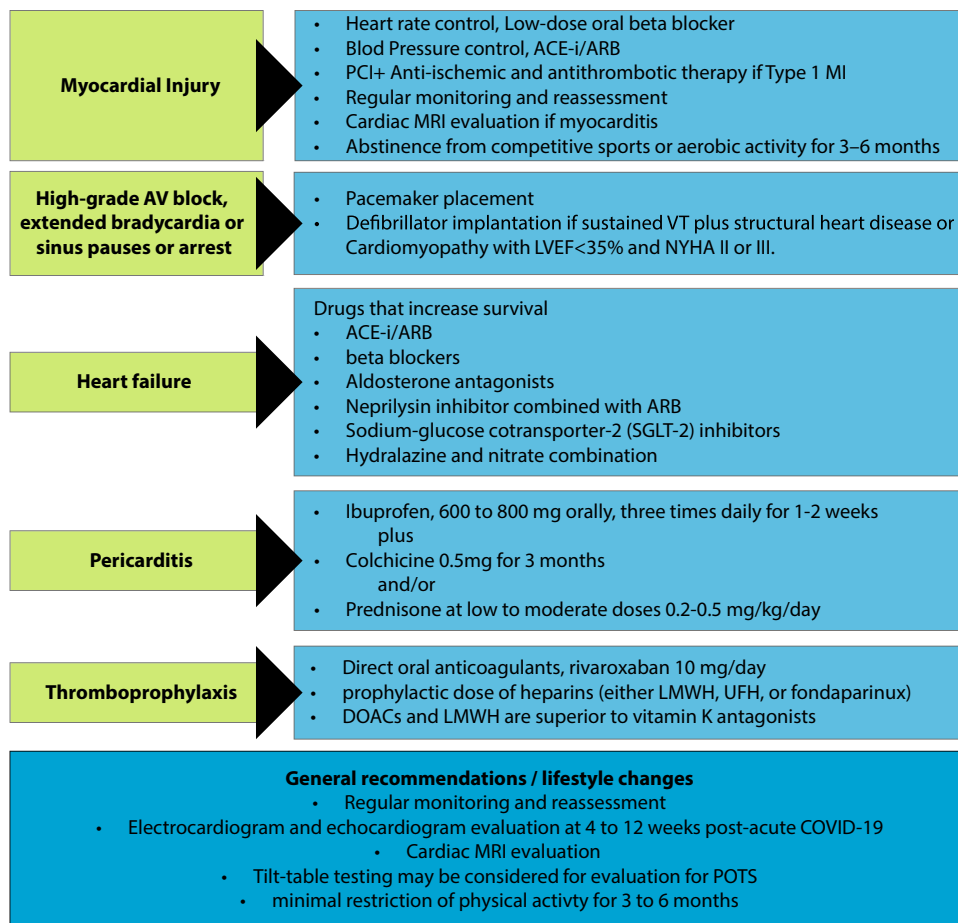
Post-Acute COVID-19 Management

Post-COVID is characterized by a diverse range of symptoms spanning multiple organ systems; therefore, outpatient care of COVID-19 survivors is important and should include multidisciplinary collaboration [155]. Priority should be given to groups of patients at high risk of developing post-COVID conditions; according to the Centers for Disease Control and Prevention CDC, this includes people who have experienced more severe COVID-19 illness, especially those who were hospitalized or needed intensive care; those who experience multisystem inflammatory syndrome (MIS) during or after COVID-19 illness; those who have not received a COVID-19 vaccination; and those who had underlying health conditions prior to SARS-CoV-2 infection. Such health conditions include advanced age, pre-existing respiratory disease, obesity, diabetes, hypertension, chronic CVD, chronic kidney disease, post-organ transplant, and active cancer [153, 156]. Chronic cardiovascular disease was associated with increased hospitalization due to SARS-CoV-2 infection, along with thromboembolic risk, septic shock, and higher mortality [10, 157, 158]. Hypertension, diabetes mellitus, and obesity were common comorbidities in patients with COVID-19, associated with high mortality rates [1, 10, 13, 159–161] and a greater number of long-term post-COVID symptoms [162, 163]. Even in the post-acute period, HF was associated with increased risk of mortality [82]. Despite initial theoretical concerns regarding increased levels of ACE2 and the risk of acute COVID-19 with the use of renin–angiotensin–aldosterone system (RAAS) inhibitors, treatment with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) should be continued by patients with CVD, including treatment for HF and hypertension management [164, 165]. None of these agents affect susceptibility to SARS-CoV-2 infection or increase the risk of severe or fatal illness [166–171]. They have been shown to be safe and should be continued in patients with stable cardiovascular disease [172, 173]. On the contrary, withdrawal from guideline-directed medical therapy was associated with higher mortality in the acute to post-acute phase [174]. Therefore, discontinuation of ACE inhibitors or ARBs is not recommended [175, 176], and indiscriminate withdrawal of these drugs could harm high-risk patients [177].

In patients who are diagnosed with myocardial injury, if necessary, heart rate should be controlled, usually by low-dose oral beta blockers and blood pressure lowering

Fig. 3 Post-acute COVID-19 management and general recommendations/lifestyle changes for cardiovascular manifestations of SARS-CoV-2 infection. PCI: percutaneous coronary intervention; ACE-i/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; MI: myocardial infarction; MRI: magnetic resonance imaging; VT: ventricular tachycardia; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association classification; LMWH: low-molecular-weight heparin; DOACs: direct oral anticoagulants; UFH: unfractionated heparin; POTS: postural orthostatic tachycardia syndrome

Myocardial Injury
- Heart rate control, Low-dose oral beta blocker
- Blod Pressure control, ACE-i/ARB
- PCI+ Anti-ischemic and antithrombotic therapy if Type 1 MI
- Regular monitoring and reassessment
- Cardiac MRI evaluation if myocarditis
- Abstinence from competitive sports or aerobic activity for 3–6 months

High-grade AV block, extended bradycardia or sinus pauses or arrest
- Pacemaker placement
- Defibrillator implantation if sustained VT plus structural heart disease or Cardiomyopathy with LVEF<35% and NYHA II or III.

Heart failure
Drugs that increase survival
- ACE-i/ARB
- beta blockers
- Aldosterone antagonists
- Neprilysin inhibitor combined with ARB
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors
- Hydralazine and nitrate combination

Pericarditis
- Ibuprofen, 600 to 800 mg orally, three times daily for 1-2 weeks plus
- Colchicine 0.5mg for 3 months and/or
- Prednisone at low to moderate doses 0.2-0.5 mg/kg/day

Thromboprophylaxis
- Direct oral anticoagulants, rivaroxaban 10 mg/day
- prophylactic dose of heparins (either LMWH, UFH, or fondaparinux)
- DOACs and LMWH are superior to vitamin K antagonists

General recommendations / lifestyle changes
- Regular monitoring and reassessment
- Electrocardiogram and echocardiogram evaluation at 4 to 12 weeks post-acute COVID-19
- Cardiac MRI evaluation
- Tilt-table testing may be considered for evaluation for POTS
- minimal restriction of physical activty for 3 to 6 months

using ACEi/ARB (Fig. 3). Emphasis should be given to the management of cardiac arrhythmias such as atrial fibrillation. Low-dose oral beta blockers metoprolol or propranolol for heart rate control may be considered; low-dose (20 mg) propranolol was found to significantly attenuate tachycardia and improve symptoms in POTS, while a higher dose did not further improve, and could worsen, symptoms [178]. In addition, tilt-table testing may be considered for evaluation for POTS. Caution should be used for anti-arrhythmic agents such as amiodarone in patients with decreased pulmonary function and/or fibrotic lung disease after COVID-19 [76], since pulmonary toxicity is among the most serious adverse effects of amiodarone [179]. Outpatient follow-up is also indicated in patients who develop high-grade AV block, sinus node dysfunction, junctional bradycardia, sinus pauses, or sinus arrest during COVID-19, as these have been suggested to be poor prognostic signs [180, 181]. These patients have been managed with standard-of-care pacemaker placement [182–184], while implantable defibrillator should be considered in patients with structural heart disease, with spontaneous sustained ventricular tachycardia whether hemodynamically stable or not,

ischemic or non-ischemic cardiomyopathy with LVEF less than 35% and New York Heart Association (NYHA) functional class II or III (Fig. 3). In addition, the choice of drug for patients with pericarditis should be based on the patient medical history. The nonsteroidal anti-inflammatory drug (NSAID) ibuprofen at a dose of 600–800 mg orally, three times daily for 1–2 weeks [94, 185], plus colchicine recommended at low, weight-adjusted doses for a total of 3 months is recommended to improve the response to medical therapy and to prevent recurrence [94, 186]. Corticosteroids should be avoided because they promote recurrence [187]. However, if they simply cannot be avoided and need to be used as an alternative in patients where NSAIDs and colchicine are contraindicated or added to NSAIDs and colchicine as triple therapy for patients with an incomplete response, prednisone is recommended at a low to moderate dose of 0.2–0.5 mg/kg/day or equivalent until resolution of symptoms and normalization of C-reactive protein, and then tapering should be considered (Fig. 3) [188]. Gastroprotection should be provided.

Given the high rates of thrombotic complications in COVID-19 [189] and the high risk for thrombotic events

after discharge, thromboprophylaxis should be considered; however, the indications and duration of anticoagulation therapy are unclear. For patients at high risk who are discharged after hospitalization due to COVID-19, thromboprophylaxis with direct oral anticoagulants (DOACs) should be considered for at least 35 days. In addition, patients with diabetes have an increased platelet reactivity and turnover, resulting in a pro-thrombotic state. Aspirin is recommended in patients with diabetes and CVD (recommendation IIb, level of evidence A). Rivaroxaban at a dose of 10 mg/day for 35 days improved clinical outcomes compared with no extended thromboprophylaxis [190]. As reported in a systematic review and meta-analysis, both prophylactic and full-dose heparins (low-molecular-weight heparin [LMWH], unfractionated heparin [UFH], or fondaparinux) in COVID-19 patients reduced the risk of all-cause mortality (HR = 0.63 [95% CI: 0.57–0.69] and 0.56 [95% CI: 0.47–0.66], respectively). Nevertheless, the full dose was associated with a higher risk of major bleeding (OR = 2.01, 95% CI: 1.14–3.53) compared to prophylactic dose, although there was no difference in overall mortality between the two regimens [191]. DOACs and LMWH are preferred over vitamin K antagonists, since they are patient-friendly, do not require frequent monitoring of therapeutic levels, and have low drug–drug interactions [7, 192]. However, in renal insufficiency, warfarin is preferred over DOACs, with monitoring of the international normalized ratio (INR). The Food and Drug Administration (FDA) recommends the use of rivaroxaban (10 mg daily) for 31–39 days and betrixaban (160 mg on the first day followed by 80 mg once a day) for 35–42 days [193].

Concerning general recommendations, for patients with CVD or who develop cardiac disease during acute infection, regular monitoring and reassessment are recommended [76]. ECG and echocardiographic evaluation at 4 to 12 weeks may be considered for patients during post-acute COVID-19 [9, 194]. Moreover, Holter monitoring should be used as indicated by symptoms, but it may also be reasonable to consider its use in asymptomatic patients, given the risk of a variety of arrhythmias in patients with COVID-19 [76]. Current evidence does not support the routine utilization of advanced cardiac imaging, and this should be considered on a case-by-case basis [153] unless there are abnormal findings on ECG or transthoracic echocardiogram, in which case additional investigation including stress testing or CMR should be performed [76]. In addition, intense, vigorous exercise, weightlifting, and competitive sports or aerobic activity should be avoided for 3–6 months until resolution of myocardial inflammation by CMR, or troponin normalization is recommended for patients with myocarditis due to COVID-19 (Fig. 3) [9, 195].

Conclusion

SARS-CoV-2 infection can degrade a person's quality of life over the long term and increase the risk of cardiovascular complications regardless of age, sex, race, or cardiovascular morbidities [54]. It is now clear that patients with COVID-19 need to continue follow-up and care after hospital discharge using a multifaceted approach. Prioritization should be considered for groups at high risk, including patients who experienced severe COVID-19 illness, those with multisystem inflammatory syndrome during or after COVID-19 illness, older patients (>65 years) and those with underlying comorbidities, respiratory disease, obesity, diabetes, hypertension, chronic cardiovascular disease, chronic kidney disease, post-organ transplant, or active cancer, and people who are not yet vaccinated against COVID-19. Although the risk of SARS-CoV-2 infection or severe disease and/or death and the risk and duration of long COVID-19 symptoms have been reduced in populations with high vaccine uptake [196, 197], there are still individuals who are not yet vaccinated, and these groups remain at great risk. We would like to draw attention to patients receiving ACEi/ARBs as a treatment regimen for HF: under no circumstances should these agents be withdrawn. All hospitalized COVID-19 patients should receive thromboprophylaxis, while decisions regarding post-discharge prophylactic anticoagulation should be individualized. Finally, we suggest that optimal screening guidelines for patients after recovery from COVID-19 should be determined to prevent cardiovascular complications in a vast majority of the population. The careful documentation, investigation, and management of symptoms, and follow-up for cardiovascular complications developing during acute illness, are important.

Declarations

Consent to Publish This is a review article. No consent is required.

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