Vol. 47 (2022) No. 2-3 TIMOK MEDICAL GAZETTE Review article

DAMAGE TO THE CARDIOVASCULAR SYSTEM AND COMPLICATIONS IN COVID-19 INFECTION WITH A FOCUS ON THE POST-ACUTE COVID19 SYNDROME

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ABSTRACT: The causative agent of severe acute respiratory syndrome, corona virus 2 (SARS-CoV-2), the etiological agent of the COVID-19 disease, can infect the heart, vascular tissues and circulating cells via angiotensin-converting enzyme 2 (ACE-2), a cell receptor host for the viral spike protein. The focus of this review article is on the prevalence, risk factors, pathogenesis, clinical course and sequelae of myocardial damage caused by the disease COVID-19. Emphasis is also placed on the interactions of platelets with the vascular endothelium, which includes consideration of the role of the SARS-CoV-2 virus protein in triggering the development of generalized endothelitis, which further in a circle triggers more intense activation of platelets. Acute cardiac lesion is a common extrapulmonary manifestation of COVID-19 with potential chronic consequences. Clinical manifestations include direct cardiac damage and indirect immune response mechanisms that affect the cardiovascular (CV) system and have implications for the treatment of patients after recovery from acute COVID-19 infection. **The most common direct cardiovascular lesion** is an acute heart lesion, present in more than 12% of all infected patients and defined by a significant increase in cardiac troponins in the serum and echocardiographic signs of damage to the myocardial texture due to inflammation, impairment of segmental mobility or global systolic and diastolic function of the left ventricle and sometimes inflammation of the pericardium. Arrhythmias, venous thromboembolism and cardiomyopathy are predominant KV manifestations described in the patient with COVID- 19. An analysis of 72,314 confirmed cases of COVID - 19 (Wuhan) showed total mortality of 1663 patients or 2.3%, with presence of a previous KV disease in 10.5%, diabetes Mellitus in 7.3% and arterial hypertension in 6%. Cardiovascular complications because of COVID-19 associated with comorbidities were: myocardial lesion (20 %), cardiac arrhythmias (16%), myocarditis and fulminant myocarditis with lowered ejection fraction (10%), non-occlusive myocardial infarction and venous thromboembolism and acute‘ cardiac insufficiency and cardiogenic shock. Hypertension and diabetes are the most frequent_comorbidities in those infected with COVID-19, for whom hospitalization was necessary. A Denmark study based on the national register of over 5000 patients with hospitalized COVID-19 revealed that the risk from the acute myocardial infarction and ischemic stroke was 5 and even 10 times higher , respectively , during the first 14 days after COVID- 19 infections in comparison with the period which preceded the known infection. Numerous individual cases point to extremely high values and troponin T dynamics typicalfor non-occlusive myocardial infarction with normal coronary arteries. **Mechanisms of indirect cardiovascular lesions** are: dysregulation of inflammatory or immune responses of hyperinflammation, vascular thrombosis and activation of platelets, autoimmune phenomena and adaptive immunological dysfunction in vascular thrombosis associated with COVID- 19. Cardiovascular dysfunction and disease are often fatal complications of a severe COVID- 19 virus infection. Cardiac complications can occur even canin patients without basic cardiac insufficiency, as a part of acute infections and they are associated with a more severe form of COVID 19 disease and increased mortality. Of COVID-19 patients treated in the intensive care unit 61% died because they had acute respiratory distress syndrome (ARDS), 44% of them had severe cardiac arrhythmias and 31% percent of them experienced a shock syndrome. Elevated troponin levels were rare in survivors of uncomplicated COVID-19 (1%–20%), common in critically ill patients (46%–100%), and almost universally elevated in critically ill (ie, those requiring intensive care or mechanical ventilation) and those who did not survive. Some autopsy findings suggested myocardial infiltration by mononuclear leukocytes and revealed some cases of severe myocarditis with a dilated phenotype. Among patients hospitalized with COVID-19, evidence about

acute damage of cardiac functions are frequent _ and include the following: acute cardiac insufficiency (3%-33%), cardiogenic shock (9%-17%), ischemia or myocardial infarction (0.9%–11%), left ventricular dysfunction (10%–41%), right ventricular dysfunction (33%–47%), biventricular dysfunction (3%–15%), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%) and arterial thrombosis as secondary viral mediated coagulopathy. COVID - 19 is associated with abnormalities of cardiac structures and functions including echocardiographic evidence of left ventricular dysfunction, regional wall movement abnormalities and mild reduction of right ventricular function. Involvement of myocardial lesion because of SARS - CoV -2- infection was very much widespread even in patients with mild symptoms.

Key words: COVID-19, ACE 2 receptor, acute myocardial lesion, venous thromboembolism, non-occlusive myocardial infarction, myocarditis, cardiovascular diseases, corona virus, post-acute COVID- 19

INTRODUCTION

Corona Virus Disease 2019 (COVID-19) has brought the life of the whole humanity to a standstill. Catastrophic loss of life, a confusion in healthcare and the vulnerability of the global economy are some of the outcomes of this pandemic. COVID-19 infection affects global population regardless of age and gender, and with comorbidities present, COVID-19 and its complications escalate at an alarming rate. Cardiovascular (CVD) diseases per se are the leading cause of death globally with an estimated 31% of deaths worldwide of which nearly 85% are due to heart attack and stroke. Scientific researchers have noted that individuals with pre-existing CV diseases and conditions are relatively more susceptible to infection with COVID-19 [1,2]. Moreover, it was shown in the comparison between subgroups: milder and more severe cases, survivors and non-survivors, patients from intensive care units and those who were not in intensive care [2]. The impact of the COVID-19 preventive measures of isolation and quarantine (lockdown) on CVD patients in Denmark showed that at that time, compared to the pre-Covid 19 era, there was no difference in the mortality of CVD patients. However, an increased out-of-hospital mortality and decreased in-hospital mortality were found. In contrast, in Germany and France, there was a significant increase in mortality, even by 12-20% in CV patients in April 2021.

Strategies for the diagnosis of SARS-CoV-2

The diagnosis of COVID-19 is based on a combination of epidemiological criteria (contact within the incubation period), the presence of clinical symptoms, laboratory tests (PCR tests) and tests based on clinical imaging. Antibody-based tests and SARS-CoV-2 antigen enzyme-linked immunosorbent assay (ELISA) are under development and not yet fully validated. Widespread testing has proven effective in the containment phase of the epidemic. The quality of sample collection (deep nasal swab) and transport (time) to the laboratory is necessary to avoid false negative results. Lung computed tomography (MSCT) can be used as a diagnostic test for COVID 19 [3] .

We know that the penetration of the SARS COV-2 virus and the cause of the COVID-19 infection, after a short incubation and various respiratory symptoms, loss of the sense of smell and general symptoms: elevated body temperature, malaise, myalgia and arthralgia, most often affect the lung parenchyma . At the beginning lung damage manifests like flu syndrome (cough and fever), which is progressing to the pneumonia (dyspnea, hypoxemia , tachypnea) and , in some cases , to _ acute respiratory distress syndrome or non-cardiogenic pulmonary edema (ARDS).

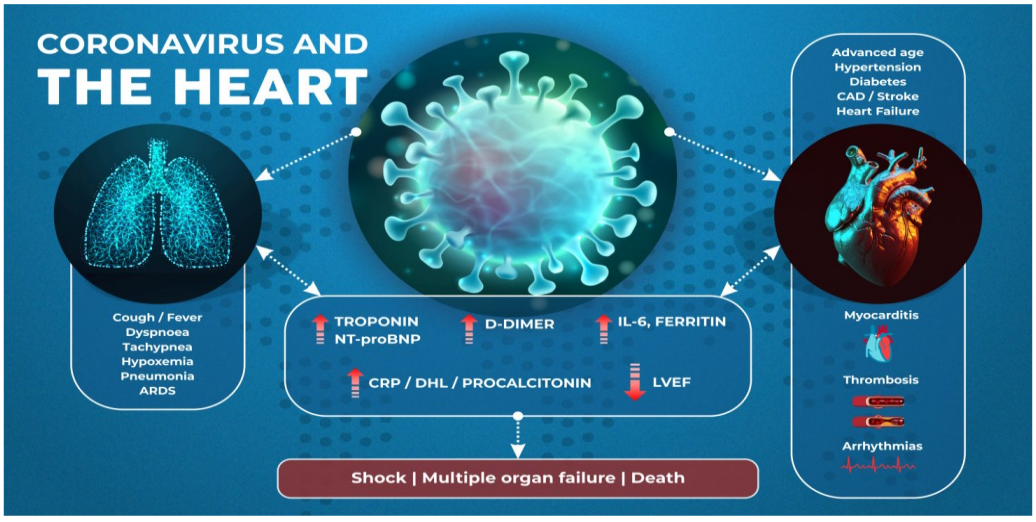
Acute cardiac lesion is an ordinary extrapulmonary manifestation of COVID- 19 with potential chronic consequences. Clinical manifestations include directcardiac involvement and mechanisms of indirect immune response which affect the cardiovascular system and implications on the treatment of patients after the recovery from the acute COVID- 19 infections [4]. Early radiography of the lungs and the heart and the most reliable MSCT (multilayer, multidetector computer-tomographic scan) of the thorax show detectable changes in the lung parenchyma in up to 85% of patients, which can be both oligosymptomatic and asymptomatic [5].

PATHOGENESIS OF ACUTE COVID-19 MYOCARDIAL LESIONS

Acute COVID-19 myocardial lesion whose marker is elevated high-sensitivity troponin T is

present in > 12% of infected patients [6]. Hence, cardiac lesions in patients infected with the SARS COV-2 virus become associated with higher morbidity and mortality. [6]. Severe acute respiratory distress syndrome-caused by coronavirus 2 (SARS-CoV-2) is manifested by the dominance of excessive production of inflammatory cytokines (IL-6 and TNF-α), which leads to systemic inflammation and syndrome of multiple dysfunction of organ systems, acutely involving the cardiovascular system. Hypertension (56.6%) and diabetes (33.8%) are the most common comorbidities in those infected with COVID-19 who require hospitalization. Cardiac lesion, defined as elevated high-sensitivity troponins T and I, is significantly correlated with inflammatory biomarkers: interleukins 6 and 2 (IL-6, IL- 2) and C-reactive protein (hsCRP), hyperferritinemia and leukocytosis, and reflects a significant association of the myocardial lesion and inflammatory hyperactivity caused by viral infection [6]. In addition, mechanisms by which activated platelets intensify pre-existing endothelial activation and dysfunction, most likely caused by the release of platelet-derived calcium-binding proteins (SA 100A8 and SA 100A9), have been described. Coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19, can infect the heart, vascular tissues and circulating cells via ACE2 (angiotensin-converting enzyme 2), the host cell receptor for the viral spike protein. Endotheliitis caused by SARS-CoV-2 [1] involves the interaction of the viral spike (S-protein part of the virus, the so-called spike) protein with the endothelial enzyme that converts angiotensin 2 (ACE2 convertase) together with alternative mechanisms via nucleocapsids and viroporins. These events create a cycle of intravascular inflammation and coagulation driven by the SARS-CoV-2 virus, which significantly contributes to poor clinical outcome in patients with more severe forms of infection. Patients with risk factors and/or cardiovascular diseases are prone to developing severe forms of COVID-19 and its complications (FIGURE 1). The host's response to the virus leads to signs of systemic inflammation, with increases in markers of inflammation (hsCRP, procalcitonin, d-dimer, IL-6, ferritin, LDH) and myocardial lesions and/or cardiac dysfunction (troponin and/or NT-proBNP), which predisposes to acute heart failure, myocarditis, thrombosis and arrhythmias. These CV complications interfere with the host's response to the virus, which can lead to shock syndrome, multiple organ failure, and death [7]. (FIGURE 1)

FIGURE 1. Corona virus and the heart.



LEGEND: CAD: coronary artery disease; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; CRP: C-reactive protein; IL-6: interleukin-6; ARDS: acute respiratory distress syndrome [7]. *retrieved from https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-20200279/0066-782X-abc-20200279-en.pdf*

COVID-19 AND CARDIOVASCULAR COMORBIDITIES

A meta-analysis of 6 studies from China with 72314 COVID-19 patients shows a high prevalence of arterial hypertension (17 ± 7%), diabetes mellitus (8 ± 6%) and cardiovascular disease (CVD) (5 ± 4%) as comorbidities [7, 8]. In 138 hospitalized patients with COVID-19 and pneumonia, Wang et al found a high prevalence of hypertension (31.2%), CVD (19.6%), and diabetes (10.1%), and these comorbidities lead to the most severe forms of COVID 19 which usually requires hospitalization (hypoxemia, need for treatment in intensive care), especially in the elderly (median 42-64 years old) [9]. Another meta-analysis of 7 studies, on 1576 out-of-hospital infected patients, shows the highest prevalence of comorbidities: hypertension (21.1%), diabetes (9.7%), cardiovascular diseases (CVD) (8.4%) and chronic respiratory diseases (1 .5%). By comparing severe forms of COVID-19 with moderate and mild ones, a statistical parameter was obtained: **ODDS** ratio **(OR)** - odds ratio for a bad outcome: for hypertension - 2.36 (95% CI: 1.46–3.83), for respiratory diseases – 2.46 (95% CI: 1.76–3.44) and the highest for cardiovascular diseases - 3.42 (95% CI: 1.88–6.22)/respectively [10].

MORTALITY IN RELATION TO PREVIOUSLY RELEVANT CHRONIC DISEASES

An analysis of 72314 confirmed cases of COVID-19 (Wuhan) found a total mortality of 1663 patients or 2.3%, with the presence of a previous disease: 10.5% with CV disease, 7.3% with diabetes mellitus and 6% with arterial hypertension. Cardiovascular complications due to COVID-19 associated with comorbidities were: myocardial lesion (20%), cardiac arrhythmias (16%), myocarditis (10%) and acute heart failure and cardiogenic shock (about 5%) [8,9,11, 12]. Guo et al, evaluating a cohort of 187 patients, found that those with myocardial lesions had a higher prevalence of hypertension (63% vs 28%), diabetes (30.8% vs 8.9%), coronary disease (32.7% vs 3%) and heart failure (15.4% vs 0%) and these are of older age (median 71.4 years) [9]. In a group of 191 patients, Zhou et al. compared those discharged from the hospital with those who died and those who died had a higher prevalence of hypertension (48%), diabetes (31%) and CVD (24%) [13].

CARDIOVASCULAR DISEASE IN PATIENTS WITH COVID-19

COVID-19 patients treated in the intensive care unit had the following diagnoses from which they died: acute respiratory distress syndrome (ARDS) in 61%, severe cardiac arrhythmias in 44% and shock syndrome in 31%. Some autopsy findings suggested myocardial infiltration by mononuclear leukocytes and revealed some cases of severe myocarditis with a dilated phenotype [14,15]. COVID-19, as well as earlier coronaviruses and influenza epidemics, suggest an association with acute coronary events, arrhythmias and exacerbation of chronic heart failure, but the data also suggest the development of DE NOVO cases of cardiovascular diseases and worsening of the existing ones [14]. Cardiac lesion in patients infected by SARS COV -2 virus (COVID - 19) is associated with higher risk from: myocardial infarction, fulminant myocarditis which quickly develops with lowered EF left ventricular function, arrhythmias, venous thromboembolism, cardiomyopathy which reminds of the acute heart attack with ST elevation - STEMI the so-called Takotzubo cardiomyopathy. In addition, SARS-CoV-2 tropism and interaction with the rennin-angiotensin-aldosterone system (RAAS), through the ACE2 receptor, enhances the inflammatory response and aggression to the heart, leading to the imperative position on the use of ACE inhibitors and angiotensin receptor blockers (ARBs, sartans) in infected patients. CV consequences lead to a poor prognosis, emphasizing the importance of their early detection and the introduction of an optimal treatment strategy [6]. Among hospitalized patients with COVID-19, evidence of acute impairment of cardiac function is common and includes the following: acute heart failure (3%–33%), cardiogenic shock (9%–17%), myocardial ischemia or infarction (0.9% -11%), ventricular dysfunction (left ventricular [10%–41%], right

ventricular [33%–47%], biventricular [3%–15%]), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%) and arterial thrombosis secondary to viral-mediated coagulopathy [4]. A Danish study based on a national registry of over 5000 hospitalized patients with COVID-19 found that the risk of acute MI and ischemic stroke was 5-fold and 10-fold higher, respectively, during the first 14 days after infection with COVID-19 compared with the period which preceded the known infection [16].

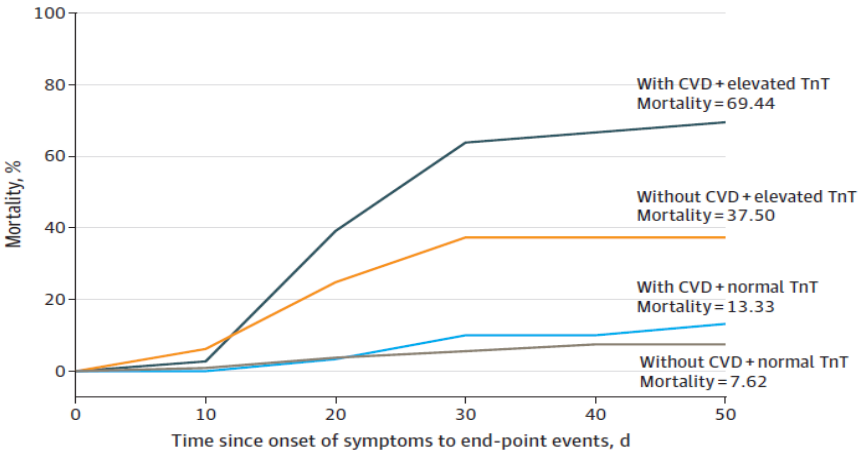
PROGNOSIS OF CVS DAMAGE IN COVID-19 AND PREDICTORS OF MORTALITY

The prognosis depends on the presence of CV risk factors (e.g. male gender, older age, population, hypertension, diabetes), comorbidities (e.g. coronary disease and other cardiac diseases, chronic obstructive pulmonary disease, chronic renal failure and malignancies) that predispose patients with COVID-19 to more severe forms of diseases and increased mortality [4]. Racial and ethnic disparities in the outcomes of COVID -19 are also evident [4]. Advanced age is an independent predictor of mortality in COVID-19 infection. The mortality rate increases with age as follows: 1.3% in patients aged 50-59 years; 3.6% in patients aged 60-69; 8% in patients aged 70-79 years; and 14.8% in patients older than 80 years. Population studies have reported an overall mortality rate of 6% in patients with hypertension, 7.3% in patients with diabetes, and 10.5% in patients with CVD. Patients with malignant tumors have a higher risk of COVID-19 due to impaired immune defenses and the consequences of antineoplastic treatment. In China, among confirmed cases of COVID-19, the prevalence of cancer ranged from 1% to 7%, which is higher than the total incidence of cancer in that country (0.2%). Patients with cancer were more likely to develop a severe form of COVID-19 compared to those without cancer (39% vs. 8%). Of cancer patients who had undergone recent chemotherapy or surgery, 75% developed severe disease compared with 3% of those who had not received recent treatment [17].

Biomarker evidence of cardiac lesion is strongly associated with worse outcomes in COVID-19. Elevation of cardiac biomarkers, such as NT-proBNP, Troponin(Tn) T and I or D-dimer, predicts poor clinical outcomes. In hospitalized patients with COVID-19, the prevalence of elevated hs-TnT (high-sensitivity troponin-T) is 20% to 30%. Based on such elevated Tn levels, acute myocardial lesions range from 8% to 62% according to various data, and more severe forms of the disease are associated with higher levels of cardiac biomarkers. Elevated Tn levels were rare in survivors of uncomplicated COVID-19 (1%–20%), common in critically ill patients (46%–100%), and almost universally elevated in critically ill (ie, requiring intensive care or mechanical ventilation and those who did not survive) [11].

Among 2736 hospitalized patients with COVID-19 in New York, even small elevations of Troponin I (>0.03–0.09 ng/mL) were associated with higher mortality.

DAMAGE to the myocardium and earlier CVD



Data of a retrospective study, of COVID-19 patients hospitalized in 7 hospitals in Wuhan in the period 23.01.-23.02.2020 [18].

Moreover, the greater the increase in TnT, the greater the risk of mortality [18]. Compared with those without elevated TnI, COVID-19 patients with elevated Tn have a higher risk of acute respiratory distress syndrome (58%–59% vs. 12%–15%), need for mechanical ventilation (22%–60% vs. 4% – 10%), malignant arrhythmias (17% vs 2% VT/VF) and death (51%–95% vs 5%–27%). Tn and NT-proBNP levels increased during hospitalization in non-survivors but not in survivors [11,13].

VISUALIZATION METHODS IN PROVING MYOCARDIAL LESIONS

COVID-19 is associated with abnormalities of cardiac structure and function including echocardiographic evidence of left ventricular dysfunction, regional wall motion abnormalities, and mild reduction in right ventricular function [19] . Several cardiovascular magnetic resonance (CMR) studies have documented myocardial abnormalities that persist after acute infection. In a study of 100 patients with COVID-19, imaging was performed an average of 71 days after the diagnosis of COVID-19. Pericardial effusion (>10 mm) was detected in 20% (20/100) of patients. Late gadolinium enhancement (LGE), reflecting fibrosis and cicatrix, was observed in 32% and was significantly more common in patients with COVID-19 than in healthy or risk-factor-matched controls. In addition, other studies have noted a high prevalence of myocardial edema following COVID-19 infection. Whether the abnormal CMR imaging findings observed after COVID-19 reflect a permanent cardiac lesion is unknown at this time due to the lack of long-term studies.

RADIOGRAPHY AND MSCT OF THE CHEST

Early MSCT (multislice, multidetector computed tomography scan) of the thorax shows detectable changes in the lung parenchyma in as many as 85% of patients, which can be both oligosymptomatic and asymptomatic. Also, in as many as 75%, there are COVID-19 bilateral lung changes with subpleural and peripheral distribution [5]. In addition to other viral pneumonias, COVID-19 pneumonia on the Rtg manifests as peripherally located ground glass opacity. Perihilar or diffuse widespread ground-glass opacification and ‘‘crazy paving" are present in MSCT findings in COVID- 19 and are difficult to distinguish from the others diseases only on the basis CT findings (other viral pneumonia, acute respiratory distress syndrome - ARDS, acute hypersensitive pneumonitis, sarcoidosis, pulmonary hemorrhage, alveolar proteinosis) [20,21].

By appearance, peripherally located consolidations with marginal zone ground glass opacity do not differ from the findings in Cryptogenic organizing C organizing_ pneumonia (COP), Eosinophilic pneumonia , Vasculitis , Invasive aspergillosis and should be interpreted within the whole clinical picture. The organizing pneumonia (pulmonary tissue consolidation) in COVID- 19 has the same characteristics as the organizing pneumonias of other causes . Nodules with a halo sign, apart from COVID-19, are also a common finding in numerous other diseases. [20,21].

Even in less severe, ambulatory-treated COVID-19 patients, signs of incipient lung congestion can be detected on a chest radiograph: Kerley B lines and redistribution of the pulmonary vascular pattern. In patients who are treated in intensive care units, enlargement of the cardiac shadow-cardiomegaly, bilateral pleural effusion as part of cardiac decompensation and pronounced lung congestion can be detected. MSCT is sovereign in the detection of thrombus in the branches of the pulmonary artery and the diagnosis of pulmonary thromboembolism [16]

ABNORMALITIES INDICATING A HEART LESION ON ECHOCARDIOGRAPHY

Echocardiography - (ultrasound of the heart) is the most accessible method that can also be performed as an emergency at the patient's bedside (point of care-POC approach). Echocardiographic abnormalities commonly registered in hospitalized patients with COVID-19 include right ventricular (RV) dysfunction (26.3%), left ventricular (LV) wall motion abnormalities (23.7%), global left ventricular dysfunction with reduced LV EF (18.4%), grade II or III diastolic dysfunction (13.2%) and pericardial effusion (7.2%) [22]. Biomarker evidence of myocardial lesion associated with echocardiographic abnormalities correlates with a higher risk of in-hospital mortality. Myocardial

involvement caused by SARS-CoV-2 infection may be important for long-term prognosis. Myocardial effects during SARS-CoV-2 infections can be characterized with advanced echocardiographic techniques. Strain imaging was performed in 18 patients with SARS CoV-2 infection assessing longitudinal, radial, and circumferential strain or left ventricular (LV) strain including rotation, torsion, and twisting [17]. LV deformation (strain) was also analyzed in a control group of healthy individuals of the appropriate age (n = 20). The dominant finding was the finding: reduced longitudinal strain observed predominantly in more than one basal segment of the LV (n = 10/14 patients, 71%). This pattern resembles a "reverse Tako-tsubo" morphology, which is not typical of other viral myocarditis. Additional findings included a biphasic pattern with maximal postsystolic thickening or negative regional radial strain predominantly in the basal segments (n = 5/14 patients, 36%); absence or dispersion of left ventricular basal rotation (n = 6/14 patients, 43%); decreased or positive regional circumferential strain in more than one segment (n = 7/14 patients, 50%); net rotation showing late post-systolic twist or biphasic pattern (n = 8/14 patients, 57%); cardiac rotation showing a polyphasic pattern and/or higher peak values during diastole (n = 8/14 patients, 57%). Descriptive myocardial damage due to SARS-CoV-2-infection was highly prevalent in the presented cohort, even in patients with mild symptoms. COVID-19 myocardial damage appears to be characterized by specific deformation (strain) abnormalities in the basal segments of the LV. These data raise an idea for prospective testing: whether these parameters are useful for risk stratification and for long-term follow-up of these patients [17].

It is important to present a large meta - analysis by Ogungbe O. et al [23] on 41013 patients, where the aim was to quantify the relationship between myocardial lesion biomarkers, coagulation and severe COVID-19 and death in hospitalized patients. Individual study effect estimates of the association of markers of myocardial lesion (troponins), myocardial dysfunction (N-terminal-prohormone BNP, NT-proBNP) and coagulopathy (D-dimer) and death or severe/critical COVID-19 were pooled using the statistical parameter Odds ratio (odds ratios for adverse events-OR) by outcomes of critical/severe COVID-19 and death. Comorbidities of hypertension - 39% (95% CI: 34–44%); diabetes, - 21% (95% CI: 18%–24%); coronary artery disease, 13% (95% CI: 10–16%); chronic obstructive pulmonary disease, 7% (95% CI: 5–8%); and history of malignancy, 5% (95% CI: 4–7%). Elevated troponin was associated with higher pooled odds of critical/severe COVID-19 and death [OR: 1.76, 95% (CI: 1.42–2.16)]; By separate OR analysis, the odds ratio for death was OR: 1.72, 95% (CI: 1.32–2.25) and for critical/severe COVID-19, OR: 1.93, 95% (CI: 1 ,45–2,40). Elevations of NT-proBNP were also associated with more severe COVID-19 and death (OR: 3.00, 95% CI: 1.58–5.70). Increased D-dimer levels were significantly associated with critical/severe COVID-19 and death (pooled OR: 1.38, 95% CI: 1.07–1.79). This meta-analysis synthesizes the existing evidence that myocardial injury and coagulopathy are significant complications of COVID-19. The reversibility and functional significance of these complications and their contribution to long-term cardiac disease outcomes are still being investigated. Patients who have recovered from COVID-19 may benefit from assessment of markers of myocardial injury, heart dysfunction-failure, and coagulopathy for early risk stratification [23].

An important aspect of COVID-19 pandemic is the associated collateral damage in the treatment of many other diseases. This includes diagnostic difficulty and treatment of all forms of cardiac and other serious chronic diseases of other organ systems and not only the treatment of infarctions and acute cardiac diseases during the COVID-19 pandemic, which has consequences for our daily cardiology practice. [24,25]

ABNORMALITIES INDICATING A LESION ON CARDIAC MAGNETIC RESONANCE (CMR)

CMR findings include: T1 mapping abnormalities (suggesting diffuse myocardial changes such as diffuse fibrosis and/or edema); T2 mapping abnormalities (more specific to myocardial inflammation, as occurs in acute myocarditis); the presence of late gadolinium enhancement (LGE), which indicates an acute myocardial lesion and/or myocardial fibrosis); or pericardial involvement – all of which may indicate cardiac lesions associated with COVID-19. In a systematic review of 199 patients, post-recovery CMR studies in patients with COVID-19, CMR diagnosed myocarditis in 40.2%,

myopericarditis in 1.5%, Takotsubo in 1.5%, ischemia in 2.5% and a double lesion: ischemia and non-ischemic changes in 2.0%. Regional wall motion abnormalities were reported in 40.6%, edema (on T2 or short tau inversion recovery) in 51.1%, LGE in 42.7%, and T1 and T2 mapping abnormalities in 73% and 63%, respectively. Additionally, perfusion and extracellular volume mapping abnormalities were described in 85% and 52% of patients, respectively. Pericardial involvement included pericardial effusion in 24% and pericardial LGE in 22%. In summary, the most common CMR diagnosis in COVID-19 patients is myocarditis, and imaging findings included evidence of diffuse myocardial edema and myocardial fibrosis. However, it is important to note that most of the reported findings were mild increases in T1 and T2 signal intensity, and the clinical significance of isolated T1/T2 abnormalities associated with COVID-19 still remains unknown [26,27].

CARDIAC INVOLVEMENT AFTER RECOVERY FROM ACUTE COVID 19 DISEASE - POST-ACUTE COVID 19 (PASC) or LONG COVID-19 SYNDROME

Certain patients infected with SARS-CoV-2 continue to have symptoms for weeks to months after apparent recovery from the acute phase of the disease. Early reports suggest that up to 10% of patients with COVID-19 may experience "PROLONGED OR LONG COVID SYNDROME" or POST-ACUTE COVID 19 (PASC). Symptoms of PASC vary widely in variety, severity, and duration [16]. **Preliminary studies suggest that up to 30% of patients may report symptoms as late as 9 months after acute infection** [28]. The most common symptoms include fatigue, decreased functional capacity and exercise tolerance, shortness of breath, sleep problems, and palpitations. Some patients describe difficulty thinking clearly ("brain fog"), anxiety and/or depression. The exact predictors, duration, extent of cardiac (or other organ) involvement, and potential effects of different treatments for PASC require extensive research, which has already begun [16].

The potential for long-term cardiac sequelae of myocardial damage associated with COVID-19 has been highlighted in CMR studies of recovered patients with evidence of myocardial fibrosis or myocarditis reported in a wide range of **9% to 78% of patients recovered from acute COVID-19.** Among 100 post-COVID-19 patients who underwent CMR 2 to 3 months after diagnosis, Puntmann et al reported **cardiac involvement in 78% with evidence of ongoing inflammation in 60%.** On the day of imaging, 71% had elevated hs-TnT. Cardiac symptoms were common and included atypical chest pain (17%), palpitations (20%), and dyspnea and fatigue (36%). Recovered patients had lower left ventricular (LV) ejection fractions and larger LV volumes compared with risk factor-matched controls. These CMR findings of myocarditis and myocardial fibrosis raise concerns about potential long-term cardiac consequences, including increased risk of heart failure and arrhythmia based on previous experience with myocarditis. The presence of late gadolinium accumulation (LGE) subepicardially and medially in the left ventricular wall associated with myocarditis often implies myocardial necrosis in addition to myocardial edema and has previously been associated with adverse outcomes in multiple CMR studies of non-Covid-related myocarditis [27]. Post-acute sequelae of SARS-CoV-2 infection, often called post-acute COVID-19 syndrome or long-lasting-LONG COVID-19, can occur in patients who are slow to recover. Of 143 patients who were treated as outpatients after infection with COVID-19, only 12.6% were asymptomatic. (Carfe A) [28]. Symptoms included fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%); 44.1% reported deterioration in quality of life. Among 1,733 discharged patients with COVID-19 followed for an average of 6 months after symptom onset, the most common symptoms were fatigue or muscle weakness (63%), difficulty sleeping (26%), and anxiety or depression (23%). Greater disease severity during hospitalization was associated with reduced pulmonary diffusion capacities and abnormal chest radiography. (Huang C. 2021). The contribution of cardiac changes after COVID and acute myocardial injury to the symptoms of post-acute COVID-19 syndrome is unclear [29].

PROOF OF DIRECT VIRAL HEART INFECTION BY PATHOHISTOLOGY

Cardiac autopsies showed cardiomegaly, right ventricular enlargement, lymphocytic myocarditis (14%–40%), focal pericarditis (19%), endocardial thrombosis (14%), or endotheliitis and thrombosis of small coronary

vessels (19%). The cardiac tropism of SARS-CoV-2 was initially established by quantitative RT-PCR detection of viral RNA in postmortem hearts of patients with COVID-19 and then in endomyocardial biopsies of patients with suspected myocarditis. The cardiac cellular tropism of SARS-CoV-2 has now been demonstrated by in situ labeling of SARS-CoV-2 RNA and electron microscopic detection of virus-like particles within cardiomyocytes, interstitial cells, and cardiac endothelial cells post mortem [30,31]. Autopsies in patients with acute myocarditis have recently shown evidence of viral infection, and replication within cardiomyocytes. The preponderance of evidence suggests that SARS-CoV-2 can readily infect human cardiac myocytes and can be detected in myocytes at autopsy or endomyocardial biopsy in patients with and without clinical evidence of cardiac involvement. There are pathohistological findings of clear myocarditis in individual cases where all elements strongly suggest COVID-19 myocarditis or direct cardiomyocyte damage in an extremely strong inflammatory reaction (cytokine storm) caused by viremia rather than a microvascular myocardial lesion [14,32]

Of 277 hearts in 22 autopsy studies of COVID-19, only 20 cases of myocarditis (7.2%) were reported. In contrast to the low prevalence of myocarditis, interstitial macrophage infiltration without cardiomyocyte degeneration was common in a multicenter COVID-19 autopsy series (18 of 21 cases, 86%) [33]. Other more common histologic findings reported in the COVID-19 autopsy series include perivascular and inflammatory myocardial infiltrates, endocardial and small vessel thrombosis, endotheliitis, and myocyte degeneration. One study of 39 autopsied hearts detected SARS-CoV-2 by qRT-PCR in 24 (61.5%) cases, with 16 hearts showing high viral loads (>1000 genomic copies per mg of total RNA) [34,35]. It remains to be determined whether the heterogeneity of cardiac histopathology in COVID-19 signifies different endophenotypes of the myocardial lesion of COVID-19 or the continuity of a single pathological process.[16] .

PROLONGED EXERCISE INTOLERANCE AND DYSAUTONOMY

There is increasing evidence of prolonged symptoms of COVID-19 after a period of acute infection (post-acute covid, long covid) with prolonged exercise intolerance (failure to exert effort) which is becoming a common finding not only in competitive athletes and active individuals, but also in many young and elderly people survivors of COVID-19 [3,16]. Common symptoms associated with myocarditis and post-COVID syndrome include chest pain, dyspnea, and palpitations. CMR findings of a cardiac lesion, small nerve fiber neuropathy caused by the COVID-19 virus, and dysautonomia are likely causes. Postural orthostatic tachycardia syndrome associated with COVID-19 is common. The relative poor cardiac fitness during periods of exercise and training limitations is often confounding in situations when trying to delineate the cause of failure to exercise [3,16].

The potential for increased risk of sudden cardiac death in post-COVID fibrosis or myocardial inflammation is of concern to athletes or active individuals returning to exercise. The wide range of LGE prevalence after COVID-19 has led to controversy over the routine practice versus targeted use of CMR. Risk stratification with noninvasive biomarkers, ECG, or echocardiography may be insensitive for detecting CMR abnormalities. Conversely, ECG changes considered abnormal in non-athletes may represent normal variants in athletes. According to the American College of Cardiology, Sports, and Exercise, athletes who have recovered from COVID-19 can return to sports based on biomarkers and noninvasive cardiac imaging, including ECG and echocardiogram [3,16]. Athletes are advised to limit exercise to 5 days a week, minimally at first with a gradual increase in exercise intensity. Cardiovascular risk assessment is recommended for mild symptoms lasting longer than 10 days; for moderate or severe symptoms, including hospitalization, further cardiac testing depends on symptoms and abnormal findings on baseline testing. The uncertainty of long-term consequences and the potential for long-term evolution into chronic myocardial disease, cardiomyopathy, and other cardiovascular complications, including heart failure, chronic sinus tachycardia, autonomic dysfunction, and arrhythmias, await further definition. In addition, studies are needed to determine whether therapeutic interventions to moderate the inflammatory response can also limit the extent of intermediate- to long-term myocardial injury associated with COVID-19. Evaluation of post-acute COVID-19 syndrome (long-COVID-19) and recommendations for long-

term surveillance, monitoring, and return to exercise or sport remain areas for further evaluation [3,16].

PRINCIPLES OF THE THERAPEUTIC APPROACH TO COVID-19 INFECTION WITH A FOCUS ON THE CARDIOVASCULAR SYSTEM

The most important principles in the therapeutic approach to COVID-19 patients [16]: A) optimal supportive measures and treatment of complications; B) treatment of existing chronic cardiovascular diseases and conditions developed as part of COVID-19 according to the current guidelines of professional societies and associations (ESC, AHA/ACC) including inhibitors of the renin-angiotensin-aldosterone system [14]; C) in cases of cytokine storm associated with the development of ARDS and myocarditis, consider the introduction of immunomodulatory therapy; D) individual risk stratification for development of KV complications in COVID-19 infection, prevention of these, early recognition and treatment [14]. Treatment of COVID- 19 and complications associated with COVID-19 [16] continues to develop rapidly as more treatments complete testing in randomized trials. Treatment in early phase includes antiviral medicines and monoclonal antibodies against SARS - CoV- 2.

Antiviral medicines . Remdesivir is nucleoside analog which inhibits RNA dependent RNA polymerase and is the only antiviral medicine approved by US Food and Drug Administration (FDA) for treatment of COVID-19 [16]. It is currently recommended to patients hospitalized with moderate COVID-19 who need extra oxygen, but its benefit has not been established in patients who require high flow oxygen , non-invasive ventilation or mechanical ventilation . Treatment lasts about 5 days, it can be prolongedto 10 days if there are no clinical improvements [36] .

Monoclonal antibodies against SARS - CoV -2 which have been approved by FDA for emergency use : Bamlanivimab plus etesevimab (applied together) have been approved for treatment of mild to moderate COVID- 19 in adults and pediatric outpatients [37]. Besides, FDA has issued permission for kasirivimab and imdevimab applied together) for treatment of mild to moderate variant of COVID-19 in adults and pediatric patients [38]. Potential cardioprotective effects of treatment by anticytokines haven't been determined yet due to inconsistencies in the results of clinical trials[16].

Corticosteroids have showed benefit in a patient subgroup with moderate COVID-19 whoneeded extra oxygen . In a randomized evaluation trial of therapy for COVID-19, dexamethasone (6 mg one time daily up to 10 days) reduced the 28 -day mortality, but patients who didn't need oxygen did not experience any benefits [16**,** 39]. In meta - analysis of 7 randomized controlled studies (CT) which included 1703 critically sick patients (including those who needed mechanical ventilation) with COVID-19, the use of systemic dexamethasone , hydrocortisone or methylprednisolone resulted in the reduction of risks of mortality from all causes by 34% after 28 days [16,40].

"A "storm" of cytokine release", which comes from T cell activation imbalance with unregulated interleukin release (IL)-6, IL -17 and other cytokines , can contribute to CVD in COVID- 19. Anti-IL-6 antibody therapy trial is ongoing. Activation of the immune system together with the changes in immunometabolism can lead to the instability of atherosclerotic plaques, contributing to the development of acute coronary events [16].

The role of anticoagulation in COVID- 19. Many observational or smaller studies have investigated which patients with COVID- 19 could benefit from anticoagulants or antiaggregation therapy, in which dose and in which phase of the disease with different results . While waiting for sufficiently strong, properly designed and performed blinded randomized trials, many institutions have adopted the prophylaxis of escalated doses in all or specific _ groups of hospitalized patients with COVID-19. Documents about consensus generally recommend tracking the available medical recommendations based on the evidence in order to avoid a widespread use higher than the prophylactic dose of anticoagulants , except if it is not used as a part of a research study [16,41]. In general , risk from venous thromboembolism (VTE) in hospitalized patients reached its climax in the early stage of the pandemic, but later the incidence decreased thanks to the adoption of prophylactic anticoagulation. A big study of Danish registers based on the national population suggests that the risk from the VTE in hospitalized patients with COVID -19 is low to

moderate and that it's not significantly higher than the risks from the VTE in hospitalized SARS - CoV -2- negative patients and patients with flu [42]. VTE Risk in the period after dismissal and in ambulatory cases of COVID - 19 can be slightly elevated, but it is much smaller than the risks in acutely ill and hospitalized patients.

Antagonists of the renin-angiotensin-aldosterone system (RAAS antagonists)

Following the discovery that SARS-CoV-2 uses ACE2 to enter the host cell, concerns have been raised about the potential for ACE inhibitors and ARBs to cause a compensatory increase in ACE2 expression and worsen prognosis among those with COVID-19. Observational studies evaluating outcomes associated with the use of ACE inhibitors and ARBs among patients with confirmed COVID-19 [43,44] and RCTs comparing continuation or withdrawal of these agents among those hospitalized with COVID-19 have shown no adverse effects on survival and other clinical outcomes [45,46] . Therefore, continuation of ACE inhibitors and ARBs during the course of COVID-19 disease is recommended for patients treated with these drugs. It also appears that in experimental models, ARBs may have a potentially protective effect. A recent observational study of over 8910 patients from 169 hospitals in Asia, Europe, and North America showed no adverse association of ACEIs or ARBs with in-hospital mortality, while a study in Wuhan showed that in 1128 hospitalized patients, ACEI/ARB use was associated with a lower risk from infection with COVID-19 or serious complications or death from infection with COVID-19. This is consistent with previous guidelines from the major cardiovascular associations, which state that patients on ACEIs or ARBs should not discontinue these medications [16].

ORGANIZATION OF CARE AND SPECIFICITY OF THE MOST IMPORTANT CVD DURING THE COVID-19 PANDEMIC

Non-ST elevation acute coronary syndromes (NSTEMI)

Management of patients with NSTE ACS should be guided by risk stratification [3]. Testing for SARS-CoV-2 should be performed as soon as possible after the first medical contact, regardless of the treatment strategy, so that the healthcare professional can implement adequate protective measures and care pathways. Patients should be categorized into 4 risk groups (ie, very high risk, high risk, intermediate risk, and low risk) and managed accordingly. Patients with an increase in troponin and without acute clinical signs of instability (ECG changes, recurrence of pain, hemodynamically stable) can be treated with a primarily conservative approach. Non-invasive imaging with CCTA can speed up risk stratification, avoid an invasive approach and allow early discharge. For high-risk patients, the medical strategy aims at stabilization while planning an early (< 24 hours) invasive strategy. In the case of a positive SARSCoV-2 test, patients should be transferred for invasive treatment to a COVID-19 hospital equipped to treat the patients positive for COVID-19. Intermediate-risk patients should be carefully evaluated considering alternative diagnoses of T1MI, such as type II MI, myocarditis or myocardial lesion due to respiratory distress or multiorgan failure, or Takotsubo. In case any of the differential diagnoses seems plausible, a non-invasive strategy should be considered and CT scan coronary angiography (CCTA) should be preferred [3].

ST segment elevation myocardial infarction (STEMI)

The COVID-19 pandemic should not compromise timely reperfusion via percutaneous balloon angioplasty with stent placement (PCI) or thrombolytic therapy in patients with STEMI [3] .

According to current guidelines, reperfusion therapy remains indicated in patients with symptoms of ischemia lasting less than 12 hours with permanent ST-segment elevation on ECG in at least two adjacent leads. At the same time, there must be safety for healthcare workers and in the absence of testing for SARS-CoV-2, all patients should be treated as if they were Covid-19 positive. The safety of healthcare professionals is of utmost importance to avoid healthcare worker infections and further spread of infection.

Chronic coronary syndromes (CCS)

Patients with Chronic Coronary Syndrome **(**CCS) with a clinical scenario of stable angina pectoris are generally at low risk of CV events, which allows delaying diagnostic and/or interventional procedures in most cases [3] **.**

Medical therapy should be optimized and/or intensified depending on the clinical status. Clinical monitoring of a patient via telemedicine is justified for the early detection of unstable angina or changes in clinical status that may require hospital admission in high-risk patients.

Acute heart failure (AHF)

Bilateral COVID-19 pneumonia often leads to worsening hemodynamic status due to hypoxemia, dehydration, and hypoperfusion. The main mechanisms of AHF in COVID-19 are acute myocardial ischemia, myocardial infarction or inflammation (myocarditis), acute respiratory distress syndrome (ARDS), acute kidney damage and hypervolemia, stress-induced cardiomyopathy, and tachyarrhythmias [3] **.**

Clinical presentation, the presence of existing CV comorbidities and the findings of X-ray thorax (cardiomegaly and/or bilateral pleural effusion, congestion of the lung wings at the bases) are of utmost importance. Significantly elevated levels of BNP and not NT-proBNP also suggest acute HF. Careful use of point-of-care (POC) transthoracic echocardiography (TTE) is recommended to prevent contamination of personnel and/or equipment from the patient. The same treatment strategy for acute HF can be applied in patients with and without COVID-19 [3,47]. Regarding prognosis, in a recent report 23% of all hospitalized patients developed AHF, while the prevalence of HF was significantly higher in fatal cases compared with survivors (52% vs. 12%, $P < 0.0001$). [3].

Chronic heart failure (CHF)

The risk of infection with COVID-19 may be higher in chronic heart failure HF patients due to age and the presence of multiple comorbidities. In ambulatory stable patients with HF, without urgent cardiac conditions, the prescribing physician should refrain from hospital treatment. Medical therapy according to the guidelines (including the five parallel pillars of therapy according to the new ESC guideline [3,47] Beta-blockers, SGLPT-2 inhibitors, mineralocorticoid receptor antagonists (MRA), loop of Henle diuretics for congestion and one of the RAAS inhibitors, preferably sacubitril/valsartan or ACEI, OR ARBa), should be continued in patients with chronic HF, regardless of COVID-19. The implementation of telemedicine to provide medical advice and follow-up of stable patients with COVID-19 is important.

Arterial Hypertension

An association between hypertension and risk of severe complications or death from COVID-19 infection was found, with a confounding lack of effect of age and comorbidities associated with aging and hypertension. However, there is currently no evidence to suggest that hypertension per se is an independent risk factor for severe complications or death from COVID-19 infection [3]**.** Despite much speculation, evidence from a recently published series of observational cohort studies suggests that previous or current treatment with an ACEI or ARB does not increase the risk of infection with COVID-19 or the risk of developing severe complications from infection with COVID-19 compared to the risk in patients taking other antihypertensive drugs. Treatment of hypertension should follow the existing recommendations in the ESC-ESH Guidelines. No changes to these treatment recommendations are necessary during the COVID-19 pandemic [3] **.**

COVID 19 Myocarditis

Limited clinical experience indicates that SARS-CoV-2 can lead to all forms of myocarditis from subclinical to fulminant myocarditis. Myocarditis should be suspected in patients with COVID-19 and acute chest pain, ST segment changes, cardiac arrhythmia, and hemodynamic instability. In addition, dilatation of the left ventricle (LV) with reduced ejection fraction (EF), global or multisegmental hypocontractility of the LV with a significant increase in cardiotroponin T and I and the level of both or only one natriuretic peptide (BNP I / or NTproBNP) with the exclusion of significant chronic coronary disease are elements for establishing a working clinical diagnosis. In particular, myocarditis should be suspected in COVID-19 patients with acute heart failure: pulmonary edema or cardiogenic shock and

without anamnestic data on previous CV disease. Echocardiography, as the first and routine imaging method, often shows diastolic dysfunction, multisegmental hypocontractility, dilatation of both ventricles and a significant decrease in systolic function - a drop in LV ejection fraction (LVEF) and sometimes a small pericardial effusion. Advanced echocardiographic methods, such as myocardial deformation imaging (strain-strain imaging) Myocardial damage due to SARS-CoV-2-infection, specific deformation (strain) abnormalities in the basal segments of the left ventricle were highly prevalent even in patients with mild symptoms [17]. MSCT of the coronary arteries (CCTA) is suggested as the best approach to rule out concomitant coronary disease and cardiomagnetic resonance (CMR), if available, can be used for further diagnostic evaluation. Endomyocardial biopsy is not recommended in patients with COVID-19 with suspected myocarditis [3].

Efficacy of anticovid vaccination and post-vaccination myocarditis

Vaccines have shown efficacy in reducing morbidity and mortality from COVID-19 in randomized clinical trials and real-world studies, which also reduce cardiovascular complications. Their widespread use has led to a significant reduction in the incidence of COVID-19.

As of July 2021, the CDC's Adverse Event Reporting System (VAERS) has received over 1,100 reports of myocarditis or pericarditis after receiving a COVID-19 vaccination (primarily mRNA vaccine) and confirmed about 70% of them. In Europe (EEA), cases of myocarditis have also been reported with mRNA vaccines and with AstraZeneca vaccine, mostly in young adults, more often in men and usually after the second dose of the vaccine. Myocarditis, which can be detected by cardiac magnetic resonance imaging, usually occurs within 3 to 5 days after vaccination and presents with chest discomfort, an abnormal EKG, and elevated troponin. Although the exact mechanism is unknown, it is probably immunologically mediated. The possible incidence of asymptomatic cases, risk factors and long-term effects remain to be determined. Overall, myocarditis following COVID-19 immunization appears to be rare (~24 doses per million vaccines), often mild, and probably self-limiting in most cases. Treatment is primarily supportive [48,49].

CONCLUSION

Acute cardiac lesion is a common extrapulmonary manifestation of COVID-19 with potential chronic consequences. Clinical manifestations include direct cardiac damage and indirect immune response mechanisms that affect the cardiovascular system and have implications for the treatment of patients after recovery from acute COVID-19 infection. Hypertension (56.6%) and diabetes (33.8%) are the most common comorbidities in those infected with COVID-19, requiring hospitalization.

Cardiovascular manifestations of COVID-19 vary, and acute infection is associated with a wide range of cardiovascular complications, including acute coronary syndromes, stroke, acute-onset heart failure, arrhythmias, myocarditis, venous thromboembolism, and cardiac arrest.

The most common direct damage to the heart is an acute heart lesion, defined by a significant increase in cardiac troponins in the serum in >12% of infected and echocardiographic signs of damage to the texture of the myocardium due to inflammation, impairment of segmental mobility, global systolic and diastolic function of the left ventricle and inflammation of the pericardium. Among hospitalized patients with COVID- 19, the evidence about acute damage of heart function is common: acute heart insufficiency (3%-33%), cardiogenic shock (9%-17%), ischemia or myocardial infarction (0.9%–11%), ventricular dysfunction (left ventricular [10%–41%], right ventricular [33%–47%], biventricular [3%–15%]), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%).

Elevated troponin T is associated with more frequent development of severe complications: adult respiratory distress syndrome (ARDS), malignant arrhythmias (VT, VF), acute coagulopathy and acute kidney damage. Numerous individual cases indicate extremely high values and dynamics of troponin T typical for non-occlusive myocardial infarction with normal coronary arteries. Pathohistological findings of myocarditis strongly suggest COVID-19 myocarditis or direct damage to cardiomyocytes in an extremely strong

inflammatory reaction, a cytokine storm, caused by viremia.

About 10% of patients with COVID-19 may experience "LONG COVID SYNDROME" or POST-ACUTE COVID 19 (PASC). The symptoms of PASC vary widely in variety, severity, and duration.

Theoretically, the predicted increases in Angiotensin II levels by COVID-19 infection can be curbed by administration of maximal doses of ACE inhibitors and AT1 receptor blockers.

Cardiovascular dysfunction and disease are often fatal complications of severe infection with the COVID-19 virus, and cardiac complications can occur, even in patients without underlying heart disease, as part of an acute infection and are associated with a more severe form of COVID-19 disease and increased mortality.

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