

Cardiovascular risk factors of poor prognosis in COVID-19 – a review

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ABSTRACT

Since the first report in 2019, COVID-19 has claimed many lives, even those previously in good health. Therefore, a proper diagnosis and identification of patients at the highest risk of serious complications is vital. In fact, COVID-19 can lead to systemic inflammation and multiorgan dysfunction. Apart from the respiratory system, the circulatory system is also affected, including numerous complications due to the cytokine storm, direct cytotoxic effects, downregulation of angiotensin-converting enzyme 2, and low oxygen blood levels. In this review, we discussed cardiovascular risk factors associated with a poor prognosis in COVID-19 patients, including pre-existing risk factors or those acquired in the course of the infection. We also analyzed the role of biomarkers, ECG, and imaging in the identification of patients at the highest risk of unfavorable outcomes, as even subtle abnormalities in additional tests may have a significant impact on disease management.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in Wuhan, China, in December 2019 and quickly escalated into a global pandemic declared by the World Health Organization on March 11th, 2020.

SARS-CoV-2 and the cardiovascular system

SARS-CoV-2 is an enveloped, positive-sense single-stranded RNA virus (+ssRNA) from the *Beta-coronavirus* genus which includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), i.e. diseases with their own pan-

demics. In fact, SARS-CoV-2 was shown to share many similarities with SARS-CoV, including their mode of entry and nearly 80% of the genomic sequence.

In order to gain entry into human cells, the virus uses a spike protein to bind to a cellular receptor angiotensin-converting enzyme 2 (ACE2). This receptor is found in various organs, such as the lungs, heart, kidneys, and intestines [1, 2], and this fact could account for the association of SARS-CoV-2 with cardiovascular (CV) complications [3].

ACE2 degrades the product of ACE, angiotensin II, and converts it into angiotensin 1-7, which has anti-hypertrophic, anti-fibrotic, vasodilatory, and anti-hypoxic effects on the heart. Thus, ACE2 acts as a counterbalance to the renin-angiotensin-aldosterone system, and participates in cardioprotection [4].

In addition to the respiratory and CV manifestations, SARS-CoV-2 can trigger thromboembolic events and a cytokine storm [3]. Cytokine storm

refers to the uncontrolled immune cell activation and overproduction of pro-inflammatory cytokines. Furthermore, it increases the levels of reactive oxygen species and causes endothelial cell dysfunction, disruption of blood supply, and multiple organ failure [5]. This, in turn, could further enhance the spreading of SARS-CoV-2, as ACE2 was found to be an interferon-stimulated gene [1].

Therefore, the CV system could be affected in a number of ways, potentially in synergy through (a) direct myocardial injury resulting from viral binding to ACE2 and the subsequent downregulation of ACE2 expression, (b) systemic inflammation resulting in the organ failure, increase in the myocardial demand-supply ratio, atherosclerotic plaque rupture, as well as electrolyte imbalance, (c) decreased blood oxygen levels as a result of pulmonary damage, and (d) COVID-19 therapies which negatively affect the CV system – including antiretroviral therapy, azithromycin and tocilizumab [3, 5]. The impact of SARS-CoV-2 on the CV system is presented in **Figure 1**.

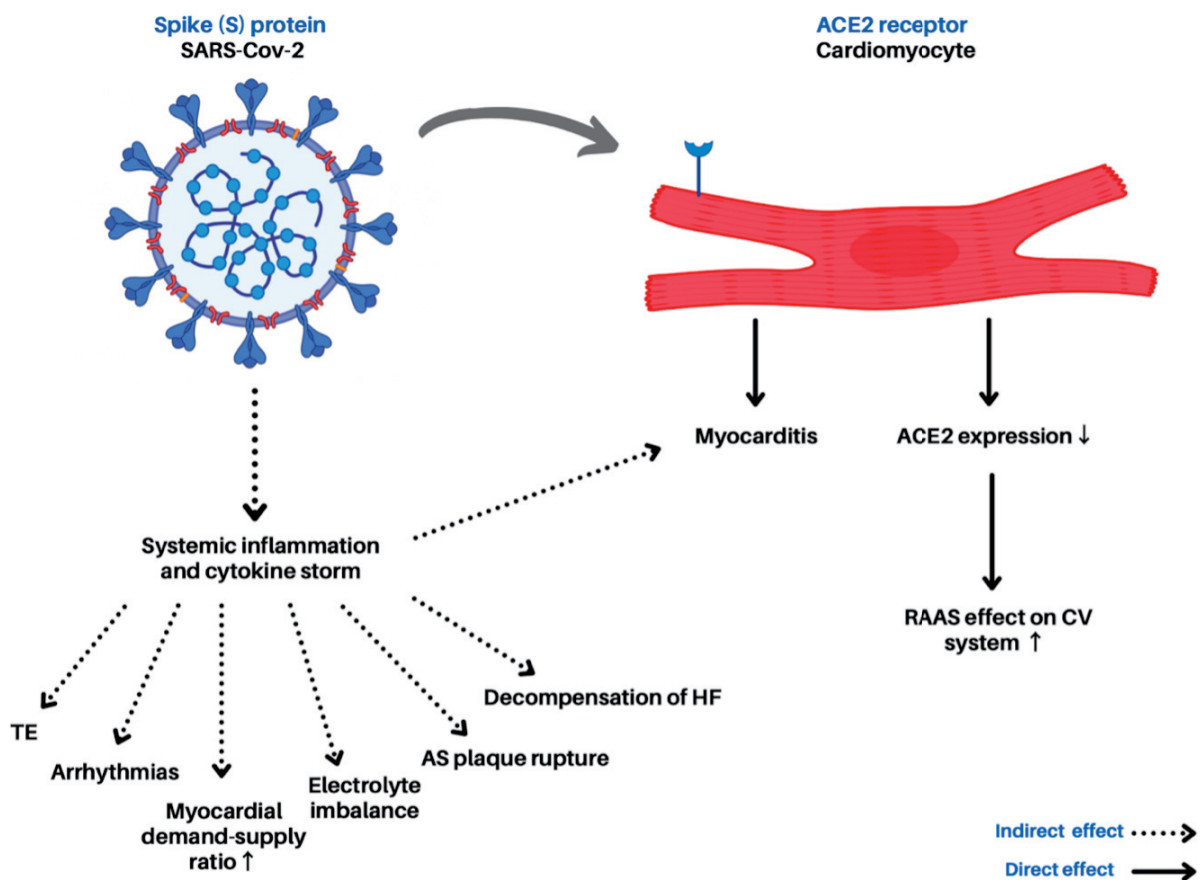


Figure 1. The impact of SARS-CoV-2 on the cardiovascular system. ACE2 – angiotensin-converting enzyme 2, AS – atherosclerosis, HF – heart failure, RAAS – renin-angiotensin-aldosterone-system, TE – thromboembolism

Due to the tropism of SARS-CoV-2 towards the heart and its ability to exacerbate, or even cause CV disease, it is vital to monitor the hearts of patients suffering from COVID-19, particularly those with CV comorbidities, since they are more likely to develop severe presentations of COVID-19. Moreover, diabetes, hypertension, and cerebrovascular diseases were also associated with a higher risk of severe COVID-19 presentations [2]. The aforementioned non-communicable diseases, in addition to cancer and chronic respiratory disease, constitute a syndemic with COVID-19 posing a significant strain on our healthcare systems and increasing the risk of premature death [6].

The link between the treatment with angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, and the upregulation of ACE2 expression is controversial, with studies showing inconsistent and mixed results [7–11]. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers do not have a direct effect on ACE2, and there is no evidence of COVID-19 susceptibility stemming from ACE2 upregulation. Therefore, several medical societies have recommended the continuation of treatment with those drugs [2].

Factors of poor prognosis in COVID-19

Cardiovascular complications

CV complications of COVID-19 include myocardial injury, myocarditis, acute myocardial infarction (AMI), heart failure (HF), arrhythmias, and venous thromboembolic events [12].

COVID-19 may disproportionately affect individuals suffering from CV diseases, in particular patients with coronary artery disease (CAD) and HF. A meta-analysis which analyzed 22,148 patients from 40 studies showed that the underlying CV disease in COVID-19 patients was correlated with a poorer prognosis, including a more severe course of COVID-19, intensive care unit (ICU) admissions, and disease progression [13].

Myocarditis

Myocarditis constitutes a potentially serious cardiac complication of COVID-19. It refers to the inflammation of the myocardium characterized by inflammatory infiltrates and myocardial injury

without an ischemic cause. Direct viral injury and further cardiac damage due to the body's immune response to the virus are believed to be the pathophysiologic causes underlying COVID-19-related myocarditis. Although it is not an uncommon complication, the true incidence of myocarditis in COVID-19 patients remains unknown. This is due to its highly variable clinical presentation, lack of reliable laboratory tests, and non-sensitive or specific findings on ECG. In fact, patients usually require further testing in order to establish a diagnosis of myocarditis using either echocardiography, cardiac magnetic resonance imaging (CMR), or endomyocardial biopsy [14, 15].

Symptoms of COVID-19-related myocarditis are most commonly mild [15]. However, if myocardial dysfunction develops, the prognosis becomes poor [16]. Patients with comorbid cardiac diseases and those with concomitant elevated troponins tend to present worse outcomes [15]. The management is focused on supportive care with fluids, remdesivir, and close monitoring. Additionally, patients who develop cardiogenic shock (CS) will require inotropes, mechanical ventilation, and possibly temporary mechanical circulatory support [14, 15].

Ischemic heart disease

Patients without prior cardiovascular disease

Several articles reported evidence of AMI type 2, or myocardial infarction with non-obstructive coronary arteries among patients with COVID-19. The former is explained by the presence of high levels of ACE2 receptors in pericytes and in endothelial cells, which inhibits a severe microvascular dysfunction also associated with cytokine storm [17].

Acute myocardial infarction

Although in certain areas a decrease of up to 50% in AMI cases was reported during the COVID-19 pandemic [18, 19], AMI has been recognized as a severe cardiac complication in COVID-19 patients, and can also develop in individuals without prior CV conditions. This is possibly accounted for by the extensive inflammation and hypercoagulability resulting from the disease. Furthermore, a direct viral injury of myocardial cells and oxygen imbalance caused by pneumonia are additional potential contributors [20, 21].

One study suggested investigating inflammatory markers and N-terminal pro-B type natriuretic peptide (NT-proBNP) in COVID-19 patients with concomitant AMI, as these were shown to be elevated and can be effective in determining the disease severity. The same study demonstrated higher mortality from COVID-19 in patients experiencing AMI compared to those without AMI [22]. Even after undergoing percutaneous coronary intervention for STEMI – in-hospital mortality, stent thrombosis, and CS remain significantly higher in COVID-19 patients [23].

Myocardial infarction with nonobstructive coronary arteries

Myocardial infarction with nonobstructive coronary arteries is clinically defined in patients who fulfil the universal AMI criteria, yet have less than 50% stenosis in coronary angiography [24]. One study investigated patients with both obstructive and nonobstructive coronary arteries who suffered AMI in the course of an underlying COVID-19 infection. Both their in-hospital mortalities were high, and no difference was found between the two groups of patients [25].

Patients with prior coronary artery disease

According to the findings of Zhou et al., CAD is a risk factor of increased mortality in the course of COVID-19 [26]. However, a study conducted in Italy on 1,252 COVID-19 patients demonstrated that age and female gender were the only independent correlates of mortality (where age was a risk factor and female gender was a protective factor). Patients with CAD presented a poorer prognosis, although this was mainly attributed to older age and a higher rate of comorbidities rather than to a direct consequence of CAD [27]. In another study from Italy, COVID-19 patients who underwent high-resolution computed tomography (CT) were retrospectively evaluated by the coronary calcium score (CCS). Only patients with subclinical CAD were included in the study, and out of 53 patients analyzed, 50% of individuals with $CCS \geq 400$ had died, compared to only 8.9% of patients with a $CCS < 400$. The independent predictive role of CCS could not be ultimately determined due to a very small study group. However, a high CCS score can be a marker of worse in-hospital outcomes, although it may also indicate an increased baseline risk. Never-

theless, including a CCS assessment in a routine high-resolution CT evaluation in COVID-19 patients can deliver useful prognostic information without additional costs [28].

Heart failure

Patients with congestive HF have a significantly poorer prognosis in the course of COVID-19. In fact, certain cases have been observed where COVID-19 has caused a decompensation of underlying HF, leading to CS [29]. A retrospective case series conducted in Wuhan, China, further consolidates the importance of early cardiac monitoring in patients with congestive HF, due to the high correlation between the disease and mortality [30]. However, acute HF also occurred in patients without underlying HF, leading to a significantly higher mortality (46.8% vs. 19.7%; $p < 0.001$) [31].

Arrhythmias

Arrhythmias are not uncommon in viral infections and were also demonstrated in COVID-19 patients. The most probable causes comprise such elements as fever, stress, hypoxia, electrolyte imbalances, and usage of antiviral drugs. In Wuhan, China, over 44% of ICU COVID-19 patients presented arrhythmias. Furthermore, sinus bradycardia is one of the most common arrhythmias seen in COVID-19 patients and it can persist for up to 2 weeks [32]. A case study following two patients with COVID-19 related bradycardia demonstrated a positive response to epinephrine, deeming temporary pacing unnecessary [33]. Interestingly, atrial fibrillation is also widely reported. The treatment is focused on rhythm control and anticoagulation simultaneously avoiding non-pharmacological interventions. Thus, catheter ablation and electrical cardioversion should be avoided, if possible, during an active infection [34]. Other atrial and ventricular arrhythmias, including ventricular fibrillation, were also reported in patients who showed no previous evidence of arrhythmia and were not on QT-prolonging medications. It is also essential to monitor COVID-19 patients with continuous telemetry, as the development of new-onset arrhythmia is associated with a severe course of the disease [32].

In addition, some patients suffering from inherited arrhythmias, such as long-QT syn-

drome, Brugada syndrome, short-QT syndrome, and catecholaminergic polymorphic ventricular tachycardia, may be at a higher risk of developing arrhythmias following SARS-CoV-2 infection [35].

Chloroquine, a medication primarily used to prevent and treat malaria, was administered to COVID-19 patients early in the pandemic, as it interferes with the terminal glycosylation of ACE2, which may disturb virus-receptor binding and thus prevent infection. The use of chloroquine and its derivative hydroxychloroquine was halted in summer 2020 due to the lack of a benefit seen in the randomized clinical trials and the potential for toxicity. Although chloroquine and hydroxychloroquine have QT-prolonging effects, they are mostly modest and do not require special attention in the long-QT syndrome. However, since they are metabolized by CYP3A4, these substances should be used with caution when in combination with other antiviral medications inhibiting CYP3A4, such as ritonavir-lopinavir, azithromycin, or remdesivir [35].

It is generally accepted that sodium channel function is sensitive to temperature. Fever stemming from COVID-19 can thus disturb the mutant sodium channels in Brugada syndrome and trigger arrhythmias. In fact, the presence of a pathogenic variant in SCN5A was shown to be of particular importance for Brugada syndrome patients who develop life-threatening arrhythmic events in the setting of fever. Hence, it is vital for Brugada syndrome patients to receive antipyretics immediately if they develop a fever [35].

In terms of the short-QT syndrome, it is extremely rare without any specific triggers for life-threatening arrhythmic events. Therefore, patients experiencing it are not expected to be at risk when infected with SARS-CoV-2 [35].

It is worth bearing in mind that exercise and stress are specific triggers for life-threatening arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Fever, however, is not. Hence, the risk of COVID-19 arrhythmias in those patients is controversial. It is important to avoid drugs with alpha- or beta-adrenoceptor mimetic activity, such as epinephrine during hemodynamic support, due to their ability to unmask ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia patients [35].

Thrombotic complications

The mechanisms of increased thrombotic complications in COVID-19 patients are not exactly understood. However, any of the three factors in Virchow's triad may contribute to thrombosis. COVID-19 can result in hypoxia, leading to increased blood viscosity, and abnormal blood flow. Additionally, SARS-CoV-2 also causes a state of increased inflammation, resulting in a hypercoagulable state due to a release of inflammatory cytokines [30]. As the virus enters cells through the ACE2 receptor, also found in the endothelial cells, it triggers the production of mitochondrial reactive oxygen species, glycolytic shift, and endothelial damage. In fact, spike protein alone can damage endothelium by down-regulating ACE2 and as a consequence inhibiting mitochondrial function [36].

Among different negative prognostic factors, a high D-dimer score on admission has been reported to be a significant risk factor for severe disease course and mortality [36].

A retrospective cohort study from China demonstrated that D-dimer levels above 1 µg/mL increased the chance of in-hospital death [26]. Another study from Wuhan further consolidated this statement indicating that a high D-dimer, high fibrin degradation products, longer prothrombin time, and activated partial thromboplastin time during admission were common in patients who died [37].

In addition, another study revealed that, although not helpful to all patients, heparin administration decreased the 28-day mortality in patients with a sepsis-induced coagulopathy score ≥ 4 , or D-dimer > 6 -fold of the upper limit of normal [38].

D-dimer levels can be used to exclude a pulmonary embolism (PE) in case of a normal value, but it is not recommended as a positive marker, due to low specificity. Bompard et al. suggest using contrast-enhanced CT to exclude PE, if supplementary oxygen is required in infected patients [39].

PE, as well as thrombotic complications in general, constitute greater threats and are tremendously more common in the ICU patients than in the non-ICU patients. A study conducted in the Netherlands enrolled 184 patients with proven COVID-19 pneumonia that were admitted to the ICU. 23 of them died, 22 were discharged home,

and 139 were still in the ICU by the end of the study. Despite receiving at least standard-dose thromboprophylaxis, 31% (95% CI 20-41) of patients suffered thrombotic complications, with PE being the most common one (n = 25.81%). The independent predictors of thrombotic complications were spontaneous prolongation of the prothrombin time (> 3 s) and activated partial thromboplastin time (> 5 s). These findings emphasize the importance of high-dose prophylactic anticoagulation in all ICU patients suffering from COVID-19 [40].

Biomarkers

Multiple studies hypothesized that measurement of cardiac damage biomarkers immediately after hospital admission for SARS-CoV-2 infection, followed by longitudinal monitoring during hospitalization, could help clinicians identify a subset of patients with a possible cardiac injury and predict the progression of COVID-19 towards a poorer outcome [41].

The prognostic value of cardiac biomarkers has been widely used in the management of CAD and HF. Troponins, B-type natriuretic peptide (BNP), and NT-proBNP are most commonly employed for the diagnosis, prevention, and safe discharge planning. Troponin is a marker of direct myocyte damage and necrosis, whereas BNP and NT-pro BNP are rather defined as markers for myocardial stretch injury. They can be also used in terms of the diagnosis, prevention, and safe discharge planning for patients hospitalized with CV diseases [42].

Troponin I (TnI) constitutes a "gold standard" biomarker of necrosis used for the cardiac risk assessment. It is released exclusively in the cardiac muscle in the presence of myocardial injury irrespective of its mechanism [43]. Interestingly, even in the absence of acute coronary syndrome (ACS), troponin elevation was identified in 20–30% of hospitalized patients with COVID-19 and has been associated with an increased risk of mortality in retrospective studies [44, 45]. A study from Zhou et al. on 191 patients, of whom 54 deceased due to COVID-19, revealed increased troponin I in over half of those who died. 91 (48%) of the patients had comorbidities, such as hypertension (most common), diabetes mellitus, and CAD [26]. A cohort study by Shi et al., including 416 hospitalized COVID-19 patients, reported that

approximately 20% of the subjects had evidence of a cardiac injury manifested by a significantly elevated high sensitivity troponin I (hs-TnI). This finding, in turn, was associated with a higher in-hospital mortality (51.2% vs. 4.5% respectively; $p < 0.001$) [43, 44]. Similarly, a cohort study by Salvatici et al. on 523 patients with COVID-19 reported a 18.3% mortality during hospitalization, and significantly higher hs-TnI levels in the deceased patients in comparison to the survivors (36.05 ng/L IQR 16.5–94.9 vs. 6.3 ng/L IQR 2.6–13.9; $p < 0.001$ respectively) [46].

Furthermore, Singh et al. conducted a single-centered, retrospective, observational study on 276 patients who presented to the emergency department. In 261 (95%) patients high sensitivity troponin T (hs-TnT) values were noted at presentation. The median initial hs-TnT value was 17 ng/L. In fact, initial hs-TnT levels above median were associated with longer hospitalization, increased need for vasoactive agents, higher mortality, along with the composite end-point (in-hospital death, cardiac arrest, intubation, or need for critical care); (OR 3.92, $p < 0.001$). From this patient group, only one (< 1%) with elevated hs-TnT had clinical evidence of ACS and underwent percutaneous coronary intervention. This finding supports the observation of Tersalvi et al. according to which elevated troponin levels are most likely the manifestation of an inflammatory response rather than true MI [41].

In addition to troponins, creatine kinase-MB (CK-MB) may also hold prognostic value in COVID-19 patients. It is an intracellular enzyme present in the skeletal muscle, myocardium, and brain. In the study conducted by Wang et al., 36 out of 138 patients (26.1%) were admitted to the ICU. All the patients had significantly elevated TnI and CK-MB levels compared to the non-ICU patients, which indicates that myocardial injury is more severe in cases with a serious course of COVID-19 [47].

Myoglobin is a cytoplasmic protein which exists in the cardiac and skeletal muscle. It increases rapidly and is among the initial markers to be elevated. In the study by Yang et al., the levels of myoglobin in the critically ill COVID-19 patients were significantly higher than in the mildly affected patients. In a cross-sectional study by Yu et al. on 162 patients requiring ICU, myoglobin was elevated in 57 (35.2%) patients.

Even though myoglobin is not as cardiac-specific as troponins, it was positively correlated with CK-MB and troponin T [47, 48].

A multicenter observational study was conducted at Sichuan province and Wuhan city to establish the predictive value of biomarkers on 357 patients with confirmed COVID-19 infection from January to March, including 22 tertiary hospitals designated for COVID-19 patients in the area. After a 28-day follow up, patients were classified into survival ($n = 332$) or death groups ($n = 25$), and recovery ($n = 314$) or non-recovery ($n = 43$) groups. Myoglobin, CK-MB, and hs-TnT were significantly elevated in death and non-recovery groups. Least absolute shrinkage and selection operator regression (a machine learning regression which chooses the independent risk factors affecting outcomes and presents only the strongest predictors in the predictive model) was employed by Yang et al. in order to identify the strongest predictive biomarkers. The area under the curve (AUC) of myoglobin and CK-MB for in-hospital death were 0.838 (95%CI: 0.729–0.947, $p < 0.001$) and 0.862 (95%CI: 0.804–0.920, $p < 0.001$), respectively. The AUC of myoglobin and CK-MB for non-recovery were 0.841 (95%CI: 0.765–0.918, $p < 0.001$) and 0.839 (95%CI: 0.786–0.892, $p < 0.001$), respectively. Myoglobin and CK-MB were considered as possible adverse prognosis predictors regarding in-hospital death and non-recovery in 28 days. In contrast, the method did not demonstrate the predictive value of hs-TnT in this study, whereas a combined use of CK-MB and myoglobin showed better predictive performance in terms of the prognosis [47, 48].

NT-proBNP is secreted in response to increased myocardial wall stress. Previous studies suggested that NT-proBNP could be a powerful predictor of mortality in community-acquired pneumonia. The elevated NT-proBNP levels are claimed to be the result of cardiac complications following complex interactions among pre-existing conditions, relative ischemia, up-regulation of the sympathetic system, systemic inflammation, and direct pathogen mediated damage to the CV system [49, 50]. A study by Gao et al. revealed that NT-proBNP correlated independently with in-hospital death of COVID-19 patients. The cut-off value of NT-proBNP to predict the fatal outcome of the disease was > 88.64 pg/ml, and was significantly decreased as compared to the

threshold used to diagnose HF (450 pg/mL for < 50 years old, 900 pg/mL for 50–75 years old and 1800 pg/mL for > 75 years old) [49].

Lactate dehydrogenase (LHD) is an intracellular enzyme found in most cells. Although LHD can be used as a marker for cardiac damage, abnormal values can also be seen with multiple organ injuries. Henry et al. showed that elevated lactate dehydrogenase values in 1532 COVID-19 patients were associated with a > 6 -fold increase in odds of severe course of disease. Moreover, a > 16 -fold increase in the odds of mortality was also observed. Elevated levels of LHD measured at the earliest time point during the hospitalization were found in $> 95\%$ deceased patients and $< 60\%$ of survivors. Therefore, since elevated LHD levels reflect multiple organ injuries, they may play a prominent role in the triage of patients with COVID-19 [51, 52].

It is also of importance to note that in terms of the massive proinflammatory and prothrombotic cytokine storm associated with COVID-19 infection, not only cardiac biomarkers are increased, but also many others, e.g. IL-6, CRP, ferritin and D-dimers [26, 53, 54].

ECG

ECG is a widely available tool which monitors the electrical activity of the heart and is often used to aid the diagnosis and stratify the risk in heart diseases. A study which continuously monitored the ECGs of 159 COVID-19 patients on admission for 7 days, found a significant correlation between abnormal ECG and major adverse events. 49.1% of patients had abnormal ECG findings on admission, and 53.5% at day 7. Ischemic changes and left ventricular hypertrophy correlated with a higher risk of major adverse events. The multivariable analysis demonstrated that abnormal ECG on the 7th day of hospitalization was an independent predictor of major adverse events (HR 3.2, 95% CI 1.2–8.7; $p = 0.02$). In addition, patients with irregular ECGs at day 7 were more likely to need renal replacement therapy and an ICU admission. The study also found that a high heart rate and its increase at day 7 could point to a strong systemic inflammatory reaction, whereas low QRS voltages could indicate significant lung damage, and the widening of QRS complex at the time of hospital stay could be significant of direct myocardial injury [55].

Another study followed the ECGs of 50 patients with COVID-19 pneumonia. On admission, 63% experienced either left ventricular hypertrophy or ST-T abnormalities. Another 26% developed new ECG irregularities, with changes indicating acute pericarditis being the most prevalent (12%). This may be due to the expression of ACE2 receptors in epicardial adipocytes, which were associated with atrial electrical remodeling and progression to atrial fibrillation. This suggests that involving the epicardial adipocytes in COVID-19 patients (for instance, by developing pericardial effusion) may increase the risk of developing atrial fibrillation [56]. Possible ECG abnormalities in the course of COVID-19 infection are presented in **Figure 2**.

in echocardiography, simplified protocols are preferred to reduce exposure, while advanced analysis can be performed in post-processing [57].

Echocardiographic examination in patients with COVID-19 allows for a hemodynamic evaluation, as well as for the identification of typical features of myocarditis, HF, ACS, or PE [58]. According to Cresti et al., left ventricular dysfunction, fortunately often reversible, is common even among patients without prior CV disease [57]. In a prospective international survey by Dweck et al., 55% of patients with suspected or confirmed COVID-19 (n = 1.216) demonstrated an abnormal echocardiogram (including 46% without pre-existing heart disease; n = 901) [59]. In another study, 26% of COVID-19 patients (n = 125) showed left ven-

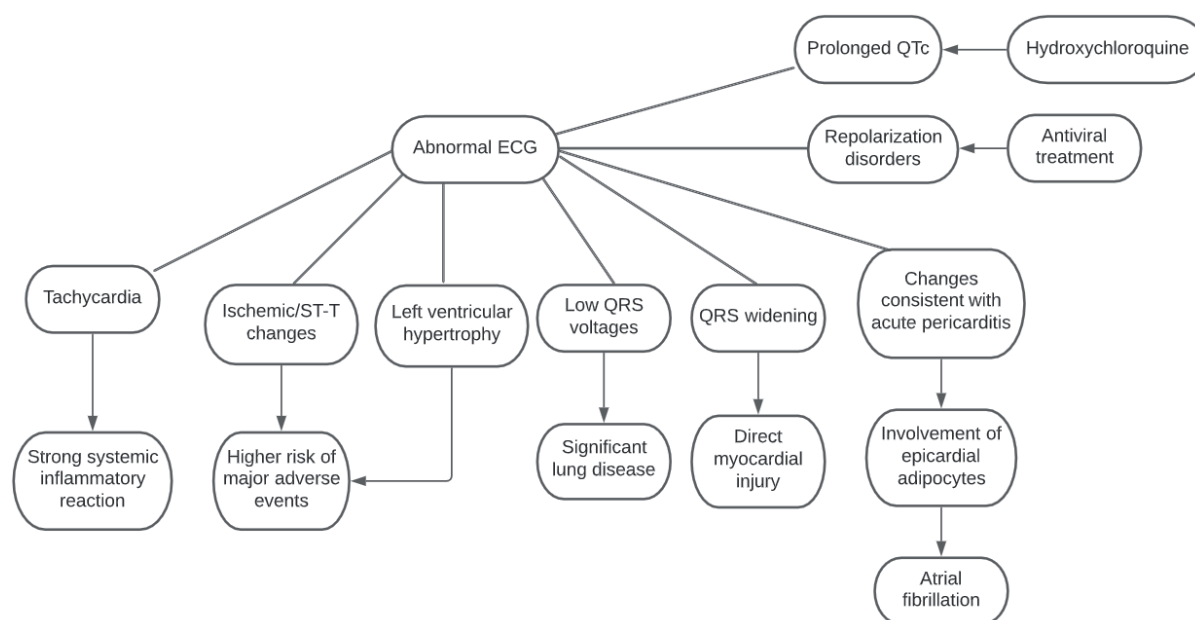


Figure 2. ECG changes in COVID-19 [on the basis of 55, 56]

Cardiovascular imaging

As cardiac involvement in COVID-19 is common and leads to an increased mortality, imaging techniques play a pivotal role in the differential diagnosis and risk stratification of CV manifestations [5]. Bedside ultrasound assessment of the heart and vessels is an effective first-line tool in detecting any abnormalities, whereas advanced techniques may facilitate final diagnosis and decision-making. In fact, echocardiography is frequently used in the initial assessment of acute myocardial injury. However, both logistic and sanitizing problems limit the use of CMR and CT. Even

tricular impairment, defined as a left ventricular ejection fraction < 50%, or segmental wall motion abnormalities [60]. However, it is postulated that it is the right ventricular (RV) dysfunction predicts mortality in COVID-19 patients, which is frequently secondary to acute respiratory distress syndrome [57]. Li et al. performed echocardiographic examination in 120 COVID-19 patients and measured the conventional RV functional parameters including RV fractional area change, TAPSE (tricuspid annular plane systolic excursion), and tricuspid tissue Doppler annular velocity, as well as RVLS (right ventricular longitudinal strain) obtained by speck-

le-tracking echocardiography. In fact, it has been recently demonstrated that RVLS is a more accurate tool to estimate RV function. It was found that non-survivors had enlarged right cardiac chambers, declined RV function, and elevated pulmonary artery systolic pressure compared to survivors. Additionally, RVLS, RV fractional area change, and TAPSE were significant univariate predictors of a higher mortality risk ($p < 0.05$). Patients in the lowest RVLS tertile, in comparison with those in the highest tertile, were more likely to have higher heart rates, as well as elevated D-dimer and CRP levels. They also required more high-flow oxygen and invasive therapy. The incidence of acute myocardial injury, acute respiratory distress syndrome, and deep-vein thrombosis was higher in the lowest tertile. Furthermore, the same association was observed in the case of mortality. The best cut-off value of RVLS for prediction of fatal outcomes was -23% (AUC: 0.87; $p < 0.001$; sensitivity, 94.4%; specificity, 64.7%). The abovementioned results support the application of RVLS in the risk stratification in COVID-19 patients [61].

CMR with its new quantitative mapping techniques is particularly effective in the diagnosis and risk stratification of acute myocardial injury in the course of COVID-19. A systematic review of 34 studies comprising CMRs in 199 patients revealed that only 21% of examinations were with the normal limits. The most prevalent diagnosis was myocarditis (40.2%) (presented in **Figure 3**). Furthermore, T1 (109/50; 73%) and T2 (91/144; 63%) mapping abnormalities, edema (46/90; 51%) and late gadolinium enhancement (85/199; 43%) were the most common findings. Late gadolinium enhancement was most commonly seen in the

subepicardial location (81%) in inferior segments [62]. Interestingly, it was present in a lower proportion in COVID-19 subjects when compared to patients with myocarditis, yet without COVID-19. This supports the hypothesis that inflammation constitutes the primary mechanism of myocardial injury in SARS-CoV-2 infection [63].

CT allows for the evaluation of lung parenchyma, patency of coronary and pulmonary arteries, and the assessment of myocardial injury, which renders it a comprehensive, non-invasive imaging modality allowing “quadruple rule-out” of most serious CV complications in the course of COVID-19 infection [64]. Although CMR is more frequently used in myocarditis detection, imaging of myocardial fibrosis by CT is feasible. Specifically, late iodine enhancement CT and extracellular volume CT are able to identify focal fibrosis and diffuse myocardial injury, respectively [65]. Furthermore, CT coronary angiogram can replace invasive coronary angiography in excluding obstructive CAD for patients with thoracic pain in the course of infection. In addition, it also allows for the estimation of the already discussed CCS, which is an independent predictor of in-hospital mortality and ICU admission [21]. Finally, CT pulmonary angiography has a crucial role in the diagnostic evaluation of COVID-19 complicated with acute PE [64].

Summary

Patients suffering from COVID-19 are at risk of developing CV complications and require close monitoring, especially those with CV comorbidities.

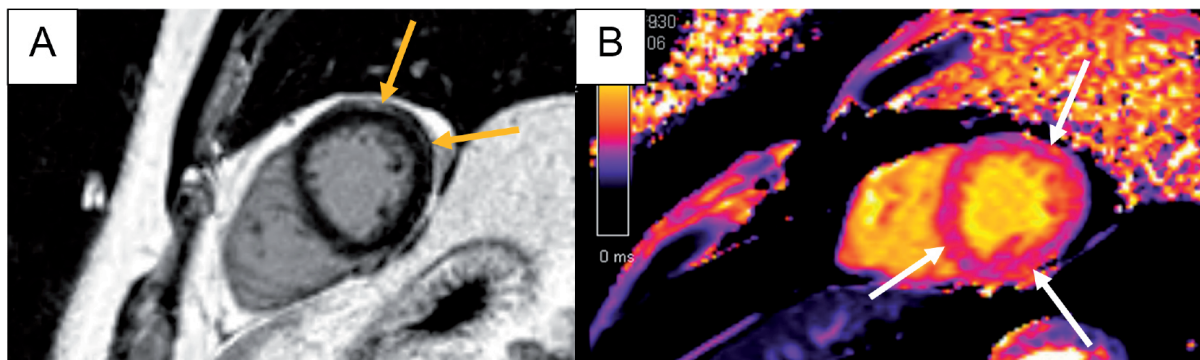


Figure 3. Myocardial injury on CMR 3 months after COVID-19: A: intramural fibrosis – late gadolinium enhancement in short axis view (arrows); B: diffuse fibrosis – T1 map in short axis view; native T1 in affected area = 1029ms (normal values: 967 ± 14 ms) [with the courtesy of Prof. Małgorzata Pyda; Poznan University of Medical Sciences CMR Unit, Cath Lab]

SARS-CoV-2 enters cardiomyocytes via their ACE2 receptor and interferes with its cardio-protective activity in the process. The systemic inflammation caused by COVID-19 further damages the heart by mis-balancing electrolyte levels and the myocardial demand-supply ratio. Decreased blood oxygen levels from pulmonary damage subsequently contribute to complications. As a result, the negative impact of SARS-CoV-2 on the cardiovascular system may manifest as myocardial injury, myocarditis, AMI, HF, arrhythmias, and venous thromboembolic events. In addition, some of the medications used to combat the disease, have a negative impact on the CV properties.

We analyzed numerous CV factors in order to identify those indicating an increased probability of a fatal outcome. As SARS-CoV-2 disproportionately affects people suffering from CV diseases, a prior CV disorder (especially hypertension, CAD and HF) is the greatest risk factor of unfavorable prognosis. Similarly, the development of any serious CV complication in the course of COVID-19 decreases the chances of survival.

Fortunately, there are certain risk factors which can also contribute to an increased alertness in terms of the anticipated disturbing symptoms and better prevention. The use of the CCS in addition to the high-resolution CT deserves special attention, since it helps in identifying patients with CAD with a higher baseline risk of adverse outcomes without additional costs. Another example is high D-dimer levels, which are vital in the process of ruling out thrombotic events. Markedly worse outcomes of COVID-19 patients with thrombotic complications highlighted the importance of thrombosis prophylaxis in all subjects admitted to ICUs. Furthermore, as the development of new-onset arrhythmia is associated with a severe disease course, continuous telemetry constitutes another useful tool in COVID-19 management. In addition, extra caution should be taken in patients with inherited arrhythmic disorders due to their increased risk of developing life-threatening arrhythmic events. ECG abnormalities during hospitalization also correlate with a higher risk of major adverse events.

Cardiac biomarkers can be used to assess the severity of the SARS-CoV-2 impact on the CV system. The elevated levels of TnI indicating myocardial necrosis have been associated with an increased risk of mortality, and have been

observed even in patients without ACS. Myoglobin and CK-MB have also been suggested as possible negative prognosis predictors regarding in-hospital death and non-recovery. Furthermore, NT-proBNP has been independently correlated with in-hospital death following adjustment for potential risk factors. In turn, the role of lactate dehydrogenase is uncertain, as elevated levels reflect multiple organ injuries. Nevertheless, it may play a prominent role in the triage of patients with COVID-19.

Overlapping clinical presentations and complex etiology of myocardial injury in COVID-19 require additional cardiac imaging to establish the diagnosis, guide therapy and stratify the risk of fatal outcome. Bedside ultrasound assessment of the heart and vessels is an effective first-line tool in detecting any abnormalities, although some patients may need advanced techniques. It is postulated that RV dysfunction predicts mortality in COVID-19 patients, and RVLS is a particularly accurate parameter. Furthermore, CMR is especially advantageous for the diagnosis of myocarditis. Finally, CT is efficient in the evaluation of lung parenchyma, patency of coronary and pulmonary arteries, and myocardial injury, making it the best non-invasive imaging modality allowing "quadruple rule-out" of the most serious CV complications.

We believe that the negative impact of SARS-CoV-2 not only on the respiratory, but also on the circulatory system, requires an integrated assessment of numerous CV risk factors of poor prognosis. Clinical evaluation of the possible CV complications, laboratory tests, ECG-monitoring, and CV imaging should be applied in order to provide the best possible management to COVID-19 patients, particularly those requiring hospitalization.

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Conflict of interest statement

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