Journal of Life Sciences & Biomedicine, vol. 2(75), No 2, p. 45-57 (2020)

Clinical features and characteristics of myocardial injure in COVID-19 (data from multicenter studies)

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Received 21 November 2020; Received in revised form 31 November 2020; Accepted 01 December 2020

In patients with COVID-19 caused by coronavirus-2 (SARS-CoV-2) and proceeding with the severe acute respiratory syndrome, studies were carried out to study myocardial damage, determine its nature and clinical significance. In an international, multicenter study, cardiovascular pathologists assessed cardiac tissue after necropsies in 21 COVID-19 patients. The presence of myocarditis was determined by the identification of multiple foci of inflammation with associated damage to myocytes, and the composition of the inflammatory cells was analyzed using immunohistochemistry. Other forms of acute damage and inflammation of myocytes, as well as damage to the coronary arteries, endocardium and pericardium, have also been described. Lymphocytic myocarditis occurred in 3 (14%) cases. Increased infiltration of interstitial macrophages was observed in 18 (86%) cases. In four cases, there was mild pericarditis. Acute damage to right ventricular myocytes, most likely due to stress/overload, occurred in four cases. In COVID-19, myocardial damage has been reported, including elevated serum troponin levels and acute heart failure with decreased ejection fraction. There was a slight trend towards higher serum troponin levels in patients with myocarditis compared with patients without myocarditis. With SARS-CoV-2, interstitial macrophages increase in most cases, and in a small proportion of cases, multifocal lymphocytic myocarditis. Other forms of myocardial injury may also occur. The risk of hospital death among patients with severe COVID-19 can be predicted from markers of myocardial damage and has been significantly associated with older age, inflammatory response, and concomitant cardiovascular disease.

Keywords: *Coronavirus Disease 2019 (COVID-19), SARS-CoV-2, myocardial injury, myocarditis, lactate dehydrogenase, cardiac troponin I, creatine kinase (-MB), myoglobin*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by Coronavirus-2 (SARS-CoV-2) and a severe acute respiratory syndrome is primarily a respiratory disease (Du et al., 2020; Fauci et al., 2020; Fauci et al., 2020), but systemic and cardiovascular damage can occur. SARS-CoV-2 can cause an intense release of cytokines and chemokines, which can lead not only to vascular inflammation and instability of atherosclerotic plaques, but also to myocardial inflammation. Acute heart injury with elevated serum troponin levels is the most frequently reported cardiac abnormality in COVID-19, reported in about 8-12% of patients, and elevated troponin levels are associated with increased mortality in COVID-19 patients (Madjid et al., 2020; Shi et al., 2020). In addition, a small proportion of patients develop acute heart failure with reduced ejection fraction, which raises clinical concerns about myocarditis (Ramirez et al., 2008; Wang et al., 2020; Zhou et al., 2020). Possible mechanisms for increasing troponin levels in these patients include ischemia, stress cardiomyopathy, microvascular thrombosis and secondary effects of systemic inflammation.

Direct viral myocardial infection is another possible route of myocardial injury. The unique affinity of SARS-CoV-2 for the host angiotensin-

doi.org/10.29228/jlsb.61

Available online 25 December 2020

converting enzyme receptor 2 increases the likelihood of direct viral infection of the vascular and myocardial endothelium, so that in some patients, myocardial damage associated with COVID-19 may represent viral myocarditis (Zhou et al., 2020). Any of these mechanisms can also exacerbate underlying cardiovascular diseases (Zhu et al., 2020).

There have been several reports describing cardiac histology in a small number of COVID-19 patients, mostly associated with endomyocardial biopsy and limited autopsy sampling (Gallagher, Ferrario and Tallant, 2008). A study was also conducted aimed at assessing heart damage in patients with COVID-19 and determining the frequency and type of myocarditis, as well as other forms of acute heart damage. Several studies have reported clinical and laboratory results related to cardiovascular injury in patients with COVID-19 infection (Corrales-Medina et al., 2013; Huang et al., 2020; Ji et al., 2020; Oudit et al., 2009).

Accumulating evidence indicates that myocardial injury is a complication associated with COVID-19, with a prevalence of 7.2% to 12%. Notably, the American College of Cardiology Clinical Bulletin highlighted the cardiac implications of COVID-19. This suggests that patients with cardiovascular disease are at higher risk and recommends triage and treatment as a priority (Wang et al., 2020). The researchers determined the predictive value of myocardial scores in relation to hospital death and studied the characteristics and potential causes of myocardial damage in cases of severe COVID-19.

This review summarized the laboratory findings and mechanism of cardiac dysfunction associated with COVID-19 infection.

MATERIALS AND METHODS

A working group on COVID-19, led by the Society for Cardiovascular Disease and the European Association for Cardiovascular Disease, was requested to provide information regarding cardiac pathology obtained from successive autopsies performed at their facilities on COVID-19 patients. Inclusion criteria were: positive nasopharyngeal swab for SARS-CoV-2, clinical diagnosis of COVID-19, and autopsy with cardiac examination by a cardiologist from the working group, including collection of myocardial samples (left ventricle, septum, and right ventricle) and epicardial coronary arteries. All sequential autopsies meeting these criteria were included. An international multicenter study assessed cardiac tissue after autopsy in 21 COVID-19 patients. Information provided included the presence of myocarditis and other types of inflammation and trauma identified on hematoxylin and eosin (H&E) -stained heart sections. The degree of stenosis of the coronary arteries and the presence of destroyed plaques were also presented. Evaluation of the myocardium by electron microscopy and evaluation of immunohistochemical spots on CD68, CD3, CD4 and CD8 were provided. For immunohistochemical staining, the number of cells with the greatest inflammation, stained in a field with a high magnification × 400 was counted. All immunohistochemical staining was performed on conventional automatic diagnostic devices for immunohistochemical staining. The presence of left ventricular fibrosis was assessed on a semi-quantitative scale: mild (<10% of the myocardial area); moderate (10-25% of the area of the myocardium); Serum troponin levels were obtained at selected institutions using the following tests: high sensitivity troponin T, normal <15 ng/L (n=6), high sensitivity troponin I, normal <35 ng/L (n=6), high sensitivity troponin I , norm <19.8 ng / l (n=4). Electrocardiographic changes were considered new if they were not present on previous electrocardiograms during the current or previous hospitalization. All electrocardiographic changes were obtained on a 12-lead ECG.

For the purposes of this study, myocarditis was defined as the presence of an inflammatory infiltrate associated with damage to myocytes not caused by any other cause that was present in multiple foci. The views expressed by them do not necessarily reflect the views of all members of the Society for Cardiovascular Disease or the European Association for Cardiovascular Disease.

Another retrospective study included laboratory-confirmed COVID-19 patients admitted to Wuhan University Renmin Hospital located in Wuhan, Hubei Province. This study was approved by the National Health Commission of China and the Institutional Review Board of Renmin Hospital, Wuhan University (Wuhan, China). Written informed consent was rejected by the Hospital Ethics

Commission appointed to treat emerging infectious diseases.

The severe COVID-19 patients included in this study were diagnosed according to the COVID-19 Diagnostic and Treatment Guidelines (Study Sixth Edition) published by the National Health Commission of China on February 18, 2020. Cases in this study included severe illness characterized by any of the following: respiratory rate> 30 / min; oxygen saturation ≤93%; PaO 2 / FiO 2 ratio ≤ 300 mmHg.; respiratory failure requiring mechanical ventilation; shock; or respiratory failure in combination with other organ failure requiring intensive care. Cases younger than 18 years of age and missing cardiac biomarkers, including cardiac troponin I (cTnI) levels, were excluded.

The patients were grouped according to whether they died (death group) or survived (survivor group). The study resulted in hospital mortality rates and clinical outcomes were determined based on information stored in the hospital's real-time medical record system.

Myocardial injury was defined as an increase in the level of cardiac biomarkers cTnI in the blood above the 99th percentile of the upper reference limit (Huang et al., 2020) ARDS was defined in accordance with the Berlin definition (Wan et al., 2020). The date of onset of the disease was considered the day when the symptom was noticed.

Studied creatinine kinase-myocardial band (CK-MB), myoglobin (MYO) and cTnI. The normal CK-MB reference range is 0–5 ng/mL; the normal MYO reference range is 0-110 μg/L; the normal cTnI reference range is 0–0.04 ng/ml and the minimum detectable concentration (analytical sensitivity) is 0.006 ng / ml. Normal range (NT-proBNP is 0-900 pg/ml.

A retrospective design was used in 20 studies to investigate cardiac damage associated with severe outcome and death in patients with COVID-19 infection in China (Jing et al., 2020; Gaze, 2020). Two studies used a prospective design (Ruan et al., 2020; Wang et al., 2020) Study sample size ranged from 10 to 645 patients (mean age of severe patients: 60.95 years, mean age of patients without severe degree: 46.95 years).

Another study was conducted in New York from February 27, 2020 to April 12, 2020, with an enrollment of 2,736 patients. in patients within 24 hours after hospitalization was measured troponin-I (normal value <0.03 ng/ml) (Anuradha et.al., 2020).

Statistical analysis

Descriptive statistics were obtained for all study variables. Continuous data are expressed as median (interquartile range, IQR). Categorical data is expressed in proportions. All categorical variables were compared for study results using Fisher's exact test or x-square test, and continuous variables were compared using Student's t-test or Mann-Whitney U test. Logistic regression analysis was performed to determine predictors of myocardial injury. Cases of missing biomarker data were excluded using statistical software. Data were analyzed using SPSS 25.0 (IBM, Chicago, Illinois). Statistical charts were created using Prism 5 (GraphPad), Minitab (version 18) and Python. For all statistical analyzes, P<0.05 was considered significant. statistical analysis.

RESULTS

21 cases met the study criteria. These autopsies were performed in March or April 2020 at Asienda Ospedaliera University of Padua, Sant'Orsola-Malpighi University Hospital in Bologna, Massachusetts General Hospital in Boston, University of Amsterdam and the Mayo Clinic in Rochester, Minnesota. For all 21 patients, COVID-19 was the leading cause of death. Causes of death: acute respiratory distress syndrome (ARDS, n=15), viral pneumonia (n=4), cardiogenic shock (n=1), and cardiac arrest (n=1). Eighteen patients died in intensive care. Two of the patients received veno-venous extracorporeal membrane oxygenation.

Since the last hospitalization, serum high-sensitivity troponin T or I levels have been available in 16 patients with a mean peak value of 56 ng/L in the range of 2.8–2494 ng/L. Troponin levels were altered in 11 of these 16 patients. Five out of 16 patients received renal replacement therapy.

Electrocardiographic changes were detected in 12 patients, including new-onset atrial fibrillation (n=5), partial right bundle branch block (n=2), nonspecific T-segment changes (n=3), transient ST-segment elevation (n=1), premature ventricular

contractions (n=1) and ST segment depression (n=1). The duration of atrial fibrillation was 12 hours in one patient, 2 days in three patients, and 3 days in one patient. Limited bedside transthoracic echocardiography was performed in five patients without myocarditis. 16 patients received one or more COVID-19 drugs, including hydroxychloroquine / chloroquine (n=15), azithromycin (n=8), atorvastatin (n=4), inhaled nitric oxide (n=2), lopinavir / ritonavir (n=6), oseltamivir (n=2), remdesivir (n=1), tocilizumab (n=3), and sarilumab (n=1).

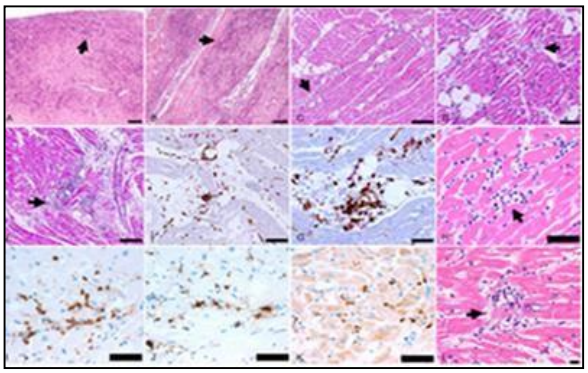

Fig. 1. Spectrum of myocarditis in COVID-19 patients. (A and B) Biventricular multifocal/diffuse lymphocytic myocarditis (arrows) with extensive myocyte injury in an 86-year-old man with previously undiagnosed cardiac amyloidosis (H&E×50). (C–G) Biventricular multifocal lymphocytic myocarditis (arrows) with myocyte injury in a 64-year-old man, who developed atrial fibrillation 2 days before death (C, H&E ×100; D, H&E ×200; E, H&E ×100; F, double immunostaining CD68 brown/CD3 red, ×200; G, double immunostaining CD4 brown/CD8 red, ×400). (H–K) Biventricular multifocal lymphocytic myocarditis (arrow) in a 59-year-old man (H, H&E ×400; I, CD3 immunostaining brown, ×400; J, CD68 immunostaining brown, ×400; K, CD4 immunostaining brown, ×400). (L) Focal myocardial lymphocytic infiltration with myocyte injury (arrow) in a 70-year-old man (H&E ×400). Scale bars represent 500 μm (A, B), 200 μm (C, E), 100 μm (D, F), 50 μm (G–K), and 20 μm (L).

At autopsy, no thromboembolism of the main pulmonary arteries was found. An average of 20 complete myocardial blocks (range 5–29 blocks) were histologically examined and immunohistochemical staining of inflammatory cell markers was assessed in all cases. Myocarditis was detected in three cases (Fig. 1). Myocarditis was multifocal in all three cases with left and right ventricular involvement, but in one case, right ventricular predominance was present. In all three cases, myocarditis was classified as lymphocytic, containing a significant number of CD3 + T lymphocytes and a significant proportion of CD68 + macrophages, without eosinophils, giant cells, or granulomas. In two cases, lymphocytes were CD4 +, and in one case, lymphocytes were with a predominance of CD8 +. In addition to the three cases of multifocal myocarditis, there were six cases of focal enlargement of interstitial T lymphocytes in the myocardium, with or without focal damage to myocytes, with the number of focal T cells ranged from 22 to 65 per field × 400 at high magnification.

In 18 (86%) cases, there was a relatively widespread increased infiltration of interstitial macrophages into the myocardium without clearly associated damage to myocytes, affecting both the left and right ventricles (Fig. 2). These diffuse macrophage infiltrates were observed in two out of three patients with myocarditis and in 16 out of 18 patients without myocarditis. In a third patient with myocarditis, the inflammatory infiltrates were relatively extensive, making it difficult to identify a distinctive single macrophage infiltrate. The average density of macrophages in these cases was 44 cells in a high power field (range 20–177). Mild pericarditis from the epicardium (visceral pericardium) was present in four cases.

Acute damage to myocytes in the right ventricle, most likely due to stress / overload, occurred in four cases and was characterized by acute coagulation necrosis of myocytes, mainly in the subendocardial region, with staining of necrotic myocytes for the complement component C4d.

When comparing cases of myocarditis and patients without myocarditis, the densities of CD3 + lymphocytes and CD68 + macrophages were higher in patients with myocarditis than in patients without myocarditis, but there were no differences in the density of inflammatory cells between the left and right ventricles. There were no differences between the two groups in duration of symptoms, length of hospital stay, age, history of hypertension, history of diabetes, history of previous immunosuppression, history of smoking, or history of previous cardiovascular disease (Table 1). There was also no discernible difference between the two groups in COVID-19 related treatment.

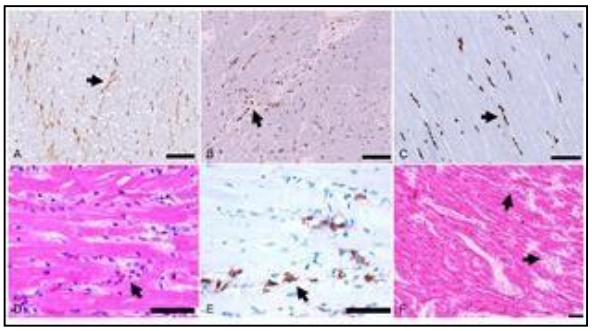

Fig. 2. Increased interstitial macrophages. The majority of patients showed increased interstitial macrophages without associated myocyte injury (arrows). (A) A 50-year-old man, (CD68 immunostaining, ×100). (B) A 44-year-old man, (double CD68 brown/CD3 red immunostaining, ×100). (C) A 64-year-old man (CD68 immunostaining, ×200). (D and E) A 60-year-old man (D, H&E, ×400; (E) CD68 immunostaining, ×400). (F) A 73-year-old woman with increased cells within the myocardial interstitium (H&E, ×100). Scale bars represent 200 μm (A, B), 100 μm (C, F), and 50 μm (D, E).

For 16 patients with documented troponin levels, there was no significant difference in serum troponin levels between patients with and without myocarditis (Table 1). While the patient with the highest troponin level (2494 ng/L) did have myocarditis, the patient with the second highest troponin level (702 ng/mL) did not have myocarditis, but had acute right ventricular myocardial injury, most likely as a result of stress. All three patients with myocarditis had troponin levels ≥60 ng/L compared with only 38% of patients without myocarditis (P = 0.20). In addition, all three patients with myocarditis had serum troponin levels ≥60 ng/mL with new ECG changes, compared with only 2 (15%) of 13 patients without myocarditis (P = 0.02).

A total of 2253 confirmed COVID-19 cases were initially screened from January 1 to February 23, 2020 at Wuhan University's Renmin Clinical Hospital. 671 cases (death, 62; survivors, 609) with severe COVID-19 were included in the study. These patients had a mean age of 63 years (IQR, 50–72 years), 48% of patients were male, and the mean time from symptom onset and admission to follow-up was 23 days and 17 days, respectively.

During hospitalization, 95.5% of patients received oxygen therapy; however, the use of extracorporeal membrane oxygenation and continuous renal replacement therapy was rare. The proportion of using antiviral treatment was 96.4% in the included patients, and 59.5%, 56.5% and 54.2% of patients, respectively, received intravenous immunoglobulin, glucocorticoids and antibiotics.

The deceased patients were older than the survivors and more often than males (all P <0.001, Table 1).

The main cause of death was a rapid deterioration in respiratory function, followed by cardiovascular complications. Table 2 summarizes the distribution of death-related complications in the included patients, including ARDS (98.4%), acute respiratory failure (90.3%), acute myocardial injury (30.6%), acute heart failure (19.4%), multiple organ failure syndrome (9.7%), shock (6.5%) and sudden death (1.6%).

Table 1. Characteristics of patients

Treatment, n (%)	All patients	Death	Survivors	p
Oxygen inhalation	527 (78,5)	16 (25,8)	511 (83,9)	<0,001
Non-invasive ventilation	76 (11,3)	17 (27,4)	59 (9,7)	<0,001
Invasive mechanical ventilation	36 (5,4)	29 (46,8)	7 (1,1)	<0,001
Extracorporeal membrane oxygenation	2 (0,3)	2 (3,2)	0 (0,0)	0,008
Continuous renal replacement therapy	4 (0,6)	4 (6,5)	0 (0,0)	<0,001
Antiviral agent	647 (96,4)	58 (93,5)	589 (96,7)	0,267
Immunoglobulin	399 (59,5)	55 (88,7)	344 (56,5)	<0,001
Glucocorticoids	379 (56,5)	53 (85,5)	326 (53,5)	<0,001
Antibiotic	364 (54,2)	49 (79,0)	315 (51,7)	<0,001

Table 2. Cause of death of included patients.

Complications	n (%)
Acute Respiratory Distress Syndrome	61 (98,4)
Acute respiratory failure	56 (90,3)
Acute myocardial injury	20 (30,6)
Acute heart failure	12 (19,4)
Multiple organ failure syndrome	6 (9,7)
Shock	4 (6,5)
Sudden death	1 (1,6)

106 patients (15.8%) had myocardial injury in all enrolled patients on admission. Patients with myocardial injury had an older age, more comorbidities and more laboratory abnormalities than patients without myocardial injury. Patients who died were more likely to suffer from myocardial injury during hospitalization compared with survivors (75.8% versus 9.7%; P <0.001). The contour plot of the characteristics of the distribution of myocardial parameters showed that these biomarkers were higher among the deceased patients. From admission to death, cardiac scores showed dynamic change in the death group, especially CK-MB and cTnI levels. Since most patients were not followed up during hospitalization, the serial biomarker results were based on a very small subgroup.

Cumulatively evaluated 17 studies 6, 8-16, 18, 20-22, 24-26 of 2,467 patients infected with COVID-19 (severe patients = 1095 and non-severe patients = 1372), higher serum lactate dehydrogenase levels were shown to be (weighted average difference = 108.86 U / L, 95% confidence interval (CI) = 75.93 to 141.79, p <0.001, I 2 = 85.4%, p heterogeneity <0.001) and creatine kinase-MB (weighted average difference = 2.60 U / L, 95% CI = 1.32–3.88, p <0.001, I 2 = 0.0%, p heterogeneity = 0.517) associated with a significant increase in the severity of COVID-19 infection. The pooled results showed that serum creatine kinase levels (weighted mean difference = 15.10 U / L, 95% CI =0.93 to 31.12, p=0.065, I2= 46.9%, p heterogeneity =0.058), cardiac troponin I (weighted average difference = 4.05 pg / ml, 95% CI= -0.20 to 8.30, p=0.062, I 2=0.0%, p-heterogeneity = 0.591) and myoglobin (weighted average difference =21.40 ng / ml, 95% CI= -0.22 to 43.02, p=0.052, I2=29.3%, p heterogeneity = 0.243) did not have a significant relationship with the severity of the disease.

Six studies 7, 14, 17, 19, 23, 27, including a total of 1217 patients with COVID-19 infection (survivor=365 and survivors=852), reported mortality as an outcome measure. The pooled results showed that higher serum lactate dehydrogenase levels (weighted mean difference = 213.44 U/L, 95% CI =129.97-296.92, p <0.001, I 2 = 90.4%, p heterogeneity < 0.001), Creatine kinase (weighted average difference = 48.10 U/L, 95% CI=0.27–95.94, p=0.049, I2=85.0%, p heterogeneity=0.001), cardiac troponin I (weighted average difference=26.35 pg / ml, 95% CI=14.54 to 38.15, p<0.001, I2=4.1%, p heterogeneity = 0.352) and myoglobin (weighted average difference =159.77 ng / ml, 95% CI= 99.54 to 220.01, p<0.001, I 2 =0.0%, p heterogeneity=0.409) were associated with a significant increase in mortality from COVID-19 infection.

In a study conducted in New York City, 506 (18.5%) patients died during hospitalization. A total of 985 (36%) patients had an increased troponin concentration. After adjusting for disease severity and related clinical factors, even minor myocardial injuries (eg troponin I> 0.03–0.09 ng/ml; n= 455; 16.6%) were significantly associated with death (adjusted hazard ratio: 1, 75; 95%). CI: 1.37 to 2.24; p <0.001), while higher amounts (e.g. troponin I> 0.09 ng / dl; n = 530; 19.4%) were significantly associated with higher risk (adjusted HR: 3.03; 95% CI: 2.42 to 3.80; p <0.001) (Anuradha et al., 2020).

DISCUSSION

Detailed information on cardiac autopsy in patients who have died from COVID-19 is currently very limited. Despite the high mortality rate worldwide, only a few studies with a small number of patients still provide information on cardiac disease in these patients. (Li et al., 2003; Mo et al. 2020; Xu et al., 2020). Some of these studies used limited diagnostic approaches such as biopsy. This training has several limitations. Molecular analysis for the virus in the myocardium was not performed. this study is still relatively small and not complete enough to identify and exclude differences between groups. The definition of a COVID-19 diagnosis in SARS-CoV-2 infected patients may have varied across settings in this multicenter study. A

small number of patients underwent only limited bedside echocardiography. The electrocardiographic data were based on documented clinical observations and were not obtained in a standardized manner. This study was retrospective and not all cases were collected for histology in the same way. For this study, the authors used a rigorous criterion for multiple lesions associated with myocardial injury to diagnose myocarditis. Thus, there is great confidence that three patients meeting this criterion have myocarditis. There were six additional cases with lymphocytic infiltrates but no or only focal myocyte injury. In some previous studies not related to COVID-19, in particular with the participation of endomyocardial biopsy, this pathology was considered as myocarditis. and the results cannot be easily generalized to all patients dying from COVID-19.

One of the key pathological discoveries in this series of studies is that patients dying from COVID-19 often have infiltration of interstitial myocardial macrophages with an average of 44 cells per field at × 400 magnification, without damaging myocytes, affecting 86% of patients. In fewer cases, true multifocal lymphocytic myocarditis affects 14% of patients. Compared to the previous SARS-CoV virus, the inflammatory heart changes seen with COVID-19 appear to be more severe overall. An early autopsy of patients who died from SARS showed that 35% of patients could detect SARS-CoV in myocardial tissue by PCR, and this subgroup of patients had a degree of myocardial macrophage infiltration comparable to that of 86% of patients. cases of COVID-19 in this series (Zhang et al., 2020). The median age of patients in the previous SARS study was 68 with 45% of men, compared to a median age of 69 with 71% of men for COVID-19 patients in this study. The mechanisms underlying this macrophage infiltration are currently unclear, but the study by Oudit et al. it has been suggested that SARS-CoV-induced myocardial inflammation is mediated predominantly by macrophages. Also, this study did not show that SARS-CoV is associated with an increase in lymphocytic infiltrates or multifocal myocarditis, as with SARS-CoV-2 infection.

Although there was a slight upward trend in troponin levels in patients with myocarditis in these studies, myocarditis does not fully explain the increased troponin levels seen in patients with COVID-19. Other forms of myocardial injury, such as right ventricular stress, clearly contribute to the increased troponin levels in these patients. All patients with multifocal myocarditis in this series had new changes in electrocardiography, including atrial fibrillation in two cases and new ST segment depression associated with chronic atrial fibrillation in a third case. Given that most patients with COVID-19 have an increase in the number of macrophages in the heart, it can also be difficult to determine with imaging studies which of these patients actually has lymphocytic myocarditis. Although electron microscopy has reported the presence of the virus in cardiac macrophages (Lo et al., 2020.). However, so far, electron microscopy in this series of patients has been performed only in three cases without real myocarditis.

Preliminary observations in the literature, together with those in this series, suggest that myocardial injury, with or without cardiac depression, in these patients may be due to an etiology other than viral myocarditis. Acute damage to myocardial tissue may be associated with increased cytokines, hypoxemia, right ventricular tension, and thrombotic complications. In some patients in this series, both myocardial microvascular thrombi and right ventricular deformity were observed. Thus, the term myocarditis should be used to describe patients with elevated troponin levels in the presence of COVID-19 using more specific diagnostic tests such as endomyocardial biopsy and / or cardiac magnetic resonance imaging.

Cardiac abnormalities associated with SARS-CoV-2 infection were found to be more severe than those associated with a previous SARS-CoV outbreak. Under the conditions of SARS-CoV-2 infection, in most cases, the number of interstitial myocardial macrophages increases, and in a small part of cases, multifocal lymphocytic myocarditis. These patients also present with other forms of myocardial injury, such as right ventricular deformity.

The main findings of this study are as follows: myocardial injury is not uncommon among patients with severe COVID-19, especially among those who die; elevated levels of myocardial markers predict the risk of death in hospital; and advanced age, inflammatory response, and concomitant cardiovascular disease are associated with myocardial injury in COVID-19 patients (Chen et al., 2020; Corrales-Medina et al., 2012).

Increases in cTnI and CK-MB can predict the risk of death. Notably, these single cut-off values may include a range of individuals with normal levels of myocardial markers at admission. While it is premature to say whether these patients are doomed to poor outcomes, as only about 30% of people have died from myocardial damage, this plays an early warning role for COVID-19 deaths when these rates exceed thresholds.

Circulating inflammatory mediators (i.e. cytokines and/or endotoxins) or direct viral invasion of cardiomyocytes, or both, can lead to myocardial damage in COVID-19. The novel coronavirus was recently reported to use angiotensin converting enzyme II (ACE2) as a cell entry receptor, and SARS-CoV was found in the heart of 35% of subjects, suggesting that SARS-CoV is capable of infecting the myocardium through ACE2 receptors (Li et al., 2003). While it can be argued that direct invasion of SARS-CoV-2 into cardiomyocytes underlies heart failure, a recent pathological study documented scant interstitial mononuclear inflammatory infiltrates in cardiac tissue without significant myocardial damage in a COVID-19 patient (Mo et al., 2020). With limited evidence, whether SARS-CoV-2 can directly damage the heart remains to be proven.

Previous data have demonstrated that risk factors for cardiac complications associated with pneumonia include older age, preexisting cardiovascular disease, and a greater severity of pneumonia at presentation (Guan et al., 2019). However, about one third of transient cardiac complications occur in patients without a history of heart disease. The SARS study also found that reversible left ventricular damage is common, even among those without underlying heart disease (Thygesen et al., 2018). However, sufficient evidence is needed to clarify whether the effects of COVID-19 and SARS on the myocardium differ. In the present study, the deceased patients had a higher proportion of both myocardial injury and concomitant cardiovascular diseases, suggesting that cardiac complications with underlying cardiovascular disease or risk usually coexist and develop to an irreversible outcome. Alternatively, the systemic inflammatory response to pneumonia may also increase the inflammatory activity in coronary atherosclerotic plaques, making them unstable and prone to rupture. Consequently, the presence of preexisting cardiovascular disease or associated risk factors can exacerbate myocardial damage, which therefore cannot be ignored when treating COVID-19. In general, patients with COVID-19 and myocardial injury are discouraged from actively participating in emergency intervention strategies due to the existing risk of cross-infection, and for most moderate to moderate myocardial injuries, the standard integrated management process is usually based on risk stratification and patient classification (Tikellis and Thomas, 2012).

Studies have confirmed the hypothesis that heart damage is associated with severe outcome and death in patients with COVID-19 infection. It should be noted that this study is the first meta-analysis to assess the relationship between serum cardiac biomarker levels and the severity of COVID-19 infection.

It is known that advanced age (≥65 years), male sex and the presence of comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease and cancer are the main risk factors for death from COVID-19 (Wang et al., 2020). The presence of myocarditis and heart damage (defined by elevated cardiac troponin I levels above the upper limit of the 99th percentile) are other independent risk factors associated with mortality (Ranieri et al., 2012).

COVID-19 can exacerbate underlying cardiovascular diseases and / or cause new heart conditions. Previous studies have shown that the incidence of acute heart damage in severe COVID-19 patients and deaths ranges from 5% to 31% and 59% to 77%, respectively (Anuradha et al., 2020; Fauci, Lane and Redfield, 2020; Han et al., 2020). The auxiliary mechanisms include hemodynamic changes, induction of procoagulant factors, and systemic inflammatory reactions, which are mediators of atherosclerosis, directly contributing to plaque rupture through local inflammation, which predisposes to thrombosis and ischemia (Davidson and Warren-Gash, 2019; Han et al., 2020; Hoffmann et al., 2020).

In addition, ACE2, the COVID-19 receptor, is expressed on vascular endothelial cells and myocytes (Smeeth et al., 2004), so there is at least a theoretical potential for direct virus damage to the cardiovascular system. In theory, this could have a potential impact on patients taking angiotensin-converting enzyme inhibitors, resulting in a greater

risk of contracting COVID-19 and an increase in the severity of the disease (Chen et al., 2020).

Other putative mechanisms of COVID-19-related heart damage include a cytokine storm mediated by an increase in the production of pro-inflammatory cytokines by innate immunity after infection with COVID-19, and hypoxia caused by excessive intracellular calcium leading to myocyte apoptosis.

Interstitial mononuclear inflammatory infiltrates in the myocardium have been reported in deaths from COVID-19 (Li et al., 2003). In addition, cases of myocarditis with reduced systolic function have been reported following infection with COVID-19 (28). Heart damage is likely associated with ischemia and / or infectious myocarditis and is an important prognostic factor in patients with COVID-19 infection. COVID-19 affects the myocardium and causes myocarditis (Li et al., 2003).

Studies of cardiac biomarkers indicate a high prevalence of cardiac injury in deaths from COVID-19 infection (Li et al., 2003; Ranieri et al., 2012). Mortality was significantly higher in patients with high serum levels of lactate dehydrogenase, cardiac troponin I, creatine kinase, and myoglobin. The mechanism by which cardiac biomarkers increase in COVID-19 infection is not fully understood. The underlying pathophysiology suggests a cardio-inflammatory response, as many patients with severe COVID-19 infection have a concomitant rise in cardiac biomarkers and acute phase reagents such as C-reactive protein (Chen et al., 2020). An increase in cardiac biomarkers with other inflammatory biomarkers increases the likelihood that this reflects a cytokine storm and may clinically present as fulminant myocarditis.

For patients admitted to hospital with COVID-19, in addition to routine clinical assessment, a standardized measurement of cTn to detect myocardial injury along with other inflammatory (e.g., C-reactive protein, ferritin, IL6, and procalcitonin) and thrombotic (D-dimeric) markers can make it easier to understand whether patients are in stage I (early infection), stage II (pulmonary phase), or stage III (hyperinflammatory phase). In addition, as an ongoing prognostic marker, initial cTn measurement can aid triage of patients, and subsequent serial measurements can help identify low-risk patients with stable concentrations or high-risk patients with increasing patterns. The latter may require additional assessments (Yader and Allan, 2020).

LIMITATIONS

The research carried out has some limitations. First, the interpretation of the results may be limited by the small sample size of a total of 2350000 COVID-19 patients worldwide, the current sample size is still small to avoid statistical bias as much as possible. Second, due to the presence of unmeasured or unknown factors that influence the outcome, the causes of death or myocardial damage can be underestimated by multivariate regression analysis. The study did not include data such as body weight, body mass index and smoking history, which are potential risk factors for disease severity.

CONCLUSIONS

Myocardial injury is not a rare complication among patients with severe COVID-19, especially among those who die. In a meta-analysis of patients with confirmed COVID-19, heart damage assessed by serum analysis (lactate dehydrogenase, cardiac troponin I, creatine kinase (-MB), and myoglobin) was associated with severe outcome and death from COVID-19 infection. CTnI and CK-MB levels predict the risk of hospital death, and myocardial injury is associated with older age, inflammatory response, and concomitant cardiovascular disease. With the rapid development of COVID-19 around the world and a deeper understanding of the mechanisms of heart damage in patients with COVID-19 infection, cardiac biomarkers can be used as an indicator of improved response due to cardioprotective intervention or as an indicator. deterioration of the clinical course.

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COVID-19 zamanı miokardın zədələnməsinin klinik xüsusiyyətləri (Çox mərkəzli tədqiqatların məlumatları)

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Koronavirus-2-nin (SARS-CoV-2) səbəb olduğu COVID-19 xəstəliyi özünü kəskin tənəffüs sindromunun inkişafı ilə göstərir. Bu xəstələrdə miokardın zədələnmə xüsusiyyətlərini öyrənmək və onun klinik əhəmiyyətini təyin etmək məqsədi ilə təqqiqat işləri aparılmışdır. Beynəlxalq çoxmərkəzli tədqiqatlarda ürək-damar patologiyalarının araşdırılması zamanı COVID-19 olan 21 xəstədə anatomik təşrifdən sonra ürək toxuması tədqiq edilmişdir. Kardiomiositlərin zədələnməsini göstərən çoxsaylı iltihab ocaqlarının aşkarlanmasına və immunohistoloji müayinə vasitəsi ilə iltihab hüceyrələrinin tərkibinin analizinə əsasən miokarditin olması müəyyənləşdirilmişdir. Eyni zamanda kardiomiositlərin kəskin zədələnməsinin və iltihabın digər növləri, həmçinin koronar arteriyaların, endokard və perikard zədələnmələri də tədqiq edilmişdir. Limfositar miokarditə 3 (14%) halda rast gəlinmişdir. İnterstisial makrofaqların artan infiltrasiyası 18 (86%) halda müşahidə edilmişdir. 4 xəstədə yüngül dərəcəli perikardit qeyd edilmişdir. Böyük ehtimalla stress/həddindən artıq yüklənmə səbəbindən 4 xəstədə sağ mədəcik miositlərinin kəskin zədələnməsinə rast gəlinmişdir. COVID-19-da serum troponin səviyyəsinin yüksəlməsi və atma fraksiyasının azalması ilə müşayət olunan kəskin ürək çatışmazlığı hallarına da rast gəlinmişdir. SARS-CoV-2 zamanı əksər hallarda interstisial makrofalar artır, az bir halda isə multifokal limfositar miokardit inkişaf edir. Ağır COVID-19-lu xəstələrdə xəstəxanadaxili ölüm riski miokardın zədələnmə markerlərinə əsasən proqnozlaşdırıla bilər və bu risk ahıl yaş, iltihabi reaksiya və yanaşı ürək-damar xəstəliyinin olmasından əhəmiyyətli dərəcədə asılıdır.

Açar sözlər: *Koronavirus xəstəliyi 2019 (COVID-19), SARS-CoV-2, miokardın zədələnməsi, miokardit, laktat dehidrogenaza, troponin I, kreatininfosfokinaza, mioglobin*

Клинические особенности и характеристика повреждения миокарда при COVID-19 (данные многоцентровых исследований)

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Известно, что COVID-19 – тяжелое острое респираторное заболевание, вызванное коронавирусом SARS-CoV-2. Пациенты с коронавирусной инфекцией исследовались с целью изучения повреждения миокарда, определения его характера и клинической значимости. В международном многоцентровом исследовании сердечно-сосудистых патологий состояние сердечной ткани было оценено после вскрытия 21 пациента с COVID-19. Исследования были направлены на выявление наличия миокардита, множественных очагов воспаления с ассоциированным повреждением миоцитов, состав воспалительных клеток анализировали с помощью иммуногистохимии. Также были описаны другие формы острого повреждения и воспаления миоцитов, поражение коронарных артерий, эндокарда и перикарда. Лимфоцитарный миокардит имел место в 3 (14%) случаях. Повышенная инфильтрация интерстициальных макрофагов наблюдалась в 18 (86%) случаях. В четырех случаях наблюдался перикардит легкой степени. Острое повреждение миоцитов правого желудочка, вероятнее всего из-за напряжения / перегрузки, имело место в четырех случаях. При COVID-19 также отмечалась острая сердечная недостаточность, сопровождаемая повышенным уровнем тропонина и сниженной фракцией выброса. В большинстве случаев при SARS-CoV-2 были увеличены интерстициальные макрофаги, а в небольшой части случаев - мультифокальный лимфоцитарный миокардит. Риск госпитальной смерти среди пациентов с тяжелой формой COVID-19 можно предсказать по маркерам повреждения миокарда, и это в значительной степени связано с пожилым возрастом, воспалительными реакциями и сопутствующими сердечно-сосудистыми заболеваниями.

Ключевые слова: *Коронавирусное заболевание 2019 г. (COVID-19), SARS-CoV-2, повреждение миокарда, миокардит, лактатдегидрогеназа, сердечный тропонин I, креатинкиназа (-MB) и миоглобин*