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ROLE OF TROPONIN IN PATIENTS WITH COVID 19; POSSIBILE MECHANISMS

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ABSTRACT

Acute SARS-CoV-2 respiratory disease is an infectious respiratory disease caused by the virus SARS-CoV-2 belonging to the coronaviridae family. A pandemic is still present as of May 2020. In addition to causing pneumonia, SARS-CoV-2 may induce a direct damage to the heart, causing myocarditis, with significant impairment of cardiac contractility, and/or pericarditis. Elderly patients and those with cardiovascular risk factors, such as hypertension and diabetes mellitus, are at increased risk of heart complications from COVID-19. In this review, we focused on the correlation between COVID-19 infection and the high sensitivity troponin T and I, and their significance in the development of myocarditis. Data emerging from the studies so far conducted indicate that a high value of high-sensitivity troponin represents a negative prognostic indicator when associated with heart damage on an infectious-inflammatory basis (i.e. myopericarditis). We should identify a safe and clear diagnostic algorithm, possibly combining patient clinical history, troponin levels and cardiac ultrasound findings that could help us in the prediction of myopericarditis.

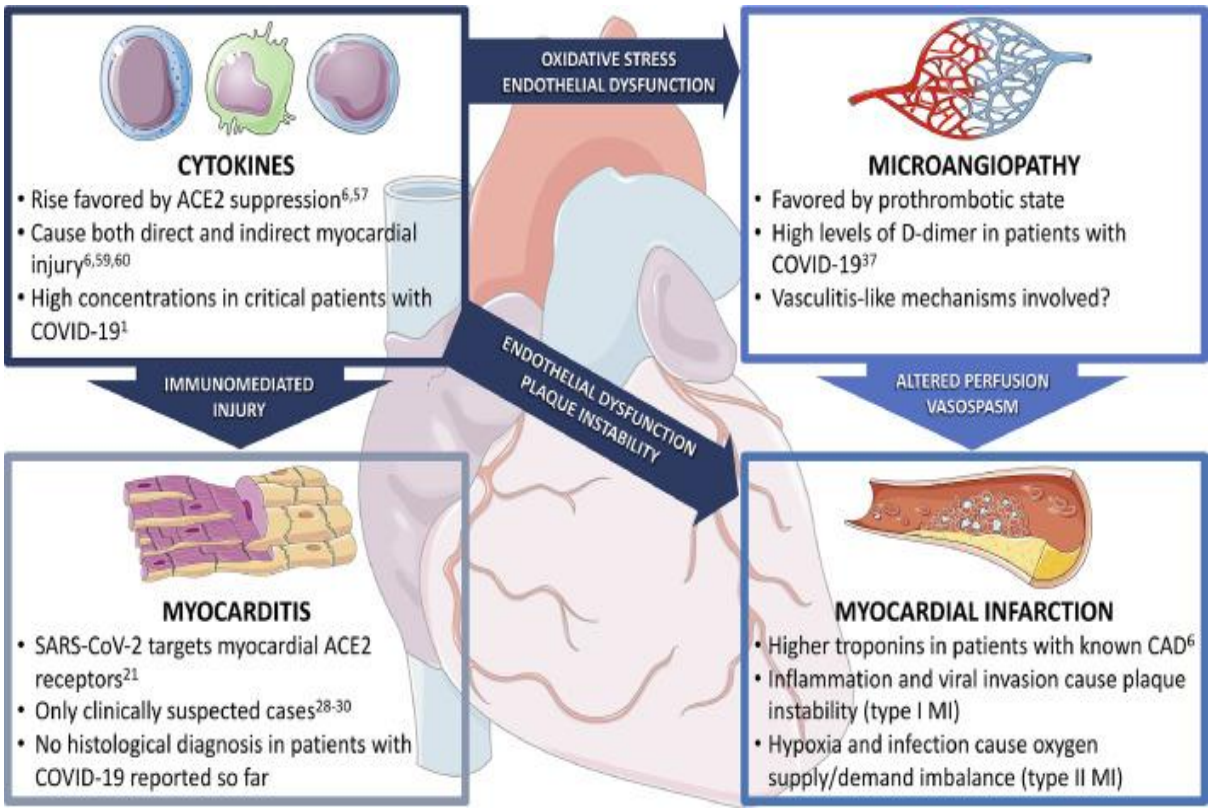
KEYWORDS: COVID-19, Troponin, Myocarditis, Pericarditis, Mayocardial injury, Emergency Department, Pandemic.

INTRODUCTION

Acute SARS-CoV-2 respiratory disease (COVID-19) is an infectious respiratory disease caused by the virus called SARS-CoV-2 belonging to the coronaviridae family. The first cases were identified during the viral pneumonia outbreak in China in November 2019 and are still present in the world as of May 2020. In addition to lung involvement, heart is also proving to be an important target of coronavirus1. Elderly patients (over 65 years) and those with cardiovascular risk factors, such as hypertension and diabetes mellitus are at risk of heart complications from COVID-192. Cardiac involvement with arrhythmic events, acute heart failure and cardiac arrest have been demonstrated, also, in other coronavirus-related infectious diseases such as Middle Eastern Respiratory Syndrome (MERS)3. In addition to causing pneumonia (the main complication of the infection), SARS-CoV-2 may induce a direct damage to the heart: on one hand, causing a myocardial infection (myocarditis), with significant impairment of cardiac contractility; on the other hand, it might affect pericardium (pericarditis) with formation of an effusion which may also impair cardiac function. Recently, the SARS-CoV-2 was found on a myocardial biopsy in a patient affected by severe myocarditis complicated by cardiac shock5. The mechanism by which the virus might attack heart cells, in case of viremic phase, could be related to the elective affinity between the viral spike proteins of SARS-CoV and type 2 angiotensin-converting enzyme receptor (ACE-2), which is well represented on myocardial cells. Another hypothesis is that the virus may migrate in myocardium from lung with infected macrophages. However, it is not clear how often this can happen. The ACE-2 is also present on the endothelial cells of the vessels, so theoretically an acute vasculitis (inflammation of the vessels) of the intra-myocardial vessels could also occur, which would end up causing ischemic damage6. Myocardial damage. could also be caused by severe general inflammation. This leads to the release of abundant quantities of inflammatory substances (cytokine storm), with a toxic effect on the heart muscle, thus compromising its function7. It is also possible that, in some cases, the adrenergic hyperactivation following respiratory distress and, possibly, the psychic stress related to the condition, causes a ventricular dysfunction typical of Tako-Tsubo syndrome, or an acute myocarditis that presents itself as a Tako-Tsubo syndrome8. Finally, it has been shown that cardiac function can be seriously compromised, as a consequence of the serious infectious state, in patients with known heart failure, myocardiopathy or serious valvular diseases9. In all these manifestations of heart damage, the evaluation of cardiac biomarkers such as troponin is important, above all to highlight an early diagnosis of cardiac involvement, to guide a possible prognosis and for a useful follow-up. In this review, we will

focus on the correlation between COVID-19 infection and the high-sensitivity troponin T and I and their significance in the development of myocarditis. a considerable proportion of patients (12%–28%) presented elevated cardiac troponin levels.[1, 6, 8, 9] Compared with patients with normal levels, those with elevated troponins were older and had significantly higher rates of comorbidities including hypertension, coronary artery disease (CAD), and diabetes.[6] Notably, patients with higher troponin levels were more likely to be admitted to intensive care.[1,5] and showed higher in-hospital mortality.[6, 7, 8,10, 11, 12, 13]

Acute respiratory infections as well as sepsis are often associated with an increase in troponin, which can be used as a marker of disease severity and predicts future cardiovascular events.[14, 15, 16] Hypotheses on COVID-19–associated myocardial injury are consistent with previous observations relating to the outbreaks of SARS and Middle East respiratory syndrome. Several mechanisms have been proposed, which are summarized in Figure 1 . In this review, we provide an overview of the available evidence regarding the possible mechanisms of myocardial injury in COVID-19.



MYOCARDITIS

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histologic, immunologic, and immunohistochemical criteria.[17] Many viruses are

cardiotropic, meaning that they bind directly on molecular targets in the myocardium. Myocardial damage may be due to different mechanisms. In the initial phase of viral myocarditis, direct virus-mediated lysis of cardiomyocytes occurs.[18] This process is usually followed by a robust T-cell response, which can lead to further heart injury and ventricular dysfunction.[19,20] In COVID-19, particular attention has been given to the role of angiotensin-converting enzyme 2 (ACE2), the binding receptor for SARS-CoV-2 cellular entry.[21] ACE2 is highly expressed in pericytes of adult human hearts, which indicates an intrinsic susceptibility of the heart to SARS-CoV-2 infection.[22] SARS-CoV-2 seems to not only gain initial entry through ACE2, but also to subsequently downregulate ACE2 expression, resulting in reduced conversion of angiotensin II (Ang-II) to angiotensin 1–7 (Ang-1–7). Ang-1–7 physiologically mediates protective cardiovascular effects in target organs.[23,24]

In autopsies of patients who died from the SARS outbreak in 2002, 35% of heart samples showed the presence of viral RNA in the myocardium, which in turn was associated with reduced ACE2 protein expression.[25] SARS-CoV-2 may share the same mechanism with the first SARS coronavirus because the 2 viruses are highly homologous in genome.[6, 26, 27] The consequences of ACE2 downregulation on the cardiovascular system is further expanded on.

Myocarditis represents one of the most challenging diagnoses in cardiology. Suspicion rises with the number of criteria fulfilled.[17] However, diagnostic certainty is based on endomyocardial biopsy or autopsy, where histologic analyses (infiltration, lymphocytes, macrophages, cellular inflammatory types) or molecular methods of viral genome identification can be performed.

To the best of our knowledge, only 3 case reports of probable COVID-19 myocarditis are available to date,[28, 29, 30] but none have been proven by biopsy. A fourth case describes the autopsy of a patient with severe COVID-19 who died from sudden cardiac arrest.[31] Interestingly, there were no obvious histologic changes seen in the heart tissue.

The emergency setting of many hospital facilities during the pandemic together with strict hygienic measures intended to prevent further contagion may hinder large studies on biopsy specimens in patients with COVID-19 and the performance of autopsies. At present, no convincing evidence of histologically confirmed COVID-19 myocarditis has been published.

MICROANGIOPATHY

SARS-CoV-2 uses ACE2 as its entry receptor, and subsequently downregulates ACE2 expression. In addition to the heart and lung, ACE2 is localized in the intestinal epithelium, vascular endothelium, and the kidneys.[32,33] In the renin–angiotensin–aldosterone system, ACE2 catalyzes the conversion of Ang-II to Ang-1–7, which opposes the vasoconstrictor, proinflammatory, pro-oxidant, proproliferative, and profibrotic actions exerted by Ang-II via AT1 receptors.[34] As a result, suppression of ACE2 expression and subsequent increase in Ang-II[35] levels may represent another threat to heart and vessels in patients with COVID-19. However, the role of Ang-II/Ang-1–7 imbalance in COVID-19 is extrapolated based on limited data from a different, albeit closely related, coronavirus (SARS-CoV).

The clinical significance of this pathway in COVID-19 complications and any possible role of modulating this receptor are not yet fully known. A clinical trial testing recombinant human ACE2 as a treatment for patients with COVID-19 is currently ongoing (NCT04335136). This drug may play a double role, both by acting as a decoy and competitively decreasing viral cell entry, and by restoring ACE2 activity and its beneficial role.[36]

Endothelial dysfunction, cytokine storm, oxidative stress, and Ang-II upregulation may explain the coagulopathy frequently seen in severe coronavirus disease.[37] A postmortem study from Singapore[38] on patients with SARS reported that 4 of 8 patients had pulmonary thromboembolic lesions and 3 patients had deep vein thrombosis. To date, there is only 1 described case of COVID-19–associated pulmonary embolism,[39] but approximately one-half of patients with COVID-19 present high levels of D-dimer,[3] which is associated to disease severity and higher mortality.[40] This marked increase in D-dimer may be due to intense inflammation stimulating intrinsic fibrinolysis in the lungs with spillover into the bloodstream.[41]

Another factor that may contribute to microangiopathy is vasculitis. Several studies have linked coronavirus infection with Kawasaki disease, especially in children.[42, 43, 44] Furthermore, a case series of 3 deceased SARS patients in 2003 described findings of systemic vasculitis, including edema, localized fibrinoid necrosis, and infiltration of monocytes, lymphocytes, and plasma cells into vessel walls in the heart, lung, liver, kidney, adrenal gland, and the stroma of striated muscles.[45] It has been suggested that, in patients with COVID-19, microvascular damage occurring in the heart causes perfusion defects,

vessel hyperpermeability, and vasospasm, leading to myocardial injury.[46, 47] Notably, a considerable proportion of critically ill patients with COVID-19 present with acute kidney injury, which is associated with worse prognosis.[8, 48] The mechanism may be the same, with microangiopathy of renal vessels, but there is no strong supporting evidence to date. Worsening of troponin clearance in patients with acute kidney injury could also contribute to the elevated levels in those patients.

MAYOCARDIAL INJURY

Patients with preexisting CAD and those with risk factors for atherosclerotic cardiovascular disease (CVD) are at an increased risk of developing an acute coronary syndrome during acute infections, as demonstrated previously in epidemiologic and clinical studies of influenza.[49, 50, 51] and other acute inflammatory conditions.[52] This outcome could result from imbalance between oxygen supply and demand in the acute setting, so that the troponin elevation may be interpreted as a type 2 myocardial infarction (MI).[53] Reduced oxygen supply in patients with COVID-19 is typically caused by hypoxic respiratory failure, a feature that is more common in deceased patients than in patients who recover[10] and is a marker of disease severity.[9] In contrast, infectious states are often accompanied by fever, tachycardia, and endocrine dysregulation, which lead to a marked increase in myocardial oxygen demand. Moreover, hypoxemia also leads to excessive intracellular calcium with consequent cardiac myocyte apoptosis.[47]

By definition, a type 2 MI can occur with or without underlying CAD. However, considering the higher prevalence of elevated troponin in patients with COVID-19 with previous CVD, it is possible that the type 2 MI when underlying stable coronary disease is unmasked by the acute infection.

Type 1 MI, caused by plaque rupture with thrombus formation, may also be precipitated by COVID-19.[53] Circulating cytokines released during a severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture.[54] In addition, the suppression of ACE2 expression and Ang-II increase may elevate cardiovascular risk through mechanisms such as oxidative stress, endothelial dysfunction, and vasoconstriction. Moreover, because ACE2 is expressed in vascular endothelial cells,[32, 33] direct viral vascular infection leading to plaque instability may also play a role in type 1 MI in patients with COVID-19.

The occurrence of acute coronary syndrome and MI in infected patients during the first SARS outbreak has been described.[38, 55] However, there are very scarce data about symptoms and electrocardiogram changes related to MI in COVID-19. Chest pain has been broadly reported and is also associated with cardiac injury,[7] but it has a very low specificity owing to the primary lung disease (ie, pleuritic pain). Interestingly, Guo et al[6] reported that on admission no patients showed evidence of acute MI. No data regarding electrocardiogram changes on larger groups have been published to date.

CYTOCRINE STROME

Severe lung inflammation and impaired pulmonary gas exchange in COVID-19 has been suggested to be due to upregulation of proinflammatory cytokines.[56] In healthy subjects, Ang-1–7 limits the synthesis of proinflammatory and profibrotic cytokines. Thus, downregulation of ACE2 by SARS-CoV-2, with a consequent decrease in Ang-1–7 levels, may magnify the cytokine storm, resulting in an overwhelming inflammatory response.[6, 57] Cytokines have been extensively studied in patients with heart failure owing to their role in inflammatory modulation, myocyte stress or stretch, myocyte injury and apoptosis, fibroblast activation, and extracellular matrix remodeling.[58]

In the study by Guo et al,[6] plasma troponin levels had a significant positive linear correlation with plasma high-sensitivity C-reactive protein levels, indicating that myocardial injury may be closely associated with inflammatory pathogenesis during the progress of the disease. In addition to their direct effects on cardiomyocytes, high levels of circulating cytokines also lead to functional reprogramming of endothelial cells, endothelial dysfunction, and atherogenesis.[6, 59, 60] In fact, endothelial cells are thought to play a primary role in the inflammatory response in viral infections.[61]

Thus, systemic inflammatory response with cytokine storm is a plausible cause of myocardial injury in the late phases of disease, usually associated with acute respiratory distress syndrome, multiorgan failure, and mortality. Overall, high cytokine levels may represent the key player of myocardial injury in COVID-19, being related to direct myocardial injury, endothelial dysfunction, destabilization of coronary plaque, and microthrombogenesis.

MATERIALS AND METHODS

The following review is articulated starting from epidemiological data, then going through the evidences regarding COVID-19 and cardiovascular biomarkers, such as troponin. Articles

were identified using the electronic PubMed database through a comprehensive search conducted by combining key terms such as “biomarkers”, “myocarditis”, “COVID-19”, “troponin”. English-language articles were screened for relevance. Full review of publications for the relevant studies was conducted, including additional publications that were identified from individual article reference lists. At first, the literature search was individually conducted by the single authors, who subsequently confronted each other in order to include in the review only the most recent and most relevant articles. Since we wanted our review to be as up to date as possible, we only selected articles published within the last few months.

RESULTS

After a thorough review of the literature and the comparison between the authors of this paper, we selected a total of 22 articles. In particular, we found 6 case-reports, 1 case series, 6 retrospective analyses, 2 prospective studies, 4 reviews, 1 metanalysis, 1 letter to editor and 1 editorial commentary: all the evidences highlighted in their main findings are summarized in Table I.

CASE REPORTS AND CASE SERIES

The first case of myocarditis associated with SARS-CoV2 infection in a 63-year-old male with pneumonia and cardiac symptoms was published by Zeng et al10. The subject was confirmed as having COVID-19 according to RT-PCR on sputum. Troponin I (cTnI) level was elevated, reaching 11.37 g/L, and diffuse myocardial dyskinesia together with reduced left ventricular ejection fraction (LVEF) were described on cardiac ultrasound. The peak level of interleukin-6 was 272.40 pg/ml. Laboratory test results for other viruses causing myocarditis were negative. Chest x-rays showed typical ground-glass changes indicative of viral pneumonia. The patient met the diagnostic criteria of the Chinese Expert Consensus Statement for fulminant myocarditis. Reduction of Troponin I (to 0.10 g/L) and interleukin-6 (to 7.63 pg/mL) was recorded following administration of antiviral therapy and mechanical life support. Furthermore, a gradual recovery of LVEF to 68% was observed. Unfortunately, the patient died of aggravation of secondary infection on the 33rd day of hospitalization. This is the first report of COVID-19 complicated with fulminant myocarditis and it showed that COVID-19 patients may develop severe cardiac complications such as myocarditis and heart failure10. A 21-year-old female patient who presented to a Korean Emergency Department with symptoms consistent with COVID-19 infection (fever, cough, diarrhea and dyspnea)

was described by Kim et al11. COVID-19 diagnosis was confirmed by RT-PCR on nasal swab. She presented high troponin I and NT-proBNP levels with severe systolic dysfunction at echocardiography. CT scan showed typical bilateral ground glass areas and consolidations. The cardiac CT scan showed normal coronary arteries and diffuse myocardial edema confirmed by cardiac MRI so that diagnosis of myocarditis related to SARS-CoV-2 was confirmed. This case teaches that even in patients without classical negative prognostic risk factors for severe COVID-19 we may suspect a cardiac involvement11. Tavazzi et al5 described a case of a 69-year-old patient admitted to an Italian hospital for fever, shortness of the breath and cough. During admission, pharyngeal swab resulted positive for SARS-CoV2 infection. The chest CT scan showed bilateral interstitial involvement of the lungs. High C-reactive protein (CRP) (52.7 mg/L) and very high Troponin I levels (4332 ng/L) were found. The coronary angiography resulted normal. A myocardial biopsy was performed and showed the presence of viral particle compatible with SARS-CoV-2 in the myocytes. The severe ventricular dysfunction observed at echocardiography with 34% of ejection fraction worsened dramatically and the patient was transferred in ICU where he was intubated and extracorporeal membrane oxygenation (ECMO) was implanted. In five days, the cardiac function improved and ECMO was discontinued. However, after 7 days he developed a septic shock and died. This report is a further proof of the hypothesis that SARSCoV-2 can directly invade the cardiac tissues causing myocarditis5. An interesting case report was presented by Inciardi et al1 in which an undoubted case of myocarditis associated with COVID-19 is reported. This case report describes a healthy 53-year-old woman, symptomatic of fever and cough, who was admitted to the ICU for myopericarditis. A nasopharyngeal swab was performed, with a positive result for SARS-CoV-2. The diagnosis of cardiac involvement was made by means of high level of NT-proBNP and high sensitivity troponin T, electrocardiographic and echocardiographic alterations. Finally, cardiac magnetic resonance imaging (MRI) was performed, showing increased wall thickness, diffuse biventricular hypokinesia and severe left ventricular dysfunction (LVEF of 35%), with conspicuous myocardial interstitial edema and circumferential pericardial effusion. These findings were all compatible with acute myopericarditis. Gradual clinical and instrumental stabilization was obtained following administration of dobutamine, antivirals lopinavir and ritonavir, chloroquine, steroids, and medical treatment for heart failure. This case highlights cardiac involvement as a complication associated with COVID-19, even without symptoms and signs of interstitial pneumonia and reinforces the hypothesis of a viremic phase rather than the migration of macrophages from infected lung1 . Li et al2 evaluated clinical and laboratory

parameters in 25 fatal cases of COVID-19. All but one patient presented elevated cTnI and the values increased during hospitalization until death. Other laboratory findings were associated to poor outcome in this study, such as PCT, D-dimer and lactate.

PROGNOSTIC STUDIES

Du et al13 recently presented a prospective study of mortality predictors for patients with COVID-19 pneumonia caused by SARS-CoV-2. This study was performed on patients admitted to Wuhan Pulmonary Hospital (Hubei, China) between 25 December 2019 and 7 February 2020. The aim was to study the relationship between clinical variables, laboratory tests and risk of death for patients with COVID-19 pneumonia. Enrollment involved 179 patients with COVID-19 pneumonia (97 males and 82 females), 21 of whom died. Univariate and multivariate logistic regression analysis revealed that in patients aged ≥ 65, with cardiovascular or cerebrovascular disease and with cardiac troponin I ≥ 0.05 ng/mL had an increased risk of mortality from COVID-1913. Han et al14 published a retrospective study in March 2020: the authors investigated the role of acute cardiovascular damage markers including CK-MB, myoglobin, cTnI and NT-proBNP on 273 patients with COVID-19 disease. Non-ischemic myocardial injury was predominant; indeed, mechanisms were due to cytokine storm as documented by raised inflammatory markers related to viral or fulminant myocarditis, stress cardiomyopathy, and hypoxia. Actually, in most studies on COVID-19 patients, an elevated troponin I level has been uniformly associated with uncontrolled inflammation secondary to cytokine storm and to increased mortality. CRP, procalcitonin, ferritin, D- dimer, Interleukin-2 (IL-2), Interleukin-7 (IL-7), granulocyte-colony stimulating factor, IgG- induced protein 10, chemokine ligand 3 and tumor necrosis alpha-2,3,6 are the main inflammatory markers that authors linked to cardiac injury, suggesting that elevated concentrations of these enzymes in venous blood are related to disease severity and poor outcome14. Another interesting study on the clinical utility of measuring cardiac troponin in COVID-19 infection was done by Gaze15. Furthermore, results from a retrospective cohort study report a significantly increased Troponin I in 54 deceased patients with respect to 137 survivors. The elevation mechanism of cTn in COVID-19 infection is not fully understood. Increases are likely to reflect non-coronary artery disease rather than acute coronary artery disease such as myocardial infarction. The underlying pathophysiology is indicative of an inflammatory response since many patients with COVID-19 in critical conditions. show an increase in inflammation indexes such as CRP and natriuretic peptides. This could present clinically as fulminant myocarditis. To support their hypothesis, the authors described a

clinical case, in which a 37-year-old man presented with chest pain and dyspnea. The electrocardiogram showed an elevation of the ST segment and the cTnT values were substantially high at > 10,000 ng/L, with concomitant increases in CK and natriuretic type B peptide. The initial diagnosis was acute coronary syndrome (ACS). However, coronary angiography did not reveal evidence of coronary artery stenosis. A positive sputum sample for COVID-19 resulted positive. The working diagnosis thus changed to fulminant coronavirus myocarditis with cardiogenic shock and lung infection. Treatment with glucocorticoid and human immunoglobulins was successful. Troponin levels decreased to 220 ng/L after one week and 21 ng/L after three weeks2. Chapman AR recently published a brief review on the role of troponin in patients with COVID-19. They confirmed that the elevation of troponin in patients with COVID-19 is probably on a multifactorial basis and less as a direct cause of coronary atherosclerosis. Yet, in this review, high hs-cTnI values were associated with a poor prognosis. The observed mortality rate was 10-fold higher in subjects with myocardial injury, thus early recognition could improve our understanding of the systemic consequences of COVID-19 and related therapy. For example, it has been suggested that in patients with COVID-19 and myocarditis diagnosis, combined early immunoglobulin and corticosteroid therapy can be very helpful. In addition, elevated cardiac troponin values in patients with COVID-19 could increase the need for an echocardiogram to assess the presence of suspicious signs of myocarditis. Conversely, recognition of a normal or modestly elevated troponin value may reduce the need for cardiac imaging. Although caution is wise, studies published to date are likely to have overestimated the prevalence of myocardial injury16. Madjid et al17 conducted a review about potential effects of coronaviruses on the cardiovascular system. In this review, it was confirmed that COVID-19 can cause viral pneumonia with further extra-pulmonary manifestations and complications. In particular, as regards acute heart damage (indirectly evidenced by high levels of high sensitivity troponin), this has been commonly observed in the most serious cases and associated with a higher mortality. In fact, in COVID-19 disease there is a high inflammatory load that can induce vascular inflammation, myocarditis and cardiac arrhythmias. But even in this review, no algorithms were effective to distinguish between the primary atherosclerotic cardiovascular cause and the cardiac damage secondary to infection (i.e., myocarditis). A retrospective study published by Guo et al18 analyzed patients with COVID-19 at the Seventh hospital in the city of Wuhan, China, from 23 January 2020 to 23 February 2020, evaluating their impact on myocardial function and its mortality rate. Among 187 patients with confirmed COVID-19, 52 showed myocardial damage as indicated by elevated TnT levels. Mortality during

hospitalization was 13% for those with underlying COVID-19 and showed an increase in TnT levels. Furthermore, plasma TnT levels demonstrated a significant linear correlation with plasma levels of CRP and with NT-proBNP levels. Subjects with increased Troponin T levels more frequently had malignant arrythmias during hospitalization. In conclusion, the study showed that myocardial damage is significantly associated with the fatal outcome of COVID-19, while the prognosis of patients with underlying COVID-19 but without myocardial damage is relatively favorable. It has been confirmed that inflammation can be a potential mechanism for myocardial injury18. Another retrospective study confirmed that heart damage in hospitalized patients with COVID-19 in Wuhan was associated with a higher mortality rate. This study was performed from 20 January 2020 to 10 February 2020, in a single center at Renmin hospital and is in line with previous literature data so that all patients hospitalized with COVID-19 and cardiac injury experienced a higher mortality rate19. Yet, a retrospective analysis was carried out on 54 subjects admitted to Tongji hospital in February 2020. Patients with or without myocardial damage, defined with a three times higher serum cardiac troponin value, were analyzed and compared. During hospitalization, 44% of cases (n=24) were complicated by myocardial damage and 48% (n=26) died in hospital. Mortality was significantly higher in patients with myocardial damage than in patients without myocardial damage and this correlated with the values of troponin, C-reactive protein, pro-BNP. This study also confirms that the involvement of myocardial tissue in COVID-19 disease correlates with the severity of the clinical picture. COVID-19 patients with severe respiratory failure and myocardial damage have a significantly higher risk of in-hospital mortality. In addition, the study suggests that it is important to monitor patients with high troponin values at the first check with the serial dosages of this biomarker to understand the evolution of the myocardial injury during hospitalization for COVID-19 patients20. It is important to underline that among the knowledge gaps of COVID-19 there are laboratory diagnostic problems as well as their interpretation in clinical management. Since serious cardiac complications have been reported to develop in a considerable number of patients with pneumonia, Lippi G and colleagues conducted a meta-analysis to assess the role of cTnI and cTnT in prediction of clinical severity in COVID-19 positive patients. Recent data from scientific literature report that cTnI levels were regarded by only a marginal increase in SARS-CoV-2 patients. However, what appears to emerge from this study is that cTnI values have significantly increased in patients with severe SARS-CoV-2 infection compared to those with milder forms of the disease. Therefore, it could be reasonable to consider immediate measurement of heart damage biomarkers at hospitalization, followed by a longitudinal

monitoring during hospital stay, so as to identify a subgroup of patients with possible heart damage21.

Table I: Summary of references considered for this review (keywords used: "biomarkers", "myocarditis", "COVID-19", "troponin").

References	Type	Month-year publication	No. of patients	Findings
Inciardi et al1 Case	Case report	March 2021	1	Even when signs and symptoms of interstitial pneumonia are not present, cardiac involvement can be a complication related to COVID-19
Zhou et al2.	Retrospective	March 2020	191	Physicians could be able to identify early patients with a poor prognosis by considering the potential risk factors of high SOFA score, elevated D-dimer and older age.
Alhogbani et al3	Case report	February 2016	1	report February 2016 1 One of the first cases that demonstrated relationship between MERS CoV and acute myocarditis, and heart failure
Chen et al4	Prospective	March 2020	150	Myocardial injury, with subsequent reduction in heart function, can be induced by SARS-CoV-2. Authors stress the importance of considering increased cTnI and past medical history of coronary heart disease as two independent determinants for clinical evolution in COVID-19 patients
Tavazzi et al5	Case-report	April 2020	1	A 69-year-old patient with flu-like symptoms rapidly degenerating into respiratory distress, hypotension, and cardiogenic shock. Myocardial localization of SARS-CoV-2 was demonstrated.
Hanff et al6	Review	March 2020	/	International research community should identify the role of RAS inhibition in COVID-19.
Tveito et al7	Editorial	March 2020 commentary	/	In the most critically ill COVID-19 patients, a cytokine profile resembling that seen in haemophagocytic lymphohistiocytosis can be observed.
Sala et al8	Case report	April 2020	1	The authors showed direct evidence of myocardial inflammation in a COVID-19 patient, undergoing both cardiac magnetic resonance tomography and endomyocardial biopsy characterization.
Dong et al9	Case report	April2020	4	COVID-19 can cause myocardial injury and is closely related to disease progression

Zeng et al10	Case report	April 2020	1	Case-report of COVID-19 complicated with fulminant myocarditis. The mechanism of cardiac pathology caused by COVID-19 needs further investigations.
Kim et al11	Case report	April 2020	1	A 21-year-old lady positive for COVID-19 with febrile sensation and dyspnea, raised troponin and NT-pro-BNP: myocarditis.
Li et al12	Retrospective	April 2020	25	Summary of clinical characteristics of 25 death cases positive for COVID-19
Du et al13	Prospective	April 2020	179	Four risk factors have been identified in SARS-CoV-2 patients: age (≥65 years), history of- and concurrentcardiovascular/cerebrovascular diseases, CD3+CD8+ T cell count less than 75 cell·μL−1, and cTnI higher than 0.05 ng·mL−1. In particular, the latter two were predictors for mortality of COVID-19 pneumonia patients
Han et al14	Retrospective	April 2020	273	Higher concentration in venous blood of CK-MB, myoglobin, ultra-TnI and NT-proBNP were associated with the severity and case-fatality rate of COVID-19
Gaze15	Review	April2020	/	Cardiac biomarkers can be used to measure worsening clinical picture or as an indicator of success in cardioprotective treatments.
Chapman et al16	Review	April 2020	/	Available prognostic markers should be used to identify patients with important systemic consequences of COVID-19 and determine those at highest risk of adverse outcomes as early as possible.
Madjid et al17	Review	March 2020	/	Cardiovascular risk factors and conditions should be carefully monitored according to evidence-based guidelines.
Guo et al18 i	Retrospective	March 2020	187	The prognosis of patients with underlying cardiovascular disease but without myocardial injury is relatively favorable. On the other hand, fatal outcome due to COVID-19 was frequently registered in presence of myocardial injury.
Shi et al19	Retrospective	March 2020	416	Cardiac damage was a frequent finding in COVID-19 patients hospitalized in Wuhan, and an association with a higher risk of in-hospital mortality was described.
He et al20	Retrospective	March 2020	54	Among severe or critically ill patients affected by COVID-19 there is a high prevalence of myocardial injury: for these subjects the risk of in-hospital mortality is significantly increased.
Lippi et	Meta-analysis	March 2020	/	It could be reasonable to consider

al21				immediate measurement of heart damage biomarkers at hospitalization, followed by a longitudinal monitoring during hospital stay, so as to identify a subgroup of patients with possible heart damage
Varga et al22.	Letter	April2020	3	SARS-CoV-2 can directly damage endothelial cells, considering their expression of ACE-2 receptors.

DISCUSSION

The role of high sensitivity troponin in SARS-CoV-2 is crucial. It can suggest the acute involvement of the cardiovascular system in the most serious manifestations. It can also make us immediately suspect an infectious acute myocardial damage and possibly optimize the therapeutic choice and the instrumental diagnostic follow-up. At the moment, it is difficult to estimate the correlation between COVID-19 and myocarditis only by troponin dosage, since those patients suspected of myocardial involvement should undergo cardiac MRI and myocardial biopsy to confirm this diagnosis. However, current data based on coronary angiography results and autoptic finding are suggestive of an inflammatory cause of the myocardium and pericardium in infected patients. Increased troponin in patients with COVID-19 may suggest the severity of the clinical picture in patients already suffering from heart disease or may be useful together with the electrocardiographic, echocardiographic picture to suggest a diagnosis of acute myocarditis. Furthermore, we need to consider that the increase in troponin may be related to pathological conditions not only confined to the heart, such as pulmonary embolism, renal failure or a general involvement of endothelial cells, as recently demonstrated by Varga et al22. Table I (Continued). Summary of bibliography considered for this review (keywords used: “biomarkers”, “myocarditis”, “COVID-19”, “troponin”). Month-year No. of References Type of publication patients Findings Guo et al18 Retrospective March 2020 187 The prognosis of patients with underlying cardiovascular disease but without myocardial injury is relatively favorable. On the other hand, fatal outcome due to COVID-19 was frequently registered in presence of myocardial injury. Shi et al19 Retrospective March 2020 416 Cardiac damage was a frequent finding in COVID-19 patients hospitalized in Wuhan, and an association with a higher risk of in-hospital mortality was described. He et al20 Retrospective March 2020 54 Among severe or critically ill patients affected by COVID-19 there is a high prevalence of myocardial injury: for these subjects the risk of in-hospital mortality is significantly increased. Lippi et al21 Meta-analysis March 2020 / It could be reasonable to consider immediate measurement of heart

damage biomarkers at hospitalization, followed by a longitudinal monitoring during hospital stay, so as to identify a subgroup of patients with possible heart damage. Varga et al22 Letter April 2020 3 SARS-CoV-2 can directly damage endothelial cells, considering their expression of ACE-2 receptors. Role of troponin in COVID-19 pandemic: a review of literature 10299 Troponin monitoring with serial doses is also useful to have a short-term follow-up to identify patients who could evolve in a more serious pathological picture than those who could improve through selective cardiac therapies. Surely, data that emerge from the studies so far conducted is that a high value of high sensitivity troponin represents a negative prognostic indicator and its diagnostic role is mainly associated with heart damage on an infectious-inflammatory basis, such as myopericarditis.

CONCLUSIONS

In light of the recognized utility of troponin dosage in COVID-19 patients with suspected myocardial damage, we should identify a safe and clear diagnostic algorithm, possibly combining patient clinical history, troponin levels and cardiac ultrasound findings that could help us in the prediction of myopericarditis. Further studies should also be planned to establish whether therapies with corticosteroids, anti-inflammatory drugs, immunosuppressant, antivirals, and highdose immunoglobulins are useful and whether they may affect the clinical course of COVID 19-related myopericarditis.

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