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COVID-19, Acute Myocardial Injury, and Infarction

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KEYWORDS

• COVID-19 • Myocardial injury • Myocardial infarction • SARS-CoV-2

KEY POINTS

- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) primarily infects the respiratory tract but can broadly affect the cardiovascular system too.
- SARS-CoV-2 can damage the myocardium by direct viral invasion or indirectly through inflammation, endothelial activation, and microvascular thrombosis.
- Myocardial injury affects about one-quarter of patients with COVID-19, even those without prior cardiovascular disease.
- Patients with COVID-19 who experience myocardial injury have higher hospital mortality rates and can present long-term complications.
- The diagnosis of myocardial injury can be particularly challenging in the context of COVID-19, particularly in patients with advanced disease.

INTRODUCTION

The new coronavirus-associated disease 2019 (COVID-19), due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), represents an unprecedented public health emergency that has been accompanied by a global health crisis. Although SARS-CoV-2 primarily infects the respiratory system, causing a variety of clinical presentations, from asymptomatic infection to interstitial pneumonia and severe acute respiratory distress syndrome (ARDS), the cardiovascular implications are also significant, especially in their contribution to disease morbidity and mortality.

When the cardiovascular system is affected, complications can include myocardial injury, acute myocardial infarction (MI), heart failure, myocarditis, dysrhythmias, and venous thromboembolic events.[1] Although various studies have demonstrated an association between preexisting

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cardiovascular disease and severe COVID-19 manifestations, it is possible that the viral infection itself may lead to cardiac complications or exacerbate preexisting cardiovascular conditions.[2,3]

Acute myocardial injury is not uncommon in patients with COVID-19 and correlates with disease severity.[4] In addition, patients with long-term coronary artery disease or risk factors for atherosclerotic disease are at heightened risk of acute coronary syndromes (ACS) if infected with SARS-CoV-2. Acute coronary events in patients with COVID-19 may be the result of the systemic inflammatory hyperactivity, triggered by the viral infection and mediated by circulating cytokines that interact with preexisting atherosclerotic plaques, potentially causing plaque instability and rupture, ultimately leading to a type 1 MI.[5] In patients who eventually overcome myocardial injury and SARS-CoV-2 infection, there is evidence of long-term cardiovascular complications, although the magnitude of these sequelae is still unclear.

PHYSIOPATHOLOGICAL INVOLVEMENT OF THE CARDIOVASCULAR SYSTEM

SARS-CoV-2 primarily infects cells in the respiratory tract, causing a wide spectrum of respiratory manifestations, from asymptomatic or mild infection to bilateral interstitial pneumonia and severe ARDS.[1] There is also evidence supporting the affinity of the virus for multiple tissues, suggesting that SARS-CoV-2 has an organotropism that extends beyond the respiratory system, involving the brain, the liver, the kidney, and the cardiovascular district.[6] When the cardiovascular system is affected a vast range of complications can occur, from myocardial injury and acute MI to heart failure, myocarditis, dysrhythmias, and venous thromboembolic events.[1]

Previously published reports have described increased incidence of myocardial injury among patients with COVID-19.[7] During SARS-COV-2 infection the myocardium may be damaged by the viral invasion of cardiac muscle cells, inflammation and production of free radicals and reactive oxygen species, microvascular thrombosis, and a disproportion between oxygen supply and demand.[8] As a result, myocardial dysfunction, heart failure, myocardial injury, and both type 1 and type 2 MI may manifest, mediated by these one or more of these underlying mechanisms. Cardiac tissue tropism of SARS-CoV-2 is supported by the findings of an autopsy series of 20 patients: detectable viral SARS-CoV genome was found in 7 of the 20 heart samples, along with increased myocardial fibrosis and inflammation.[9]

Direct viral invasion is not the only mechanism through which SARS-CoV-2 can damage the heart. A particularly interesting interaction has been described between SARS-CoV-2 and the renin angiotensin system (RAS).[10] The main hypothesis is that the RAS may be involved in the pathophysiology of COVID-19 via activation of the classic pathway. The angiotensin-converting enzyme 2 (ACE2) serves as a master regulator of the RAS. By metabolizing the vasoconstricting and proinflammatory angiotensin II (Ang II), ACE2 generates Ang 1 to 7, which counteracts the proinflammatory and prooxidant effects of Ang II.[11] Molecular studies have demonstrated that ACE2 is the SARS-CoV-2 cell entry receptor, through the activation of the viral outer membrane spike protein S by transmembrane protease serine 2 (TMPRSS2).[12] SARS-CoV-2 uses ACE2 as the port of entry by binding the extracellular domain of the host receptor through the S1/s2 subunits of the transmembrane spike glycoprotein.[13,14] Once a cell becomes infected with SARS-CoV-2, ACE2 is internalized, the virus can enter the cell and release its RNA to initiate replication and transcription of the viral genome. After synthesis and assembly of structural proteins, new virus is released from the cell by exocytosis, whereas host cells may be disabled or destroyed in the process.[15] Beyond causing direct cell damage through viral infiltration, SARS-CoV-2 downregulates ACE 2 expression and Ang 1 to 7 production, leading to the loss of the RAS counterregulatory protective arm.[16] By hampering the expression of ACE2, the beneficial degradation of Ang II to the counterregulatory $Ang^{1–7}$ decreases, leading to unopposed Ang II effects, mediated by the receptor AT1. The AngII/AT1 activation yields several unfavorable effects, which include vasoconstrictive effects, but also host potentially detrimental effects on the endothelium, inflammation, and coagulation, ultimately increasing vascular permeability and promoting organ damage (**Fig. 1**).[17,18] These findings are supported by the fact that COVID-19 patients often present with increased AngII levels.[19,20] ACE2 is widely expressed in the lung but can also be found in high concentrations in the circulatory system at the level of arterial and venous endothelium as well as largely expressed by myocardial pericytes.[21,22]

Cardiovascular damage mediated by SARS-CoV-2 may therefore be the result of 3 different pathways:

- Direct myocardial damage due to viral entry through ACE2, resulting in myocardial cell destruction and inflammation;
- Indirect injury due to ACE2 downregulation following viral replication, with subsequent hyperactivation of the Ang II/AT1 system, responsible of vasoconstrictive, proinflammatory, and prooxidant effects

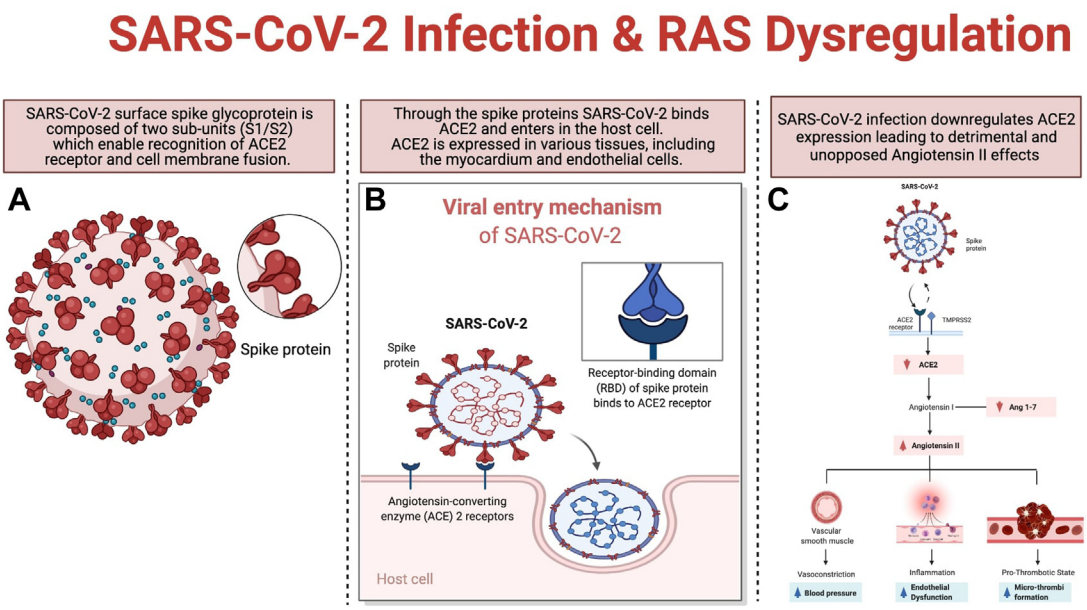

Fig. 1. SARS-CoV-2 entry in host cells (*A*, *B*) and downregulation of ACE2 expression (*C*).

- Indirect injury through the activation of B and T immune cells, leading to a systemic inflammatory response and increased cardiac stress due to hypoxemia.[23,24]

The immune-mediated pathway can generate a cytokine storm with high circulating levels of interleukin-2 (IL-2), IL-7, IL-10, and tumor necrosis factor, as a result of alternate immune response. This mechanism has been observed in severe forms of COVID-19 and can mediate myocardial injury as well as lung injury (particularly diffuse alveolar damage), finally leading to multiorgan failure. Components of the systemic inflammatory response can exert a negative inotropic effect, promote cardiomyocyte apoptosis and fibrosis, and induce the release of procoagulant factors.[25] The high plasma levels of activated macrophages that usually accompany conditions of hypercytokinemia can lead to further release of cytokines, including IL-1β and IL-6, which promote the expression of adhesion molecules, inflammatory cell infiltration, and vascular inflammation, contributing to formation and propagation of microcirculatory lesions and endothelial dysfunction.[26] Macrophages can also release procoagulant factors, further accelerating inflammation and augmenting a prothrombotic condition and thrombotic microangiopathy.[27] High circulating levels of macrophages might also interact with preexisting atherosclerotic plaques, leading to rupture of the fibrous cap and possibly causing type 1 MI.[28] These pathways are not unique to SARS-CoV-2, as viral infections are known to determine adverse cardiovascular events by precipitating plaque rupture in the setting of inflammation and a prothrombotic state.[29] It is also possible that hyperinflammation may generate a supply-demand mismatch at the level of the myocardium. SARS-CoV-2 infection can therefore precipitate myocardial injury by determining an oxygen supply–demand imbalance, either with or without acute coronary plaque pathology (type 1 and 2 MI).

SARS-CoV-2 can attack the cardiovascular system through different strategies: through direct damage of myocytes mediated by the virus as well as indirect mechanisms due to RAS pathway dysregulation, hyperinflammation leading to endothelial disfunction in different districts, and activation of procoagulant factors with microvascular thrombosis and oxygen supply–demand imbalance (**Fig. 2**). These mechanisms can take place in the presence of preexisting cardiovascular conditions or in patients without a clinical history of cardiovascular disease (CVD). Nonetheless, individuals with cardiovascular comorbidities or diabetes are at greater risk of experiencing a more aggressive SARS-CoV2 infection and the related cardiovascular complications.[30]

PREVALENCE AND CLINICAL OUTCOME OF MYOCARDIAL INJURY IN COVID-19

The detection of least one elevated cardiac troponin value greater than the 99th percentile upper reference limit defines myocardial injury. Although MI represents a manifestation of

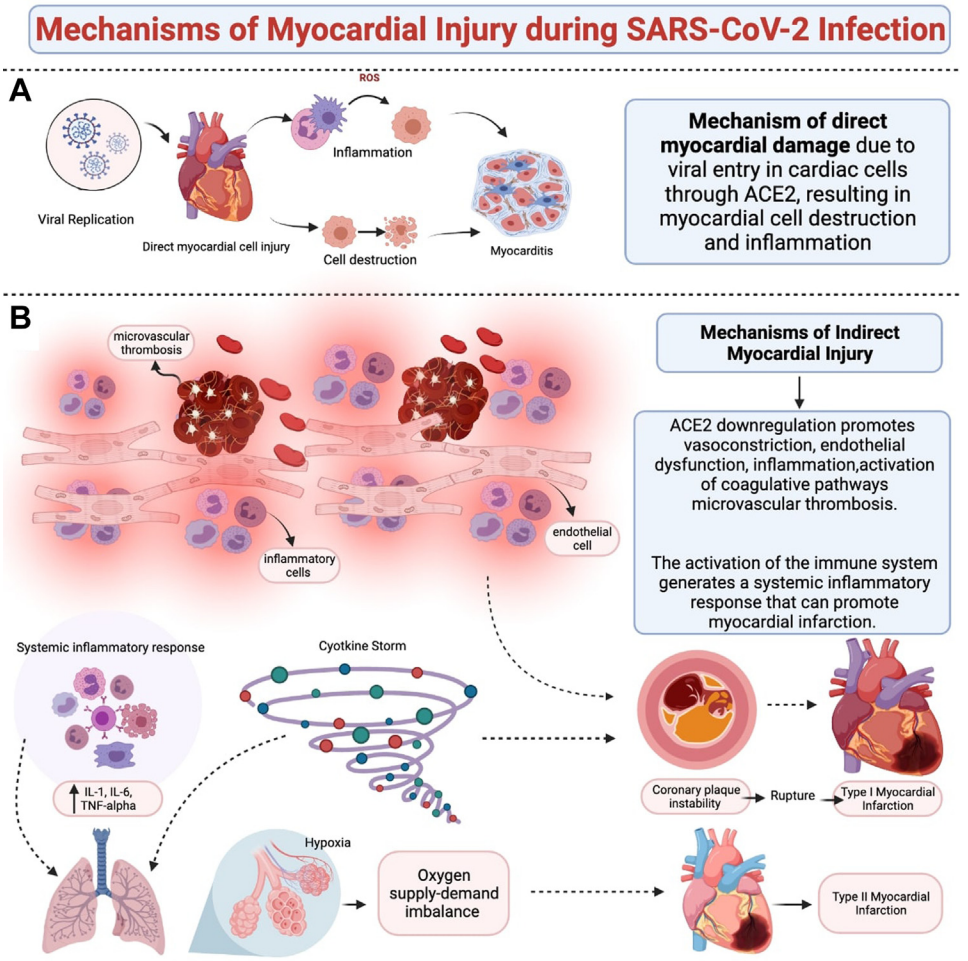

Fig. 2. Direct (*A*) and indirect (*B*) mechanisms of acute myocardial injury during SARS-CoV-2 infection and clinical outcomes.

myocardial injury, it requires clinical evidence of acute myocardial ischemia in order to perform the diagnosis. There are various subtypes of MI, the most common being type 1 infarction (characterized by plaque rupture, ulceration, erosion, or dissection resulting in coronary thrombosis) and type 2 infarction (secondary to myocardial oxygen supply–demand mismatch in the absence of coronary thrombosis).[31] Individuals infected with SARS-CoV-2 seem to be in a condition of increased susceptibility to various forms of myocardial injury.[32]

A study conducted in Wuhan showed evidence of cardiac damage with high levels of circulating troponin in up to 28% of patients with SARS-CoV-2. Furthermore, patients with evidence of cardiac injury had higher mortality rates compared with those without (51.2% vs 4.55%, $P < 0.001$). Complications such as acute respiratory syndrome distress, electrolyte alteration, and acute kidney injury were prevalent in patients with cardiac injury, suggesting how the cardiac involvement plays a detrimental effect in the prognosis of these patients[33]

A recently published review, composed of 26 studies including a total of 11,685 patients, estimated a lower prevalence of acute myocardial injury among SARS-CoV-2–infected patients, with around 20% showing evidence of myocardial injury (detected through the sample of troponin and/or creatine-kinase MB). In discussing the physiopathological mechanisms, the investigators also suggest a possible clinical role of cardiac biomarkers in the risk stratification of COVID-19.[34,35]

A systematic review published in 2021 estimated the rate of new cardiac injury between 7.2% and 77%, respectively, in live and dead SARS-CoV-2–infected cases, reiterating the concept that cardiac injury is associated to worse outcomes and higher rates of mortality,

predominantly driven by development of shock and malignant arrythmias. In fact, about 46.3% of patients with cardiac injury required mechanical ventilation, 58.5% experienced acute respiratory distress syndrome, and 15.9% suffered from electrolyte disturbance. In addition, the levels of troponin I seemed to be inversely correlated with the days of survival.[36]

In a multicenter retrospective cohort study including 2736 patients, 36% were found to have elevated troponin concentration. Even small increases in troponin I levels (ranging from 0.03 to 0.09 ng/mL), found in the 16% of the entire cohort of patients, were significantly associated with the death of the patients (adjusted hazard ratio: 1.75; 95% confidence interval [CI]: 1.37–2.24; $P < .001$). Patients with evidence of more robust damage to the myocardium may experience more than a 3-fold increase in the risk of mortality. Patients with preexisting CVD are more likely to experience myocardial injury compared with those without.[37]

PRINCIPAL IMAGING FINDINGS IN PATIENTS WITH COVID-19 WITH MYOCARDIAL INJURY

The clinical presentation of myocardial injury in patients with COVID-19 is usually atypical and therefore hard to diagnose. The cause of the increase in troponin levels in patients with COVID-19 has not been clearly defined. Cardiac damage can arise in patients with no previous history of CVD and in the absence of chest pain. Diagnosing pathologies such as myocarditis in patients with COVID-19 and increased levels of troponin is quite challenging, given the scarcity of studies that correlate the evidence from imaging techniques such as cardiac MRI or invasive methods such as endomyocardial biopsy to the clinical and echocardiographic findings in these patients. In addition, the latency between the onset of symptoms and the evidence of myocardial injury (about 14 days) raises doubts as to whether myocyte damage can be considered only as a marker of advanced disease severity or if it directly implies a greater risk of COVID-19 mortality.[8,38–40] A recent study evaluating a total of 201 patients with COVID-19 with critical and noncritical clinical conditions and with myocardial injury, detected through an elevation of CK-MB and troponin I levels, reported 18.7% of cases showing evidence of echocardiographic abnormalities. The main abnormalities were right ventricular dilatation and dysfunction (prevalent in critical patients). The investigators were able to highlight the direct contribution of COVID-19 to the myocardial injury of these patients. In addition, 43.7% of patients had new changes at electrocardiography and 36.3% had signs of ST depression.[41]

Cardiac MRI (CMR) represents the hallmark of the morphologic definition and classification of myocardial tissue pathology, especially in patients with myocardial edema. In a systematic review by Ojha and colleagues including 199 patients from 34 studies, myocarditis was the most common diagnosis at cardiac MRI in patients with evidence of myocardial injury (40.2% of cases). Mapping abnormalities, edema, and late gadolinium enhancement (LGE) represented the most frequently detected myocardial findings.[42] In a prospective observational trial by Puntmann and colleagues including 100 recently recovered COVID-19 cases, abnormal findings at CMR were found in 78% of patients, of which 60% showed ongoing myocardial inflammation with an increased native T2 (in a minority of cases regional scar and pericardial enhancement were detected), regardless of preexisting conditions and COVID-19 severity, raising concerns on the long-term consequences of SARS-CoV-2.[43] Most of the patients experienced only mild forms of illness.[43]

The prevalence of cardiac damage at CMR was quite lower in another recent multicenter trial involving 148 cases of severe COVID-19 recruited from 6 different facilities and with laboratory evidence of troponin elevation. The trial evaluated patients after discharge through CMR. The CMR protocol included adenosine stress perfusion (where clinically appropriate) and was performed at a median of 68 days postdischarge. Twenty-six percent of CMRs showed evidence of a myocarditis-like scar, 22% of infarction or ischemia, and 6% characterized by combination of both. Most of the myocarditis-like lesions involved 3 or less segments and was not accompanied by left ventricular dysfunction, although 30% of these patients had active myocarditis. Stress perfusion revealed inducible ischemia in 26% of cases and myocardial infarction findings in 19%. These findings suggest how even after discharge the rate of cardiac injury remains high. About a quarter of all patients included in the trial experienced ischemic heart disease (in the absence of previous CVD history in two-thirds of cases).[44] The discrepancy in prevalence of cardiac abnormalities at CMR that emerges from the 2 previously cited studies can be explained by differences in the selection of study participants and in the definition of myocardial injury and inflammation using isolated or combined CMR parameters and, in addition, by the different latency periods between the acute phase of COVID-19 and the timing of CMR. Moreover, abnormal T1 sequences and LGE may overdiagnose myocardial

inflammation if used alone. The studies did not investigate the possibility of underlying and silent pathologic cardiac conditions not directly related to COVID-19. Several limitations affected these studies, including the absence of a description of patients' symptoms and their correlation to imaging findings.[45] A recent literature review examining 277 patients with COVID-19 undergoing autopsy showed that the true prevalence of myocarditis was lower than 2%. Cardiovascular histopathologic findings potentially related to COVID-19 infections were found in the 47.8% of cases. The findings included myocardial microvascular thrombi, inflammation, or intraluminal megakaryocytes The investigators specified that the wide differences in histology reports found in the studies may be a marker of observer bias.[46] There are several ongoing studies with larger sample sizes, an accurate standard protocol of imaging assessment, and longer follow-up periods that aim to explore the mid- and long-term cardiac sequelae following COVID-19 and identify factors that could significantly affect the outcomes of these patients.

MYOCARDIAL INFARCTION TYPE 1, 2, AND 3

This paragraph explores the challenges in the management of the different types of MI and the possible overlap of acute pathologies (whether myocardial, pulmonary, or systemic) that further nuance the diagnosis.[47,48]

The largest study investigating COVID-19 and acute cardiovascular events is a Swedish study involving 86,742 patients diagnosed with COVID-19 and a matched population of controls (348,481 patients). The investigators calculated the incidence rate ratio (IRR) of acute MI following COVID-19. The IRR was calculated in 2 separate analyses: including the day of exposure to SARS-CoV-2 (day 0) and excluding day 0. Excluding day 0 from the analysis led to the estimation of the IRR of acute MI of 2.89 (95% CI 1.51–5.55) in the first week of infection and 2.53 (95% CI 1.29–4.94), and 1.60 (95% CI 0.84–3.04), respectively, in the second week and in the third and fourth weeks. The inclusion of day 0 in the analysis resulted in a significant increase in the IRR during the first week (IRR 8.44; 95% CI 5.45–13.08) followed by comparable rate ratios in the remaining weeks. The analysis that excludes the day of viral exposure ensures potential elimination of testing bias because there is a possibility of a higher likelihood of detecting even asymptomatic forms of SARS-COV-2 in patients who are admitted to the hospital for MI or ischemic stroke. On the other hand, the exclusion of the day of viral exposure may lead to an underestimation of the true risk of cardiovascular events.[49] These results seem to clash with the significant reduction in hospital admission rates for acute ischemic cardiovascular events (both acute coronary syndromes and ischemic strokes) that has been described during the initial phases of the pandemic.[50,51] A possible explanation of this discrepancy is that particularly during the first wave of the pandemic several patients experiencing ACS and acute ischemic stroke did not seek timely medical attention for fear of exposure to SARS-CoV-2 at the hospital or to respect measures of physical distancing. Another possible explanation is related to the clinical instability of patients with COVID-19 and the rapid deterioration of the conditions of patients with severe forms, preventing a complete diagnostic evaluation.[49,52]

There are also certain characteristics of patients hospitalized for STEMI and affected by COVID-19 that have been recently described in the literature and that raise concern among providers. Specifically, a study including a nationwide registry of 1010 consecutive patients treated within 42 specific STEMI care networks investigated the clinical, procedural, and in-hospital prognostic features of COVID-19 patients affected by STEMI. This population showed a significant increase in stent thrombosis (3.3% vs 0.8%, $P = .020$), cardiogenic shock (9.9% vs 3.8%, $P = .007$), and in-hospital mortality compared with non-COVID-19 STEMI patients (23.1% vs 5.7%, $P < .0001$).[53]

A single-center observational study of 115 consecutive patients with STEMI managed by primary percutaneous coronary intervention (PCI) showed a higher thrombus burden and higher rates of multivessel thrombosis (17.9% vs 0%, $P = .003$) and stent thrombosis (10.3% vs 1.2%, $P = .04$) in patients with COVID-19 compared with non-COVID patients. Although the thrombolysis in MI flow and thrombus grade were similar in the 2 groups, the modified thrombus grade after first device resulted higher in patients with COVID-STEMI (75% vs 31%; $P = 1⁄4$ 0.0006). Of these cases of COVID-STEMI a high percentage (about 60% vs 9.2% $P = .002$) received a Gp IIb/IIIa and underwent thrombectomy (17.9% vs 1.3%) when compared with non-COVID patients. The patients in the COVID-19 group had higher proportions of hypertension, diabetes, dyslipidemia, and previous PCI. The myocardial blush grade (MBG) resulted significantly lower in the COVID-STEMI (MBG of 2–3 in 54% vs 93%, $P < .0001$); the postprocedural median left ventricular ejection fraction resulted lower in COVID-STEMI patients (42.5% vs 45.0%; $P = .019$) as well as higher peak plasma troponin levels. The higher thrombus burden found in the COVID-STEMI group may represent a requirement

for a more aggressive antithrombotic therapy in selected cases, although the actual evidence supporting this conduct is still poor.[54]

Data investigating ACS and COVID-19 remain conflictual, and the association is still uncertain. A systematic review and meta-analysis including 50,123 patients from 10 studies revealed a nonstatistically significant difference in admission rates of patients with STEMI during the pandemic compared with the previous year (IRR = 0.789, 95% CI 0.730–0.852 P = .01) and no increases in mortality for STEMI patients treated during the pandemic (odds ratio [OR] = 1.178, 95% CI 0.926–1.498, P = .01). What emerged from this review is that door-to-balloon time was significantly prolonged in STEMIs treated during the pandemic. Although these results harbor uncertainty regarding the impact of the pandemic on STEMI admission rates or mortality, they shed light on the organizational strain that facilities faced in the midst of the pandemic response.[55]

Diagnosis and management in patients with type 2 MI and COVID-19 are challenging, with repercussions on time to coronary angiographic evaluation. Inaccurate diagnosis of type 1 MI instead of type 2 and difficulties with differential diagnosis between MI and myocarditis might lead to an overestimation of acute MI. In a study by Stefanini and colleagues conducted on 28 patients with a diagnosis of STEMI that were promptly referred to the catheterization laboratory for urgent coronary angiography, 60.7% had a culprit lesion requiring urgent percutaneous treatment, whereas 39.3% did not show any signs of coronary obstructive lesion at angiography.[56]

Unfortunately the investigators did not investigate if the clinical presentation was attributable to a type 2 MI or to myocarditis or to SARS-CoV-2–related endothelial dysfunction. It is reasonable to hypothesize that a type 2 MI due to demand ischemia might be much more common in patients experiencing COVID-19. The condition of systemic inflammation triggered by viral infections, such as coronavirus and influenza virus,[57] may lead to oxygen supply–demand mismatch in the myocardium. It is also critical to highlight that it is clinically challenging to perform a correct differential diagnosis between non-STEMI ACS from other conditions that imply a form of myocardial injury such as hypoxemia, arrhythmias, sepsis, or myocarditis. To further complicate the matter, it is possible that these conditions may overlap, particularly in complex patients experiencing severe COVID-19. Sudden cardiac deaths or unexplained deaths have been reported in patients with SARS-CoV-2 infection and a previously diagnosed coronary artery disease. In this subset of patients it is possible to speculate a type 3 MI as the cause of the demise.[58–60]

The Takotsubo syndrome (TTS) is another cardiomyopathy that may determine myocardial injury in patients with COVID-19. TTS consists in a transient acute myocardial dysfunction, often characterized by circumferential myocardial regional akinesia/hypokinesia, leading to clinical acute heart failure, and in some cases mimicking an acute MI. Although the definite physiopathology of TTS has not yet been totally clarified, it is known that the sympathetic stimulation (ie, catecholamine-induced microvascular impairment) driven by sudden stress represents a trigger, and other evidences suggest how ongoing inflammation, infections, and other clinical conditions such as respiratory failure may be involved in the etiology.[61]

A case series of 118 consecutive patients with COVID-19 undergoing transthoracic evaluation found ultrasound features of TTS in 4.2%. These patients also had higher level of plasmatic troponin compared with patients without TTS myocardial injury and high rates of in-hospital complications and mortality.[62] These findings are in line with the findings of other investigators who reported high rates of severe respiratory and cardiac insufficiency eventually leading to greater oxygen requirements, use of vasopressors, and cardiac ventricular support devices in patients with TTS myocardial injury associated with COVID-19.[63–65]

The available evidence on COVID-19 and myocardial injury highlights the necessity to perform an accurate evaluation of the troponin elevation (ie, of the myocardial injury), the patients' clinical features, and an appropriate risk stratification. Direct invasive testing should be reserved for patients with a high pretest probability of coronary artery disease (CAD), whereas computed tomography scan or CMR is the appropriate test for patients with an intermediate probability of CAD, in order to evaluate either epicardial arteries or coronary arteries and rule out myocarditis. Patients with a low risk of CAD should be referred to strict follow-up.

Patients with COVID-19 that in addition experience an STEMI or very high-risk NSTEMI should be referred to the catheterization laboratory within the timeframe suggested by the current guidelines. Fibrinolysis should be considered only in case of difficulties in patients' transfer to a hub center in order to perform timely PCIs.[66,67]

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Although COVID-19 usually represents a mild entity among children, with approximately 2% to 6% requiring intensive care, the infection should

not be underestimated in the pediatric population.[68] A multisystem inflammatory syndrome (MIS-C) caused by SARS-CoV-2 has been reported among the pediatric population from several countries. MIS-C can lead to a large spectrum of symptoms that mimic a Kawasaki-like disease. Clinical manifestations range from persistent pyrexia to polymorphic rash, conjunctivitis, mucosal abnormalities, and myocardial involvement (including acute myocardial dysfunction, arrythmias, and acute pericarditis).[68]

Once again the cytokine storm plays a role in the pathogenesis of MIS-C. The condition of hyperinflammation can generate multiple consequences within the cardiac district. In severe cases there have been reports of coronary artery dilatation and aneurysm (8%–24% of patients), which may be due to the state of hyperinflammation with disruption of the arterial wall, as seen in Kawasaki disease (KD).[69]

Other clinical features described in children affected by MIS-C are acute myocardial dysfunction, hypotension requiring fluid resuscitation, and, in some cases, cardiogenic shock requiring cardiac inotropic support, mechanical ventilation, and extracorporeal membrane oxygenation.[69]

A key clinical difference between MIS-C and KD is represented by the fact that ventricular dysfunction and eventually shock are common presentations in MIS-C (50% of cases) and occur less frequently in children with KD (5%–10%).[69]

Recent evidence suggests that the administration of immunomodulatory drugs during the acute phase of the illness, such as intravenous immunoglobulins and steroids, may reverse the dysregulated inflammatory response yielding to recovery within days or a few weeks. Anticoagulation therapy is also suggested in the pediatric patients presenting with severe ventricular dysfunction and in case of evidence of giant coronary aneurysm.[69]

Although MIS-C is associated to low mortality, nothing is known of its mid- and long-term sequelae.

SUMMARY

Based on the current literature on myocardial injury during COVID-19, it is possible to conclude that this association is not uncommon. Myocardial injury can be considered as a concerning complication of SARS-CoV-2 infection, which can eventually lead to a large spectrum of myocardial pathologies (ie, myocarditis, myocardial infarction, Takotsubo syndrome) through the interaction between the virus and myocardial and endothelial cells, mediated by direct viral invasion or indirect mechanisms such as the downregulation of ACE2 receptor expression. Immune-mediated overresponse, cytokine storm, and activation of prothrombotic pathways are further mechanisms of myocardial damage that contribute to the various forms of myocardial injury that have been described.[22,23,70]

Although a trend of reduction in the number of hospital admissions for MI has been described, particularly during the first wave of pandemic, it is necessary to interpret these findings with caution and to consider the weight of other factors such as patient's reluctance to seek medical attention due to fear of in-hospital SARS-CoV-2 exposure or the strain on the organizational capacity of facilities in building the response to the pandemic.[49,52,71]

The direct impact of acute myocardial injury on the mortality of patients with COVID-19 has been described, whereas there is also evidence of long-term sequelae of myocardial injury (both inflammatory and ischemic) that are particularly concerning in older patients and in patients with cardiovascular comorbidities.[72]

There is therefore a pressing need to continue investigating these new and complex clinical entities in order to understand how to treat and manage these patients. It is possible to hypothesize the need for dedicated protocols that involve a strict cardiovascular follow-up through both clinical and sequential imaging evaluation, based on the patients' comorbidities and overall risk stratification.

CLINICS CARE POINTS

- Myocardial injury during COVID-19 can manifest through a large spectrum of pathologies (myocarditis, myocardial infarction, Takostubo Syndrome and MIS-C).
- Cardiac damage during SARS-CoV-2 infection can arise in patients with no previous hystory of heart disease or in the absence of symptoms and is therefore challenging to diagnose.
- There is evidence of long-term effects in patients affected by myocardial injury during SARS-CoV-2 infection, although the impact and reversibility of these sequelae is still not fully understood.
- Patients that experience myocardial injury during COVID-19 should undergo regular follow-up through clinical and imaging evaluation and dedicated protocols should be designed, based on their individual risk.

CONFLICT OF INTEREST

All the authors report no conflict of interest.

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