

Role of troponin in COVID-19 pandemic: a review of literature

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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.

Key Words:

COVID-19, Troponin, Myocarditis, Pericarditis, 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 out-

break 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 function⁴. 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, cardiomyopathy 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.

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 pos-

itive 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 SARS-CoV-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 arrhythmias 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

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

References	Type	Month-year of publication	No. of patients	Findings
Inciardi et al ¹	Case-report	March 2020	1	Even when signs and symptoms of interstitial pneumonia are not present, cardiac involvement can be a complication related to COVID-19.
Zhou et al ²	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 al ³	Case-report	February 2016	1	One of the first cases that demonstrated relationship between MERS-CoV and acute myocarditis, and heart failure.
Chen et al ⁴	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 al ⁵	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 al ⁶	Review	March 2020	/	International research community should identify the role of RAS inhibition in COVID-19.
Tveito et al ⁷	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 al ⁸	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 al ⁹	Case-report	April 2020	4	COVID-19 can cause myocardial injury and is closely related to disease progression.
Zeng et al ¹⁰	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 al ¹¹	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 al ¹²	Retrospective	April 2020	25	Summary of clinical characteristics of 25 death cases positive for COVID-19.
Du et al ¹³	Prospective	April 2020	179	Four risk factors have been identified in SARS-CoV-2 patients: age (≥ 65 years), history of- and concurrent- cardiovascular/cerebrovascular diseases, CD3+CD8+ T cell count less than $75 \text{ cell} \cdot \mu\text{L}^{-1}$, and cTnI higher than $0.05 \text{ ng} \cdot \text{mL}^{-1}$. In particular, the latter two were predictors for mortality of COVID-19 pneumonia patients.
Han et al ¹⁴	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.
Gaze ¹⁵	Review	April 2020	/	Cardiac biomarkers can be used to measure worsening clinical picture or as an indicator of success in cardioprotective treatments.
Chapman et al ¹⁶	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 al ¹⁷	Review	March 2020	/	Cardiovascular risk factors and conditions should be carefully monitored according to evidence-based guidelines.

Table Continued

Table 1 (Continued). Summary of bibliography considered for this review (keywords used: “biomarkers”, “myocarditis”, “COVID-19”, “troponin”).

References	Type	Month-year of publication	No. of patients	Findings
Guo et al ¹⁸	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. 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. 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. 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. SARS-CoV-2 can directly damage endothelial cells, considering their expression of ACE-2 receptors.
Shi et al ¹⁹	Retrospective	March 2020	416	
He et al ²⁰	Retrospective	March 2020	54	
Lippi et al ²¹	Meta-analysis	March 2020	/	
Varga et al ²²	Letter	April 2020	3	

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.

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.

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 high-dose immunoglobulins are useful and whether they may affect the clinical course of COVID-19-related myopericarditis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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