Review Article

Interventional Cardiology

Cardiac involvement and outcomes in patients with COVID-19 infection

Antonio Vacca[1], Stefano Marcante[1], Sebastiano Cicco[2], Luca Bulfone[1], Laura Scandolin[1], Sabrina Vidoni[1], Gabriele Brosolo[1], Cristiana Catena[1], Leonardo A. Sechi[1*]

[1]Department of Medicine, Clinica Medica, University of Udine, 33100, Udine, Italy

[2]Department of Biomedical Sciences and Human Oncology (DIMO), Unit of Internal Medicine and Clinical Oncology, University of Bari Aldo Moro Medical School, Bari, Italy

*Author for correspondence:
Leonardo A. Sechi, Department of Medicine, Clinica Medica, University of Udine, 33100, Udine, Italy, E-mail: sechi@uniud.it

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Abstract

Cardiac involvement can be a prominent feature in patients hospitalized with SARS-CoV-2 infection and is associated with a greater risk of death. Moreover, clear evidence indicates that outcomes of COVID-19 infection are closely related with pre-existing cardiovascular conditions. A broad spectrum of clinical manifestations has been described during SARS-CoV-2 infection and multiple mechanisms could be involved in the pathogenesis of cardiac involvement including hypoxia, direct viral injury, cytokine storm, generalized endothelitis, and sympathetic activation. Biochemical and instrumental testing including cardiac imaging studies have been performed in these patients reporting different types of cardiac dysfunction. In this narrative review we overview the clinical spectrum of cardiac involvement with the related short-term outcomes of COVID-19 infection and the biochemical and instrumental findings that could be part of the diagnostic workup that might allow timely therapeutic interventions.

Keywords: Sudden cardiac death • Biomarkers; Echocardiography • Electrocardiography • Magnetic resonance imaging • SARS-CoV-2 • Short-term outcome

Introduction

Since its recognition in December 2019, the Coronavirus Disease 2019 (COVID-19) has rapidly spread globally causing a pandemic and representing a public health emergency of international concern [1]. COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that predominantly infects the lungs, causing interstitial pneumonia and severe Acute Respiratory Distress Syndrome (ARDS) [2]. Cardiovascular implications of infection, however, could be particularly relevant and are closely related to disease severity and progression [3].

SARS-CoV-2 Spike (S) protein binds to Angiotensin-Converting Enzyme II (ACE2) expressed on surface of pulmonary cells thereby explaining viral tropism for the lung. The S1 subunit of S protein binds to the cell surface receptor while the S2 subunit mediates the fusion between the viral and cellular membranes. This process requires S protein priming by host cell proteases which entails S protein cleavage at the boundary of S1 and S2 proteins or within the S2 subunit [4]. SARS-CoV-2 uses Transmembrane Serine Protease 2 (TMPRSS2) and the endosomal cysteine proteases cathepsin B and L (CatB/L) for S protein priming [5]. After SARS-CoV-2 infection, the related condition may occur with different severity, ranging from asymptomatic to fatal disease. The most common presentation in severely ill patients is bilateral interstitial pneumonia with moderate to severe oxygen desaturation and hypoxia [6]. In this context, lung damage may begin with "silent hypoxia" [7] subsequently worsening to a severe respiratory failure [8]. Severely ill patients may

develop Respiratory Failure (RF) and Acute Respiratory Distress Syndrome (ARDS), requiring prompt admission to Intensive Care Units (ICU). While pulmonary impairment is the most evident clinical manifestation of COVID-19 infection, other organs can be involved as a consequence of diffuse endothelitis [9].In fact, hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, hormonal, neurologic, ocular, and cutaneous involvements have been reported in patients with COVID-19 infection [9,10].

Cardiovascular involvement can be a prominent feature in COVID-19 infection and is associated with a worse prognosis [3,11] with higher death rate [12]. Furthermore, clinical data indicate that the susceptibility to SARS-CoV-2 infection and outcomes of COVID-19 are closely associated with pre-existing cardiovascular diseases [11,13]. On one hand, cardiac injury could indirectly result from a systemic inflammatory response causing an unrestrainable cytokine storm [14]. Systemic inflammation increases shear stress in the coronary arteries due to increased coronary blood flow and this mechanism could lead to plaque rupture resulting in acute myocardial infarction. In addition, systemic inflammation promotes a prothrombotic status, inducing an additional risk for cardiovascular events [15]. On the other hand, because viral localization was detected in the heart [16], SARS-CoV-2 might directly act on cardiomyocytes and coronary vessels [17] prompting hypoxia and myocardial changes. Hypoxia due to acute respiratory illness and increased cardiometabolic demand can impair the myocardial oxygen demand-supply balance resulting in acute myocardial injury (Figure 1). All these mechanisms might be more impactful in subjects with preexisting cardiovascular conditions. In fact, observational studies conducted by the Italian Society of Hypertension in thousands of hospitalized patients with COVID-19 infection have clearly demonstrated that presence of cardiovascular risk factors predicts ICU admission [18] and death [19], and that absence of cardiovascular comorbidities is associated with more frequent healing [20]. This narrative review summarizes the clinical spectrum of cardiac manifestations that have been reported in patients hospitalized with COVID-19 infection with the related outcomes, outlines the mechanisms that potentially contribute to cardiac damage in these patients, and examines the biochemical and instrumental findings that might be part of a diagnostic workup aimed at providing prompt supportive care.

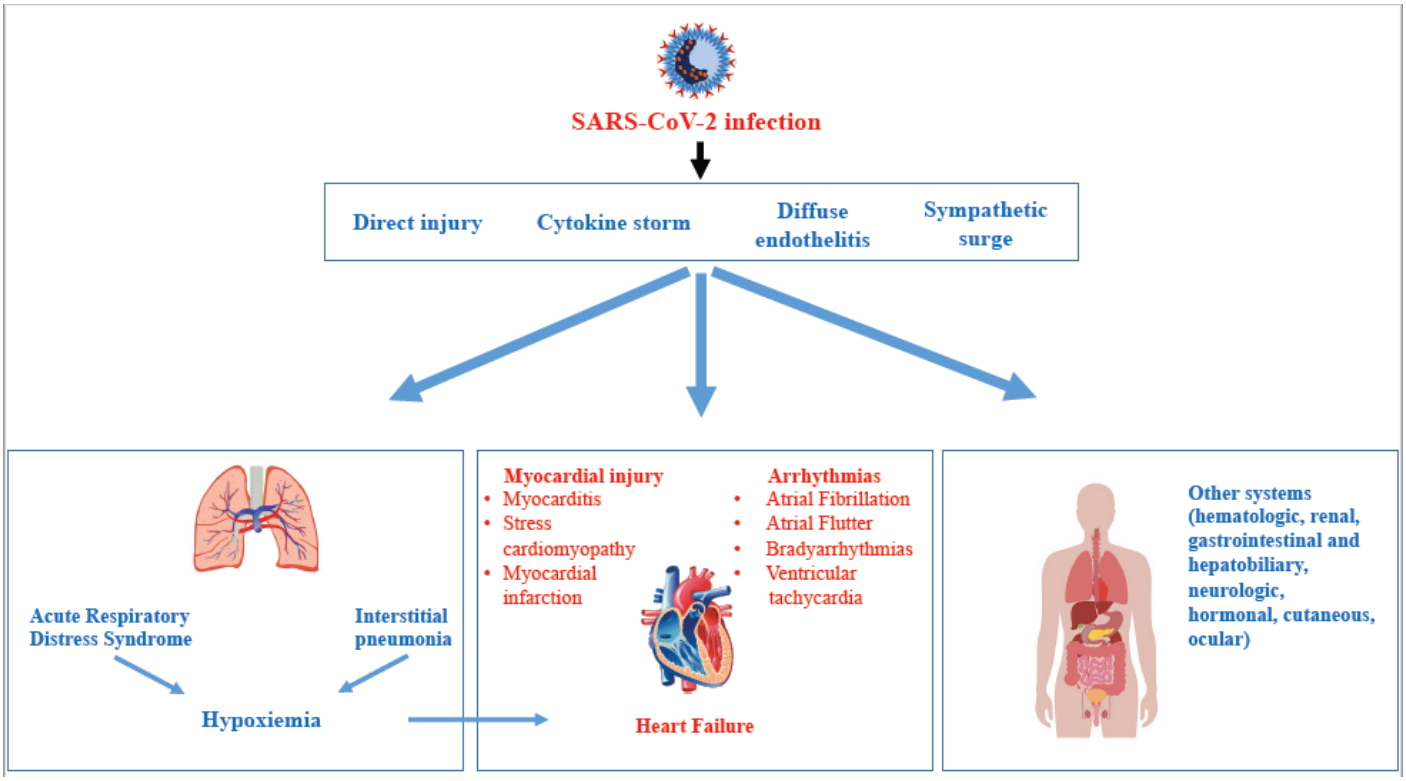

Figure 1: Mechanisms involved in the pathogenesis of pulmonary and cardiac damage during SARS-CoV-2 infection and involvement of additional organ systems.

The Clinical Spectrum

Cardiac involvement in COVID-19 infection is heterogeneous, ranging from right heart overload due to pulmonary embolism to myocarditis with heart failure, acute coronary syndromes, and sustained arrhythmias with cardiac arrest. Most of these complications occur within the first two weeks from presentation [21].

Myocardial injury

In patients with COVID-19 infection prevalence of myocardial injury, as defined by elevation of troponin levels during SARS-CoV-2 infection, ranges from 10% to 46% [22]. Clinical conditions associated with myocardial injury are myocarditis, stress cardiomyopathy, and acute myocardial infarction. Pathogenesis is multifactorial and it relates to imbalance of oxygen supply-demand, direct viral myocardial invasion, inflammation, coronary plaque rupture, microvascular thrombosis and adrenergic stress [23]. In a study by Guo, et al. 28% of 187 hospitalized patients with COVID-19 infection who had elevated troponin T exhibited activated inflammatory biomarkers including leukocytosis, lymphocytopenia, C-reactive protein, pro-calcitonin and D-dimer, suggesting that myocardial injury was likely related to myocarditis due to viral infection [24]. Occurrence of malignant tachyarrhythmias in the setting of troponin elevation could also rise the suspicion of underlying myocarditis [25]. Similarly to ARDS, fulminant myocarditis could result from SARS-CoV-2-related changes in ACE2 with accumulation of angiotensin II [26], although the massive systemic cytokine storm is surely involved [14,27].

Stress-induced cardiomyopathy has also been associated with COVID-19 infection [28], but mechanisms are not fully understood. Three leading factors that have been reported in SARS-CoV-2 infection should be considered in this context, including an overactive immune response, increased activity of the sympathetic nervous system, and presence of microvascular dysfunction [29].

Last, Acute Myocardial Infarction (AMI) has been associated with SARS-CoV-2 infection and patients with S-T Elevation Myocardial Infarction (STEMI) and concomitant COVID-19 have increased in-hospital mortality [30]. Because of increased myocardial oxygen consumption and decreased oxygen supply, coronary involvement during COVID-19 infection could lead to type 2 AMI, whereas type 1 AMI that is associated with thrombotic coronary occlusion is less frequent [31]. In this context, SARS-CoV-2 damages endothelial cells causing activation of the hemostatic cascade and complement system, thereby leading to coronary thrombus formation.

Myocardial injury has emerged also as a rare side effect of RNA vaccines against COVID-19. Retrospective data of myocarditis in vaccinated persons were detected by two groups of investigators in Israeli population after receipt of the BNT162b2 mRNA vaccine (Pfizer-BioNTech) [32,33]. These two studies had an important limitation in the lack of endomyocardial biopsy and therefore diagnosis of myocarditis could be only suspected. Also and most important, in both studies patients had favorable outcome with a benign course of disease.

Arrhythmia

Arrhythmias are common in patients with COVID-19 infection. Myocardial hypoxia, metabolic abnormalities and neurohormonal and inflammatory activation could explain occurrence of arrhythmia in patients with or without prior cardiovascular disease [34]. Wang, et al. reported 16.7% incidence of arrhythmia in an outcome study of 138 Chinese patients with COVID-19 [11]. In this study, arrhythmia required transfer to an ICU in 44% of patients. In a meta-analysis of 19 observational studies including 21653 hospitalized patients with COVID-19, prevalence of Atrial Fibrillation (AF) was 15% among Europeans and 11% among Americans [35]. In patients with severe COVID-19 prevalence of AF was 6-fold that of patients with milder disease. Many additional observational studies have reported elevated incidence of all sort of arrhythmias in patients hospitalized with COVID-19 [36,37].

Heart failure

Acutely Decompensated Heart Failure (ADHF) is a frequent complication of COVID-19 infection and is associated with a higher risk of death in the short-term. In a systematic review and meta-analysis, Zuin, et al. found that about one out of five patients develops ADHF as a complication of SARS-CoV-2 infection [38]. Consistently, in a follow-up study of 3080 patients with COVID-19, an elevated incidence of ADHF was reported [39]. In this study, patients with previous history of chronic heart failure (HF, n=153%) were more prone to develop ADHF, whereas among 77 patients (2.5%) who were diagnosed with new onset HF the majority (78%) had no previous history of disease.

Multiple mechanisms could contribute to cause HF in patients with COVID-19 infection and many important triggers including myocardial ischemia, sympathetic activation, renal impairment with volume overload, increased metabolic demand and thrombotic activity could prime worsening of cardiac function [40]. SARS-CoV-2 infection leads to formation of viral inclusions with subsequent attraction of inflammatory cells [41] and subsequent release of cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α),

Monocyte Chemoattractant Protein-1 (MCP-1), and many others. These cytokines increase the tissue levels of Matrix Metalloproteinases (MMPs), Protease-Activated Receptor (PAR) and Nitric Oxide Synthase (NOS) thereby causing severe oxidative stress, cardiomyocyte apoptosis, and tissue edema. Concomitant inflammatory changes in the lung stimulate further recruitment of pro-inflammatory cells initiating a vicious cycle [42].

Involvement of the right heart has also been demonstrated in many studies conducted in hospitalized patients with COVID-19 infection [43]. Right HF or dysfunction can occur in subjects with pre-existing diseases (i.e. chronic obstructive pulmonary disease, obstructive sleep apnea, pulmonary hypertension) or as a new onset condition in critically ill patients [44-46]. Acute right HF caused by acute pulmonary hypertension associated with acute pulmonary embolism (acute cor pulmonale) or Adult Respiratory Distress Syndrome (ARDS) has been reported in patients with COVID-19 infection [47,48]. In a retrospective study of 870 hospitalized patients with COVID-19 infection, 17% had Left Ventricular (LV) dysfunction (LV ejection fraction <50%) and 29% had Right Ventricular (RV) dysfunction (RV free wall strain >20%) [49]. In a study of 120 COVID-19 patients, those who died had higher pulmonary artery systolic pressure, dilated right heart chambers, and impaired RV function as compared to survivors [50]. To underline the relevance of right ventricular involvement in COVID-19, a multivariate analysis reported that RV dilatation was the only cardiac factor significantly associated with mortality [51].

Laboratory Tests and Cardiac Imaging

Cardiac involvement is associated with an increased risk of death in patients with COVID-19 infection. This is why timely detection of heart damage is important for a better care of these patients. In this view, assessment of cardiac biomarkers and use of cardiac imaging should be appropriately included in the diagnostic workup of COVID-19 (Table 1).

Table 1: Proposed algorithm for assessment of cardiac complications in patients hospitalized with COVID-19 infection.

Clinical manifestation	What to do	What to look for
Myocarditis	Biomarkers	Increase in TnI, CRP, BNP/NT-proBNP, IL-6, serum ferritin
	ECG	Changes S-T tract/T wave
	Echocardiography	Ventricular wall motion changes
	MRI	Myocardial edema, wall motion changes, T1/T2 weighed signal changes, LGE
Ischemia	Biomarkers	Increase in TnI
	ECG	Changes S-T tract/T wave, Q wave
	Echocardiography	Ventricular wall motion changes
	Angiography	Coronary thrombosis
Arrhythmia/Atrial fibrillation	ECG	Characterization of arrhythmia
	Echocardiography	Cardiac valves function
	Holter ECG	Characterization of arrhythmia
Heart failure	Biomarkers	Increase in TnI and BNP/NT-proBNP
	Echocardiography	Changes in systolic/diastolic function

Abbreviations: BNP: Brain Natriuretic Peptide; CRP: C-Reactive Protein; ECG: Electrocardiogram; IL-6: Interleukin-6; LGE: Late Gadolinium Enhancement; MRI: Magnetic Resonance Imaging; NT-proBNP: N-Terminal fragment of pro-Brain Natriuretic Peptide; TnI: Troponin I.

Biomarkers

Because of the cardiac involvement of SARS-CoV-2 infection and its relevance for patients' prognosis, early monitoring of cardiac damage and inflammatory status with use of biomarkers in hospitalized patients has been recommended. This approach could have specific relevance in patients with COVID-19 infection and preexisting cardiovascular conditions [52]. Increased circulating levels of troponins and brain-type natriuretic peptide demonstrate cardiac involvement in many patients with COVID-19 infection [24] and elevated levels of C-Reactive Protein (CRP) suggest occurrence of inflammation [53]. In a retrospective multicenter cohort study of 191 patients with COVID-19 infection, patients who died had higher levels of troponins and inflammatory biomarkers than survivors and these levels were associated with higher rates of HF. Similarly, in another smaller retrospective study COVID-19 patients who died had higher levels of troponin, myoglobin, CRP, IL-6 and serum ferritin than survivors [3].

Electrocardiography

Abnormal ECG tracings have been reported in many patients with COVID-19 and troponin elevation. In a retrospective study of 756 COVID-19 patients, premature atrial beats were found in 7.7%, premature ventricular beats in 3.4%, AF or atrial flutter in 5.6%, right bundle branch block in 7.8%, left bundle branch block in 1.5%, and abnormalities of repolarization in more than 40% [54]. In a much larger study, Musikantow, et al. reported incidence of AF of 10% in patients with COVID-19 infection without previous history of atrial arrhythmias. Incidence of AF was comparable to that of patients with influenza infection, suggesting that atrial arrhythmia is not specific to COVID-19 but might be associated to disease severity [55]. Another retrospective analysis of ECG data of COVID-19 patients demonstrated that right bundle branch block and poor R wave progression assessed upon in-

hospital admission are associated with worse clinical course [56].

Echocardiography

Early assessment of cardiac function in patients with COVID-19 infection could be easily performed with use of Transthoracic Echocardiography (TTE). TTE is a first-line imaging modality for assessment, and it is an essential bedside tool, allowing non-invasive quantification of cardiac structure and function in patients hospitalized in isolated wards [57]. Initial studies conducted in patients who were hospitalized for COVID-19 infection reported greater left and right ventricular dimensions, reduced LV ejection fraction, and more frequent pericardial effusion in patients with severe disease [58]. In a prospective international survey of 1216 patients with COVID-19 infection, echocardiographic abnormalities were found in 55% of patients, mostly related to LV (39%) and RV (33%) abnormalities, AMI (3%), myocarditis (3%), and Takotsubo cardiomyopathy (2%) [59]. In this study, however, 74% of patients had preexisting cardiac disease and severe cardiac functional impairment was detected in less than 15% of patients. These data suggest that clinically relevant cardiac involvement is relatively unusual in patients with COVID-19 infection, mostly occurring in patients with severe disease and very often related to pre-existing cardiac abnormalities.

Because the fatality rate of COVID-19 is relatively low, most patients survive infection leaving open a question about its possible cardiac sequelae. In a short-term follow-up study, patients who had been hospitalized with COVID-19 were compared to controls who were matched for demographics and comorbidities [60]. No considerable structural or functional differences with controls were found in the heart of survivors of COVID-19 infection, nor differences were observed between COVID-19 patients who recovered from mild/moderate or severe disease. Separate follow-up analysis with comparison of COVID-19 survivors with or without prior biochemical evidence of cardiac injury (increased troponin) did not show structural or functional cardiac differences [61].These echocardiographic data suggest that patients who recover from COVID-19 infection do not have considerable cardiac sequelae.

Magnetic resonance imaging

Cardiac Magnetic Resonance Imaging (MRI) has received little attention during the COVID-19 pandemic due to the infectious risk of these patients and long duration of image acquisition. This is why data obtained with cardiac MRI during the acute phase of COVID-19 infection are limited to single case reports, and most of the literature focuses on the post-recovery phase. Ojha, et al. analyzed data of 34 studies including 199 patients with COVID-19 infection and reported cardiac MRI changes indicative of myocarditis in 40% [62]. The findings of this study, however, are limited by the high heterogeneity of patients in terms of comorbidity and severity of disease. Two cross-sectional cardiac MRI studies have investigated the heart of patients with COVID-19 infection in the early recovery phase. In a first study, cardiac MRI was performed in 100 patients a mean of 71 days after diagnosis, reporting increased LV volumes and reduced LV ejection fraction, associated with evidence of ongoing myocardial inflammation in comparison to controls [63]. Another study reported on cardiac MRI of 26 young athletes 4 of whom had imaging data suggestive of myocarditis and 8 of possible prior myocardial injury [64]. It is important to notice that the majority of patients included in these two studies were not hospitalized and were asymptomatic or only mildly symptomatic, suggesting that their clinical conditions were not severe. This observation raises an important question on what could be the meaning, in terms of clinical relevance, of the cardiac MRI changes that were observed in these patients.

Another cardiac MRI study by Kotecha, et al. reported evidence of myocardial injury in patients with prior severe COVID-19 infection associated with troponin elevation [65]. After a median of 68 days from diagnosis, three different patterns of injury were observed: myocarditis-like scars in 26% of patients, infarction/ischemia in 22%, and mixed pattern in 6%. Data of cardiac MRI obtained in COVID-19 survivors have been recently examined in a systematic analysis of 16 observational studies that included 2954 patients [66]. In this analysis, detection of cardiac MRI abnormalities was extremely variable: from 0% to 73% of patients had raised T1-weighed images, from 2% to 60% had raised T2-weighed images, and myocardial/pericardial Late Gadolinium Enhancement (LGE) ranged from 4% to 100%. This analysis highlights the striking heterogeneity of cardiac MRI findings in patients who recover from SARS-CoV-2 infection, once again raising an important question about the functional relevance of these MRI changes. Notably, this systematic analysis did not include any clinical information on patients with COVID-19 infection, further limiting the possibility to attribute any clinical meaning to the cardiac MRI findings obtained in this context.

Discussion

Cardiac involvement during COVID-19 infection might be considered as part of disease, in particular in those patients with severe infection who develop systemic inflammatory response. When it is present, cardiac damage occurs just after lung involvement and is associated with an increased risk of death. As outlined in this narrative article, cardiac involvement is highly heterogeneous ranging from inflammatory myocarditis with left HF, acute

coronary syndromes, and sustained arrhythmias to right HF due to pulmonary embolism. Most of these complications follow lung involvement and occur a few days after presentation. This is why early detection of cardiac involvement during the acute phase of COVID-19 infection would be extremely important for a better care. Timely assessment of cardiac biomarkers and appropriate use of imaging techniques that can be readily applied to patients with COVID-19 infection become fundamental to identify those patients who have developed or are at risk of developing cardiac complications. Measurement of troponins, brain-type natriuretic peptide, CRP and other proinflammatory molecules and cytokines would provide important information. Similarly, repeated ECG registration and use of bedside TTE should be integral part of the diagnostic workup of patients with COVID-19 infection in order to appropriately establish cardiac supportive care when needed.

There is now considerable interest in the characterization of residual/persistent cardiac damage in survivors of COVID-19 infection. This is because cardiac abnormalities may persist after clearance of SARS-CoV-2 infection, or even arise in a chronic stage of disease. Therefore assessment of cardiac structure and function in patients with COVID-19 infection who recover from acute disease would be of great relevance. Many studies have addressed this issue in the short and long-term after acute COVID-19 infection. Studies conducted with TTE indicate that patients who recover from COVID-19 infection do not have significant structural or functional cardiac involvement. This is true even when patients with biochemical evidence of cardiac injury detected during the acute phase of infection are examined. Conversely, a highly heterogeneous picture has been reported with use of cardiac MRI, and findings obtained with this technique in cumulative analyses are extremely variable. This raises some important questions about the functional/clinical relevance of the MRI changes that have been detected in survivors of COVID-19 infection. This issue needs to be further investigated in appropriately designed MRI studies that collect detailed information on the clinical status of patients. Thus, with a few exceptions, available evidence would suggest that patients who recover from COVID-19 do not have considerable cardiac sequelae and meet a favorable outcome.

Conclusion

In conclusion, current knowledge on the involvement of the heart during SARS-CoV-2 infection, both in the acute phase and after recovery, has to be considered just preliminary. In the future, more extensive and well organized studies will help to gain better understanding of this important aspect of this infection that has represented an unprecedented challenge for the entire healthcare community.

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