Cardiac manifestations of COVID-19

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COVID-19 is a novel viral infection caused by severe acute respiratory syndrome (SARS) beta-coronavirus. Epidemiological status changes dynamically as the pandemic is far from ending. Several complications of presented virus may be similar to those observed in other viral infections. Despite lacking data, the heart involvement may be comparable to cardiac complications observed previously in those with SARS as well as Middle East Respiratory Syndrome (MERS). In COVID-19 we observe elevated levels of cardiac biomarkers, such as natriuretic peptides, troponins, myoglobin, C-reactive protein (CRP), interleukin-2 (IL-2), interleukin-6 (IL-6) and ferritin, which is likely the result of myocardial injury. The possible mechanisms of cardiovascular injury include direct toxicity through the viral invasion of cardiac myocytes, ACE-2 receptor-mediated CV (cardiac and endothelial) injury, microvascular dysfunction and thrombosis and cytokine release syndrome (mainly IL-6 mediated). Cardiac manifestations of COVID-19 are focal or global myocardial inflammation, necrosis, ventricular dysfunction, heart failure and arrhythmia.

Keywords
COVID-19, Coronavirus, SARS-CoV-2, Heart failure, Cardiac manifestations

1. Introduction

Viral infection is known as one of the most common infectious causes of myocarditis, most often in influenza or parvovirus B-19 infection [1, 2]. It has been widely described that during influenza infection, elderly patients with cardiovascular diseases have higher rates of heart failure-related events, cardiac arrhythmias and acute coronary syndromes [3]. The reasons underlying this may be connected with increased viscosity during febrile illnesses, procoagulation and proinflammatory effects or endothelial cell dysfunction [3, 4]. Previous severe acute respiratory syndrome (SARS) beta-coronavirus infections were associated with symptoms of heart failure and arrhythmias [4]. It is difficult to expect that this might differ in case of coronavirus disease 2019 (COVID-19), caused by SARS-CoV [4]. The first observations were focused on respiratory problems often with hypoxic respiratory failure and bilateral infiltrates on computed tomography [5]. Complications from different organs have also been diagnosed, including cardiovascular manifestations, as one of the most important that essentially effect the prognosis. It seems that the heart injury in patients with COVID-19 may be comparable to cardiac complications observed previously in those with SARS as well as Middle East Respiratory Syndrome (MERS), but we are still lacking data. Cardiac injury may be a direct manifestation of COVID-19. On the other hand, it can be a complication of acute lung injury [6]. In addition, elevated filling pressure and exacerbation of heart failure may also play a role in lung failure caused by SARS-CoV-2 [6].

2. Search strategy

We searched the electronic database PUBMED (2019 to 2021). Furthermore, abstracts from national and international cardiovascular meetings, summaries of product characteristics and selected monographs were searched. The main data search terms were: cardiac manifestations, coronavirus, COVID-19, heart failure, SARS-CoV-2, severe acute respiratory syndrome.

2.1 Epidemiology of COVID-19

COVID-19 is the public health challenge of the century. The pandemic is spreading dynamically across the world and any information published may soon need to be updated. In the beginning of the COVID-19 outbreak the most valuable and complete data were provided by Chinese researchers, as this country was the first one to successfully reduce both transmission and mortality [7]. The epidemiological data are still difficult to summarize as the number of patients tested positive as well as fatalities increases daily. Another issue with the data is their regional variability depending on the onset of the epidemic in each country and the healthcare efficiency as a derivative of growth in cases.

SARS-CoV-2 is highly contagious, although it is not very lethal. At the time this article was written 142,066,934 confirmed cases globally had resulted in 3,034,412 deaths and 120,633,661 recoveries [8]. The situation is not evenly distributed across the world, as the most severely affected re-
gions are both Americas (mostly the USA & Brasil), Europe (France, Russia and UK leading the statistics) & Asia (India & Indonesia with the highest numbers of detected positive patients) [9]. The global fatality rate estimation so far is approximately 2.13%, although we present also ongoing cases, so the final result may vary. It is important to acknowledge the fact the case fatality rate differ across the world and it is highly dependent on the local healthcare capacity, prevention and vaccination strategies and initial testing of any suspicious cases. It may also correlate with the number of cases as the waves of the infection are connected with higher fatality and overall mortality. The mortality rate increases among patients older than 60 years up to 8.8%, while it stays low for under 60 years old patients—0.46% [10]. The US research shows differences in prevalence and mortality among races as COVID-19 infection occurs with higher probability in Latino and African American vs “white” individuals (1000 and 925 vs 389 per 100,000 respectively) and is more fatal in the African American group vs Latino and white individuals (73 vs 36 and 22 per 100,000 respectively) [11].

2.2 Risk factors and the course of COVID-19 with cardiac manifestation

The mortality risk factors in patients with COVID-19 are: obesity, hypertension, diabetes, chronic lung, cardiac, hepatic and kidney diseases, cancers, immunodeficiencies and pregnancy [12]. To be precise according to cardiovascular diseases the main risk factors are coronary artery disease, heart, arrhythmias and current tobacco smoking. In fact, cardiovascular comorbidities occurring with SARS-CoV-2 can be both risk factors of poor outcome and eventually manifestations of COVID-19 itself. Furthermore, they are markers of bad prognosis as myocardial damage and heart failure are associated with 40% of deaths in Wuhan [13]. Many of patients with a severe course of the disease had increased plasma high-sensitivity troponin-I (>28 pg/mL: 46% among non-surviviors vs 1% among survivors) and Ddimer (>1 µg/mL: 81% among non-survivors vs 24% survivors) [14]. Further research also provides valuable data on N-terminal proB-type natriuretic peptide (NT-proBNP) levels, which were increased in approximately 27.5% of infected patients [15]. NT-proBNP can be an independent risk factor as higher values (>88.64 pg/mL) predicted higher risk of death with sensitivity of 100% and specificity of 66.67% [16].

Most common cardiac manifestations in symptomatic SARS-CoV-2 patients are arrhythmias (16.7%) with ventricular tachycardia/fibrillation (5.9%) [17], shock (7–8.7%) [18, 19], acute myocardial injury (7.2%), chest pain (3.4%), and ST-depression on electrocardiogram (ECG) (0.7%) [20]. Zhou et al. [14] found high prevalence of heart failure (23%) as an extrapulmonary manifestation of infection and the rate was higher (52%) in non-survivors. It is still debatable if it is caused by viral affliction of myocardium or as a result of cytokine storm and a rapid inflammatory response. There are cases of acute myocarditis developing before the pulmonary symptoms; thus ventricular tachyarrhythmias may become the first clinical manifestation of COVID-19 infection and leads to increased risk of sudden cardiac death [21, 22].

Survival of cardiac arrests of inpatients in Wuhan was poor. Restoration of spontaneous circulation (ROSC) among 136 patients was reported in 18 patients (13.2 %), while only 4 (2.9%) survived for at least 30 days and 1 was in a favorable neurological condition [23]. The main cause of cardiac arrest was respiratory (87.5%) and at the onset of resuscitation the most common rhythm was asystole (89.7%), while pulseless electrical activity (PEA—4.4%) and shockables were the rarest (5.9%) [23].

The early US data gathered after the outbreak in New York City provided initial information about 5700 cases hospitalized due to infection [24]. 2634 patients had reached the outcome of death (21%) or discharge, 14.2% been treated invasively at the ICU and 12.2% required use of mechanical ventilators. Among hospitalized patients the most common comorbidities were hypertension (56.6 %), obesity (41.7 %) and diabetes (33.8 %). For comparison, American prevalence for hypertension is 33.2%, obesity 39.8% and diabetes 15% [25].

Despite the early data, year after global coronavirus outbreak there was also observed strong relation between coexistence of cancers with cardiovascular diseases and high-risk of death due to COVID-19. Patients with cancers and cardiac comorbidities died more frequently in comparison with cancer (35% vs 17%; P = 0.004) or cardiovascular disease solely (35% vs 21%; P = 0.009) [26].

2.3 Pathophysiology of cardiac involvement in COVID-19

In patients with SARS-CoV-2 one of the observations is an elevated level of cardiac biomarkers, such as natriuretic peptides, troponins, myoglobin, C-reactive protein (CRP), interleukin-2 (IL-2), interleukin-6 (IL-6) and ferritin, which is likely the result of myocardial injury [19, 27, 28]. It was confirmed by Xu Z et al. [27], that myocardium of patients with SARS-CoV-2 infection was infiltrated with inflammatory cells. Such viral invasion of cardiac myocytes remains one of the mechanisms of cardiac involvement, which can explain the development of myocarditis frequently observed in cardiac magnetic resonance imaging and echocardiography of COVID-19 patients. On the other hand, the most likely explanation for increased levels of these biomarkers is direct cardiac involvement leading to cardiac apoptosis. Other possible explanations include hypoxia, tachycardia, arrhythmias, myocarditis, microvascular dysfunction, thrombosis, Takotsubo cardiomyopathy and auto-immune-like mechanisms related to the release of proinflammatory cytokines [29, 30]. There have been a few attempts described worldwide to explain cardiac toxicity mechanisms in COVID-19 patients. SARS-CoV-2 enters the cell by a host receptor angiotensin-converting enzyme 2 (ACE2) [31, 32]. ACE2 protein, which is expressed in the lungs, heart and vessels, is a convertase capable of angiotensin II to angiotensin (1–7) and angiotensin I to angiotensin (1–9) transformation. Those proteins have cardioprotective activity [33]. On the other hand, ACE2 binds the SARS-CoV-2 spike protein and
transfers it into lung alveolar epithelial cells [34] by cell surface associated transmembrane protein serine 2 (TMPRSS2) [35]. The SARS-CoV-2 infection leads to dysregulation of the renin-angiotensin system (RAS) and ACE2, which serves as a main entry site to the human host while normally being protective for the lungs. Additionally, it has been observed that patients with hypertension more often had a severe course of COVID-19 compared with those with normal blood pressure [36, 37].

Characteristics of Chinese patients showed that diabetes, hypertension and cardiovascular disease are common among SARS-CoV-2 positive patients and may be associated with poor outcomes. Usually patients who suffer from cardiovascular diseases are older and therefore they have a worse functioning immune system that is less able to fight infections [38]. One potential explanation of these results is that bilateral pneumonia is capable of deterioration of the blood oxygenation within lungs, which in turn leads to a poor outcome in patients with cardiac comorbidities, such as heart failure, cardiomyopathies and congenital cyanotic heart diseases. However, the direct relationship is not fully understood [19, 27, 28].

Despite initial suggestions that the treatment of hypertension and other cardiovascular diseases with RAAS inhibitors may trigger COVID-19 due to altered the virus binding to the receptor ACE2 [39], the European Society of Cardiology and the European Society of Hypertension did not recommend the withdrawal of such therapy. While ACE2 is considered essential for SARS-CoV infection, absence of SARS-CoV was observed in some ACE2 expressing cell types, whereas infection was present in apparently ACE2-deficient cells. It suggests that collateral cofactors may play a role in successful cell infection. More research is needed to elucidate the complex role of the RAAS in connection with SARS-CoV-2 infection [40]. Moreover, the poor outcome of COVID-19 is mainly due to the severity of the lung injury.

The RNA viral genome is released in cytoplasm of host cells and starts rapid replication. The virus can then be released outside the host cell through the cell membrane. The virus directly attacks the lungs and triggers an inflammatory response which affects the heart and vessels as well. Immune system activation is connected with another way of viral invasion, which involves differentiation cluster 209 (CD209) expressed in macrophages [41]. CD209 enables viral entry to immune cells located in the heart and vessels. In severe COVID-19 cases cytokine release storm (CRS) was observed [42]. The cytokines which take part in that process are: IL-2, IL6, IL-7, chemokine C-C motif ligand 2, C-X-C motif chemokine 10 (CXCL10), granulocyte colony stimulating factor and tumor necrosis alpha factor (TNF-alpha) [43]. Laboratory tests may reveal increased levels of ferritin, D-dimer, CRP, IL-6, lactate dehydrogenase (LDH) and lymphopenia [44]. Early studies showed that one of those cytokines, IL6, can be a predictor of increased mortality in COVID19 [45]. The inflammatory process may also lead to plaque instability and as a consequence to acute coronary events. Common cardiac disease may be easily mistaken for SARS-CoV-2.

The pathomechanisms of cardiac manifestation of COVID19 are shown in the Fig. 1.

![Pathomechanism of COVID-19](image)

**Fig. 1. Pathomechanism of COVID-19 (the SARS-CoV-2 spike protein is activated by TMPRSS2, which allows for its attachment to ACE2. ACE2 receptor is a way for host cell entry. SARS-CoV-2 attacks lungs and heart, leading to dysfunction of heart and cytokine storm).**

### 2.4 Management approach for patients with COVID-19 associated cardiovascular involvement

Myocarditis is often suspected in patients with chest pain during or after an influenza-like syndrome, with changes on electrocardiography or laboratory testing suggesting an acute coronary syndrome with wall motion abnormalities but without coronary artery disease on coronary angiography [46]. Some reports of patients presenting cardiac symptoms in COVID-19 infection, myocardial inflammation, necrosis and ventricular dysfunction and arrhythmia shown in Table 1 [47–54] suggest not only myocardial injury but also potentially viral myocarditis or stress cardiomyopathy [46, 55]. Moreover especially critically ill COVID-19 patients admitted to intensive care unit develop different arrhythmias like sinus bradycardia, and tachycardia, supraventricular tachycardia, atrial fibrillation, and also non-sustained ventricular tachycardia [49, 56]. COVID-19 patients may be tachycardic due to fever, pain, etc. They can also develop rhythm abnormalities in the setting of prolonged QTc, and electrolyte disturbances, especially high risk patients such as those with pre-existing cardiovascular disease, cancer or combination of both [57]. To date, there is a scarcity of publications mentioning adults with congenital heart defects (ACHD) facing COVID-19 [58]. Because there are no published cases of patients with congenital heart defects, all the management strategies are adapted and based on treating congenital heart
### Table 1. Reports of patients presenting cardiac symptoms in COVID-19.

| Manifestation                                      | Diagnostics                                                                 | Treatment, outcome                                                                 |
|----------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Inciardi RM, Lupi L, Zaccone G, et al. [47]         | Acute myopericarditis with systolic dysfunction                            | - Elevated levels of hsTnT, NT-proBNP, CRP with normal blood cell counts.         |
|                                                    |                                                                             | - Dobutamine                                                                      |
|                                                    |                                                                             | - Lopinavir/ritonavir                                                              |
|                                                    |                                                                             | - Steroids                                                                        |
|                                                    |                                                                             | - Chloroquine                                                                     |
|                                                    |                                                                             | - Heart failure treatment                                                         |
|                                                    |                                                                             | - Methylprednisolone                                                              |
|                                                    |                                                                             | - Immunoglobulin                                                                  |
| Hu H, Ma F, Wei X, Fang Y. [48]                     | Fulminant myocarditis with cardiogenic shock and pulmonary infection in 37-year-old male patient. | - Elevated Troponin T > 10000 ng/L. Creatine kinase isoenzyme (CK-MB) 112.9 ng/L. NT-proBNP-21025 ng/L. | - Methylprednisolone              |
|                                                    |                                                                             | - Electrocardiogram                                                               | - Immunoglobulin                  |
|                                                    |                                                                             | - Echocardiography                                                               | - Norepinephrine                 |
|                                                    |                                                                             | - Left ventricle end diastolic dimension (LVEDD) - 58 mm                          | - Diuretic                       |
|                                                    |                                                                             | - LVEF 27%                                                                        | - Milrinone                      |
|                                                    |                                                                             | - Chest X-ray and thoracic computed tomography (CTT): pleural effusion.          | - Piperacillin sulbactam.         |
|                                                    |                                                                             | - coronary angiography: no obstructive coronary disease.                          |                                   |
| Babapoor-Farrokhran S, Port Z, Gill D, et al. [49]  | Multiple Arrhythmias in COVID-19 Patients: A Case Series                    | LVEF and cardiac biomarkers normalized within 3 weeks.                            |
| Chen C, Zhou Y, Wang DW. [50]                       | Viral myocarditis in 120 SARS-CoV-2-infected patients                       | - Non-sustained monomorphic ventricular tachycardia was the most common arrhythmia |
| Gao L, Jiang D, Wen XS, et al. [51]                 | 54 patients                                                                 | - Steroids and immunoglobins                                                      |
| Wang D, Hu B, Hu C, et al. [52]                     | A retrospective, case series of 138 COVID-19 patients reported that 7.2% and 16.7% of patients had acute cardiac injury and arrhythmia respectively | - Neuraminidase inhibitors                                                      |
| Huang Ch, Wang Y, Li X, et al. [53]                 | Cardiac injury of COVID-19 was common in severe patients with the TnI over 40-fold higher than normal value. | - Active mechanical life-support treatments.                                       |
| Shi S, Qin M, Shen B, et al. [54]                   | In group of 416 patients hospitalized of COVID-19 19.7% had cardiac injury. | Patients with cardiac injury required more noninvasive ventilation (46.3% vs 3.9%; P < 0.001) and mechanical ventilation (22.0% vs 4.2%; P < 0.001), higher use of antibiotics (82.9% vs 50.0%), glucocorticoids (87.8% vs 69.5%), and immunoglobulin (82.9% vs 57.2%) (all P < 0.001). | Patients with cardiac injury had higher mortality (51.2% vs 4.5%; P < 0.001). |
defects like any other cardiovascular morbidity, especially heart failure [59]. It seems logical to perceive grown-up congenital hearts as ones with much higher risk than the general population. According to the ACHD Anatomical and Physiological Stage Classification from the latest American Guidelines, patients with complex congenital heart disease—anatomical stage III or symptomatic stage B, C, or D—could have high risk for complications related to SARS-CoV-2 infection [60].

These observations suggest a high incidence of lethal cardiac events, arrhythmias, heart failure which are similar to a stress cardiomyopathy or cytokine-related myocardial dysfunction in progressive stages of COVID-19 with fulminant cytokine release. The terminal phase could potentially be avoided by anticytokine therapy such as corticosteroids and the IL-6 blocker tocilizumab [61–63]. Nevertheless, the effect of immunosuppression on the course of this illness is unclear. While in vitro evidence suggests that immunosuppressive medications may inhibit viral replication, long-term such therapy like used for recipients of heart transplant (HT) increases susceptibility to infection [64]. Among twenty-eight HT patients in New York, mycophenolate mofetil was discontinued in 70% (16 patients), and 26% (6 patients) had a dose reduction of calcineurin inhibitor [65].

Attempts are being made to develop a structured approach to care of COVID-19 positive patients with heart involvement (Table 2). A classification of these patients in the early stage and algorithms of diagnostics could provide effective triage for the management of patients [62, 66–69].

### Table 2. Classification of COVID-19 patients—a structured approach to COVID-19 positive patients with heart involvement.

| Type                      | Manifestation                  | Cardiological diagnostics                                      | Treatment                                                                 |
|---------------------------|--------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------|
| A                         | Asymptomatic or mild symptoms | Mild pneumonia                                                  | - basic treatments: antivirals, antibiotics, oxygen therapy, glucocorticoids |
|                           | (cough, fever, diarrhea and headache) |                                                                               | - no evidence that ACEi or ARBs should be discontinued                      |
|                           |                                | Consider evidence of myocardial injury: | - antivirals, symptomatic treatments |
|                           |                                | - TnT                                                            | - antihypertensives, hypoglycemic therapy and continuous renal replacement therapy |
| B                         | Moderate disease with shortness of breath/hypoxia | Different degrees of pneumonia, with serious comorbidities | - NT-proBNP                                                             |
|                           |                                | - echocardiography                                               | - avoid excessive fluids due to underlying pulmonary edema               |
|                           |                                | - lung ultrasound, CTT, CCTA, CMR                               |                                                                         |
|                           |                                | - invasive angio + ventriculography when suspected coronary artery disease, lung embolism, other lung complications |                                                                         |
| C                         | Critical stage disease         | Multiple organ injuries                                         | - antigens, symptomatic treatments                                       |
|                           | with hypoxia, vasoplegia and shock |                                                                               | - glucocorticoid                                                        |
|                           |                                | - check for evidence of hyperinflammation or a cytokine release storm (elevated CRP, IL-6, ferritin, troponin and natriuretic peptides levels) | - mechanical ventilation                                                   |
|                           |                                |                                                                   | - circulatory support systems: extracorporeal membrane oxygenation and intraaortic balloon pump |

3. Conclusions

Myocardial injury during COVID-19 can be explained by three potential mechanisms: myocardial dysfunction from the direct viral effect on cardiomyocytes—ACE2 mediated direct damage; cardiac injury indirectly due to an excessive immune inflammatory response like cytokine storm; and hypoxia, oxidative stress due to acute respiratory damage resulting in myocardial necrosis from increased myocardial oxygen demand [67]. Cardiovascular diseases are common among SARS-CoV-2 infected patients and can be associated with bad outcomes. It is important to stratify holistic risk by taking all other comorbidities such as diabetes, neurological disorders, disabilities or pulmonary diseases into consideration. Patients diagnosed with COVID-19 may be treated the same way as the general population unless they develop cardiac manifestations. It is necessary to analyze the ECG and measure the levels of biomarkers, such as NT-proBNP, troponins, myoglobin, D-dimers, C-reactive protein, interleukin-2, interleukin-6 and ferritin, to evaluate in a high-risk patients presenting with acute COVID-19, and to help in early detection of patients in need of hospitalization.

Author contributions

ABD—performed the first literature searching, wrote a first manuscript and revised the final version of article, ACR—performed additional literature searching, wrote the part of the draft and improved the paper, JL—wrote the part of draft and prepare a figure, FP—wrote the epidemiology section and improved a draft, MM—prepared a table and improved a draft, MB—revised and improved the draft. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.
Ethics approval and consent to participate
Not applicable.

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Conflict of interest
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