



# Coronavirus disease 2019 and cardiovascular diseases: collateral damage?

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## Purpose of review

Cardiovascular involvement in coronavirus disease 2019 (COVID-19) is relatively common and portends an increased risk of morbidity and mortality. Manifestations of myocardial injury may exhibit significant overlap and result in diagnostic uncertainty. This review will summarize recent literature around cardiovascular complications of COVID-19.

## Recent findings

Venous thromboembolism, atrial fibrillation, and type II myocardial infarction are observed commonly in COVID-19, while severe acute respiratory syndrome coronavirus 2 viral myocarditis remains quite rare. Although infrequent, COVID-19 vaccination has been associated with myocarditis and pericarditis in young individuals.

## Summary

Various forms of COVID-19-related myocardial injury have been associated with increased utilization of mechanical ventilation, hemodynamic deterioration, and mortality. Manifestations of myocardial injury in COVID-19 are varied, but share common drivers of illness including sequelae of sepsis, immune-mediated factors, and a prothrombotic state. Understanding the forms of myocardial injury in COVID-19 may aid in rapid diagnosis and treatment.

## Keywords

cardiovascular disease, coronavirus disease 2019, myocardial injury

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), the infectious syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) virus, is associated with significant cardiovascular morbidity and mortality. Myocardial involvement defined by elevated serum cardiac biomarkers was estimated near 40% during the early pandemic, and has since been confirmed near 35% in more recent analyses [1,2<sup>a</sup>]. In the United States, COVID-19 exhibits a bimodal age distribution with 20% of patients age 18–29 and 20% age 50–64. However, mortality is significantly skewed toward the elderly in a step-wise fashion [3]. Similarly, patients with myocardial injury are noted to be elderly and more likely to have medical comorbidities, including hypertension, diabetes mellitus, coronary disease, heart failure, chronic kidney disease, and atrial fibrillation [4]. Patients with elevated cardiac troponin are more likely to have adverse outcomes and those with the largest troponin rise are at highest risk [2<sup>a</sup>,5,6]. However, serum troponin remains a non-specific marker of myocardial injury and does not differentiate between various pathophysiologic

mechanisms of myocardial involvement. Significantly, in non-COVID acute respiratory distress syndrome (NC-ARDS), up to 38% of patients will exhibit elevated cardiac biomarkers. Objectively, cardiac injury in COVID-19 is associated with an over two-fold hazard for death. However, after adjusting for age, sex, and multisystem organ dysfunction, the association of myocardial injury with mortality is similar to that seen in NC-ARDS [7]. It is therefore crucial to understand the specific mechanism underlying myocardial injury in each patient, differentiating between direct myocardial injury as a result of COVID-19 infection or exacerbation of existing cardiovascular disease (Fig. 1).

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**KEY POINTS**

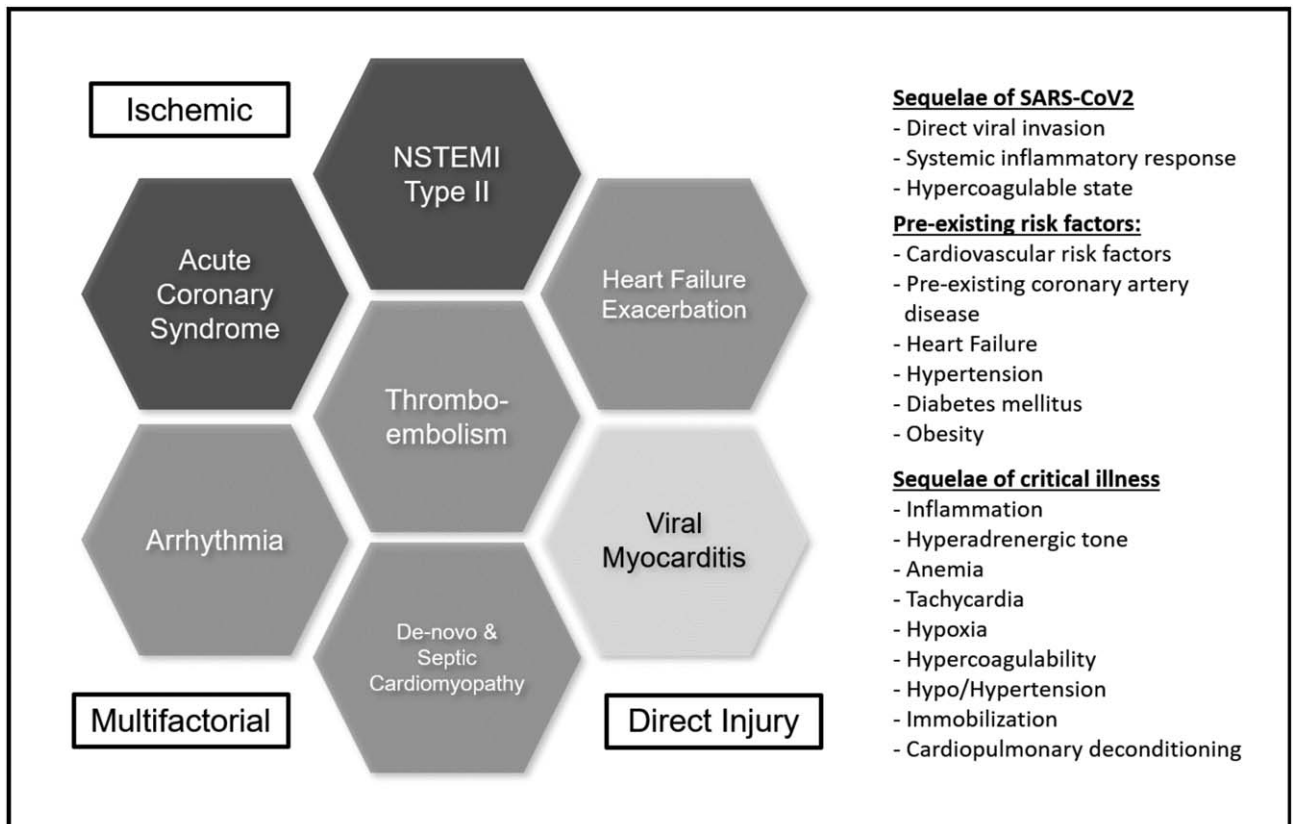
- Manifestations of myocardial involvement in COVID-19 include acute coronary syndromes, de-novo or exacerbation of chronic cardiomyopathies, thromboembolism, tachy and brady-arrhythmias.
- Myocarditis as a result of severe acute respiratory syndrome coronavirus 2 infection is rare.
- Exacerbations of cardiac injury may often be driven by sequelae of critical illness, including tachycardia, hypoxia, hypotension, anemia, fever, and a dysregulated inflammatory response.

**ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME**

Type I myocardial infarction (MI) secondary to plaque rupture has been less frequent during the pandemic. One review from 77 centers demonstrated a clear reduction in the volume of ST elevation MI (STEMI) as well as primary percutaneous coronary intervention (PCI) [8]. This was confirmed in several large-scale studies, showing up to 48.4% reduction in both STEMI and NSTEMI and an increase in STEMI fatality rate [risk ratio 3.3, 95% confidence interval (CI) 1.7–6.6] [9]. Management of STEMI in

the setting of COVID-19 is understandably complex with the added priority to minimize healthcare personnel exposure [10]. Whereas primary PCI is the preferred revascularization strategy, there was liberalized use of fibrinolytic therapy during the pandemic to minimize resource utilization, invasive procedures in critically ill patients, and viral exposure risk to healthcare personnel. On the contrary, COVID-19 patients who present with STEMI exhibit a worse prognosis than those without COVID-19. Retrospective analyses have shown an in-hospital mortality rate as high as 26%, which may be compounded by an increased rate of acute respiratory distress syndrome, fibrinolytic use with associated hemorrhagic complications, and necessity for CPR. During the pandemic, out of hospital cardiac arrest response times were longer, with the percentage of cases with ambulance response at least 6 min increasing from 57% in 2019 to 71% in 2020 ( $P=0.002$ ). There was also a decline in bystander-initiated cardiopulmonary resuscitation (CPR) and survival to hospital discharge (14.7–7.9%,  $P=0.02$ ) [11]. Clearly, the increase in STEMI case fatality is multifactorial, and may also be hindered by socio-economic pressures during the pandemic.

Importantly, it should be stressed that classical ECG criteria for STEMI in COVID-19 may exhibit



**FIGURE 1.** Manifestations of cardiovascular involvement in coronavirus disease 2019.

reduced specificity in the setting of stress cardiomyopathy or myocarditis. Once acute coronary syndrome has been excluded, alternative diagnoses for myocardial involvement must be considered.

Type II MI secondary to supply–demand mismatch is common among patients hospitalized with COVID-19. The true incidence is difficult to quantify but may be more likely to occur in patients with preexisting coronary disease or structural heart disease. Multiple sequelae of COVID-19 infection, including anemia, inflammation, tachycardia, fever, as well as hypotension or hypertension can contribute to the increased incidence of type II MI in these patients. Patients with the greatest degree of troponin elevation have the highest mortality [2<sup>o</sup>].

### EXACERBATION OF PRE-EXISTING HEART FAILURE

An analysis of 38 patients with implantable cardiac devices revealed a decline in average activity levels and an increase in thoracic impedance following the onset of the pandemic, implying an increase in pulmonary congestion [12]. Patients with COVID-19 infection and preexisting heart failure are more likely to be critically ill, with increased rates of ICU utilization, mechanical ventilation, and renal replacement therapy [13<sup>o</sup>]. Adverse outcomes are more pronounced in heart failure patients who are elderly, morbidly obese, and with comorbid diabetes. Importantly, preexisting heart failure represents an independent risk factor for mortality during COVID-19 hospitalization, with an adjusted odds ratio (OR) of 1.88 (95% CI 1.27–2.78). This association persisted regardless of stratification based on left ventricular (LV) ejection fraction [13<sup>o</sup>,14]. These findings are corroborated in international multicenter analyses, where a history of heart failure resulted in an adjusted hazard ratio for death of 2.25 (95% CI 1.26–4.02) even after adjustment for clinical variables related to COVID-19 and heart failure severity, including comorbidities, oxygen saturation, lymphocyte count, and plasma troponin [15].

Multiple mechanisms may contribute to heart failure decompensation during COVID-19. Activation of the sympathetic nervous system, neurohormonal activation leading to volume retention, and inflammation leading to myocardial depression may all play a role. Likewise, an increased cardiac demand as manifested through tachycardia, intravenous fluid administration for the treatment of sepsis, and dexamethasone administration with resultant volume retention may all contribute to pulmonary edema [16]. These patients can present in a hypertensive state, possibly related to increase circulating angiotensin II levels. As such, a high

level of suspicion should be maintained when assessing COVID-19 patients with cardiovascular comorbidities, as the presence of infiltrate and edema on chest imaging are not mutually exclusive, and elevations in serum basic natriuretic peptide (BNP) are common in both disease processes.

### NEW-ONSET CARDIOMYOPATHY AND SEPTIC CARDIOMYOPATHY

Although the majority of heart failure decompensations occur in patients with preexisting cardiomyopathy, de-novo cardiomyopathy has been described in COVID-19 [17]. Out of 550 patients who experienced complications during COVID-19 hospitalization, acute HF occurred in 50 with 4.4% experiencing new-onset heart failure. Importantly, COVID-19 patients with heart failure may present with preserved LV systolic function, so the presence of a normal ejection fraction does not rule out heart failure. Acute right ventricular (RV) failure occurred frequently in patients hospitalized for COVID-19 [15]. Out of 100 hospitalized COVID-19 patients, 39% presented with RV dilation or systolic dysfunction, while 16% exhibited LV diastolic dysfunction [18]. The degree of RV or LV systolic dysfunction as measured by global longitudinal strain are independent predictors of in-hospital mortality in patients with COVID-19 [19].

Reversible myocardial depression in septic shock was described in 1984, and is characterized by a transient, global reduction in myocardial function not explained by ischemia [20]. This reversible form of myocardial dysfunction typically resolves within 7–10 days, and may be more frequent in patients with a prior history of heart failure [21]. Sepsis may also trigger stress-induced cardiomyopathy. Drivers of myocardial injury include inflammatory cytokines and oxygen demand/supply imbalance [22]. This entity may be difficult to separate from type 2 MI when LV wall motion abnormalities are present.

### MYOCARDITIS

Myocarditis is commonly suspected in COVID-19 patients with elevated cardiac biomarkers, and has been described in numerous case reports. Electrocardiographic findings can include ST elevation and there may be regional or global wall motion abnormalities on echocardiography. Elevated biomarkers with a negative coronary angiogram should significantly increase the level of suspicion for myocarditis and prompt further work-up. However, there are few reports of histopathologic confirmation of viral invasion of the myocardium [23,24]. Pathologic analyses of COVID-19 patients with elevated serum

troponin values most commonly demonstrate diffuse macrophage infiltration (88%), followed by evidence of RV strain (19%), focal pericarditis (19%), small vessel thrombi (19%), and endocardial thrombosis (14%) [25]. Histologic evidence for myocarditis has been described at an incidence of 4.5–14% [26]. Notably, a systematic review of 277 cardiac autopsy reports from 22 studies demonstrated 20 reports of myocarditis. Further review of these cases cast doubt on 16 of these diagnoses, estimating the true myocarditis rate at less than 2% [27<sup>■</sup>]. The prevalence is significantly lower (1.4%) in healthy athletes screened by cardiac MRI [28].

Although clinically confirmed myocarditis as defined by the Dallas criteria remains quite rare in SARS-CoV2 infection, it should be noted that myocarditis has been observed following mRNA vaccination. In the Vaccine Adverse Events Reports System, myocarditis rates were significantly higher in youths between the ages of 13–23 ( $P < 0.0001$ ) with ~80% occurring in males. Within 8 weeks of offering COVID-19 vaccines to individuals 12–15 years of age, there were 19 times the expected number of myocarditis cases, with more occurring following the second dose [29<sup>■</sup>]. In over 2 million individuals who received at least one dose of the COVID-19 vaccine, there were 20 cases of myocarditis and 37 cases of isolated pericarditis. Myocarditis and pericarditis occurred at a median of 3.5 and 20 days following most recent immunization, respectively [30]. COVID-19 vaccination remains a critical tool in decreasing the morbidity, mortality, and disease impact during the ongoing pandemic. A heightened level of suspicion is warranted in younger patients presenting with cardiovascular symptoms following vaccination.

## THROMBOSIS

COVID-19 predisposes patients to thrombosis through all three aspects of Virchow's triad. SARS-CoV2 infection may trigger endothelial dysfunction through direct invasion of vascular endothelial cells or through indirect mechanisms including hypoxia and an induced inflammatory response [31]. Immobilization during illness contributes to venous stasis. Infection has been associated with increased levels of fibrinogen, factors V, VII, VIII, X, and von Willebrand Factors [32,33]. Antiphospholipid antibodies have been identified in some patients [34].

Importantly, major arterial and venous thromboembolic events (VTE) occur at a higher frequency over 30 days in COVID-19 ICU patients despite a 85–90% thromboprophylaxis rate [35]. A recent systematic review and meta-analysis places the overall incidence of VTE among COVID-19 inpatients at

17.3% (95% CI 13.4–20.9), with approximately two-thirds of events being deep venous thromboembolism (DVT). Higher rates were noted with inclusion of catheter-associated thromboembolism, isolated distal DVT, and isolated subsegmental pulmonary emboli. The pooled incidence of VTE was 7.1% for patients admitted to the general wards and 27.9% for those admitted to the ICU. Significantly, studies which utilized routine screening for VTE demonstrated a combined incidence of 3.1%, compared to 9.8% for those who included patients diagnosed clinically, highlighting that many subclinical VTEs in COVID-19 patients may be undiagnosed in clinical practice [36].

Despite a clearly increased risk of thromboembolism in COVID-19, a strategy of prophylactic therapeutic-dose anticoagulation in critically ill patients has not been associated with improved outcomes. Results from the REMAP-CAP, ACTIV-4a, and ATTAC trial platforms demonstrated similar survival to hospital discharge between patients randomized to therapeutic dose anticoagulation and those assigned to usual-care thromboprophylaxis (62.7 and 64.5% respectively, adjusted OR 0.84, 95% CI 0.64–1.11). Major bleeding was observed more frequently with full-dose anticoagulation (3.8 vs. 2.3%) [37<sup>■</sup>]. As such, the most recent American Society of Hematology guidelines recommend use of prophylactic-intensity over intermediate-intensity anticoagulation in patients with COVID-19 related critical illness who do not have suspected or confirmed VTE [38<sup>■</sup>].

## ARRHYTHMIAS

When considering that hypertension, inflammation, autonomic nervous tone, and volume overload all contribute to atrial fibrillation in the general population, it is unsurprising that atrial arrhythmias are common in COVID-19 [39–41]. Arrhythmias have been seen more commonly in elderly patients with higher levels of C-reactive protein and D-dimer but not increasing levels of BNP or troponin. In the setting of vasopressor use in critically ill patients, new-onset atrial fibrillation has been observed to precede hemodynamic deterioration [42]. A multicenter analysis of 171 consecutive patients suggested that both new-onset and preexisting atrial fibrillation are strongly associated with the need for mechanical ventilation and increased mortality in COVID-19 infection. It is unclear whether atrial fibrillation represents a marker of severe illness in this setting or represents a contributing factor to decompensation, since patients with atrial fibrillation who expired had worse markers of disease severity (higher levels of ferritin, lactate dehydrogenase and troponin) [43].

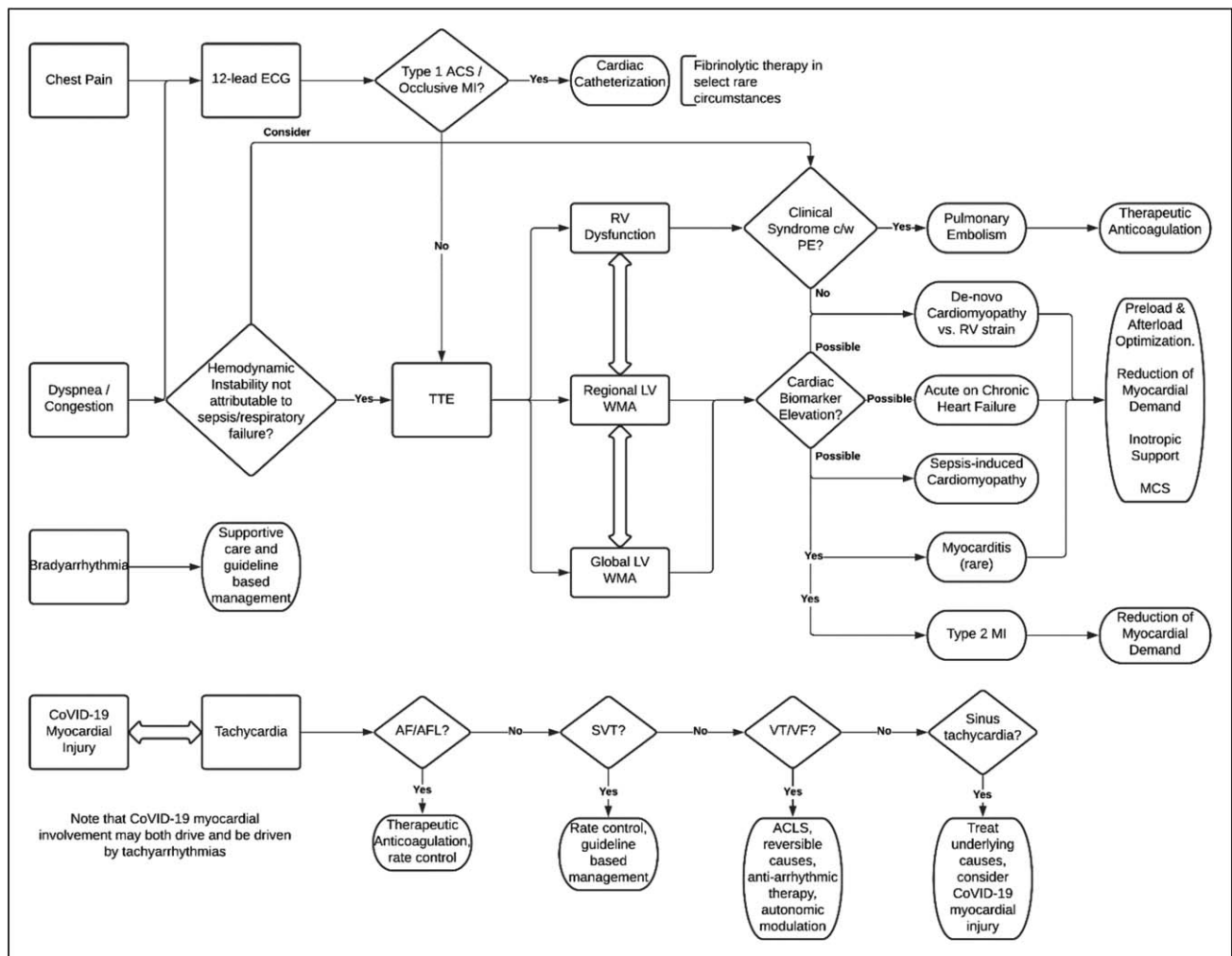


In the largest retrospective analysis of cardiac arrhythmias during COVID-19, the majority of studied patients did not have a preexisting history of arrhythmia. Out of 4526 patients, approximately 18.3% (827 patients) developed arrhythmias. The vast majority of these were supraventricular in origin (81.8%), followed by bradyarrhythmias (22.6%) and ventricular arrhythmias (20.7%).

Among patients with ventricular tachycardia, an equal distribution of patients experienced monomorphic and polymorphic morphology. Regardless, ventricular arrhythmia was associated with significant mortality, with 38% of these patients surviving to hospital discharge. Patients with ventricular arrhythmias were 1.3× more likely to be mechanically ventilated and had 1.4× mortality than patients with atrial or bradyarrhythmias. However, among those patients who died, ventricular

arrhythmias were recorded in only 2.4% of patients at the time of death, with 23.7% of analyzed patients having nonshockable rhythms, including bradycardia, pulseless electrical activity, or asystole.

In the same study, bradyarrhythmias developed in 172 patients, with sinus bradycardia, atrioventricular block, or sinus pauses more than 3 s occurred in 12.8, 8.6, and 1.2% of patients, respectively. Bradyarrhythmias were more likely to be observed in centers in Asia, while atrial fibrillation was less common [44]. There has been some recognition that elderly COVID-19 patients may have an impaired heart rate response to fever [45]. Relative bradycardia, defined as heart rate less than 90bpm and concomitant fever, was observed in 40 out of 110 retrospectively reviewed patients in Switzerland. These patients were significantly older (median age 62 vs. 49 years) and presented with significantly



**FIGURE 2.** A simplified clinical heuristic framework for the assessment of myocardial involvement in coronavirus disease 2019.

higher maximum temperatures (median temperature 39.3 vs. 38.7 °C) compared with patients with fever and an appropriate heart rate response [46]. A retrospective analysis from Japan demonstrated similar findings, where the predicted change in pulse rate was 7.37 bpm for each 1 °C increase in body temperature, as opposed to the expected rise of 18 bpm [47]. These findings have yet to be reproduced in large-scale studies, and the effect that antipyretic administration may have had on results is unclear. Several mechanisms of relative bradycardia have been suggested, including a cytokine-driven increase in vagal tone and decrease in heart rate variability, direct viral toxicity to autonomic heart rate control, and direct or indirect virally mediated sinus node dysfunction. Ultimately, it is clear that the development of cardiac arrhythmias may represent a manifestation of critical illness, metabolic derangement, and sympathetic dysregulation during severe COVID-19. Treatment of these comorbidities should not differ significantly than in any other form of sepsis.

## CONCLUSION

The manifestations of myocardial injury in COVID-19 are varied but share common characteristics. COVID-19 pneumonia induced hypoxia, tachycardia, hypotension, and hypertension, coupled with immune-thrombotic and inflammatory upregulation predisposes to venous and arterial thromboembolism, acute coronary syndrome, heart failure decompensation, de-novo depressions in LV and RV function, and arrhythmias. Venous thromboembolism, atrial fibrillation, and type II MI are observed quite commonly in COVID-19 illness. Direct myocardial invasion of cardiomyocytes and SARS-CoV2 myocarditis remains exceedingly rare. Although the majority of cardiovascular manifestations of COVID-19 may represent ‘collateral damage’, they are clearly associated with heightened morbidity and mortality. Recognition of myocardial injury, prompt diagnosis and treatment are crucial (Fig. 2).

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Twitter Handles: @AjayPMD, @b\_law16.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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