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# The impact of cardiac complications on COVID-19 outcomes

This review discusses cardiac complications in patients with coronavirus disease – 2019 (COVID-19). The data from 65 articles published from 2020 to 2023 were reviewed, except one study on the pathophysiology of the coronavirus published in 2015. The prevalence, probable mechanisms of the development of cardiac complications of COVID-19, and early and late outcomes of the disease were analyzed. Heart rhythm and conduction disorders, acute coronary syndrome, myocarditis, heart failure, and pericardial damage were the most often associated with COVID-19. Cardiovascular diseases are common risk factors for various infectious diseases, including COVID-19, and are also predictors of poor in-hospital and long-term prognosis. Possible mechanisms of cardiac damage are the high affinity of the SARS-CoV-2 adhesion protein to angiotensin-converting enzyme 2 receptors, cytokine storm, ischemia, inflammation, and acute respiratory distress syndrome. Accumulated data should be systematised to create evidence-based recommendations and clinical protocols.

**Key words:** COVID-19, cardiovascular diseases, acute coronary syndrome, myocardial infarction, pericardial effusion, heart failure, myocarditis, arrhythmia, myocardial injury.



Since 2019, doctors around the world have been dealing with a coronavirus disease – 2019 (COVID-19) that continues to cause deaths up to the current moment. It is well known that the SARS-CoV-2 virus predominantly affects the respiratory system and may cause severe pneumonia with acute respiratory distress syndrome. Other mild, moderate, or severe cardiac complications may occur in acute settings of SARS-CoV-2 infection during hospitalisation or in the long-term perspective after discharge. The underlying pathophysiology of cardiac involvement in these patients is still unclear, although many reports on that topic worldwide exist. Different studies show us the importance of understanding the mechanisms of cardiac pathology development to improve management recommendations for COVID-19 patients. In this review, we are trying to analyse the currently available data about such coronavirus disease complications as myocarditis, arrhythmias, acute coronary syndrome, cardiac injury, heart failure and others. Accumulated knowledge can lead us to make a prognosis of these coronavirus patients in the hospital phase and also, in a long perspective, define and manage major risk factors and provide new complex recommendations.

It seems to be clear now that patients with cardiovascular diseases are at higher risk of worse outcomes during COVID-19 [1]. Pre-existing cardiac pathology may be a risk factor for coronavirus disease and increases the chance of getting infected. On the other hand, patients affected by the SARS-CoV-2 virus tend to get such complications as myocarditis, arrhythmias, heart failure and myocardial infarction [2]. In the study of, L. Wang and colleagues, 339 elderly COVID-19 patients were investigated [3]. Among them, eight people were diagnosed with shock, 58 with cardiac insufficiency, 35 with arrhythmia, and 70 with acute cardiac injury (21 %). The major factors for poor outcome in this group of patients were pre-

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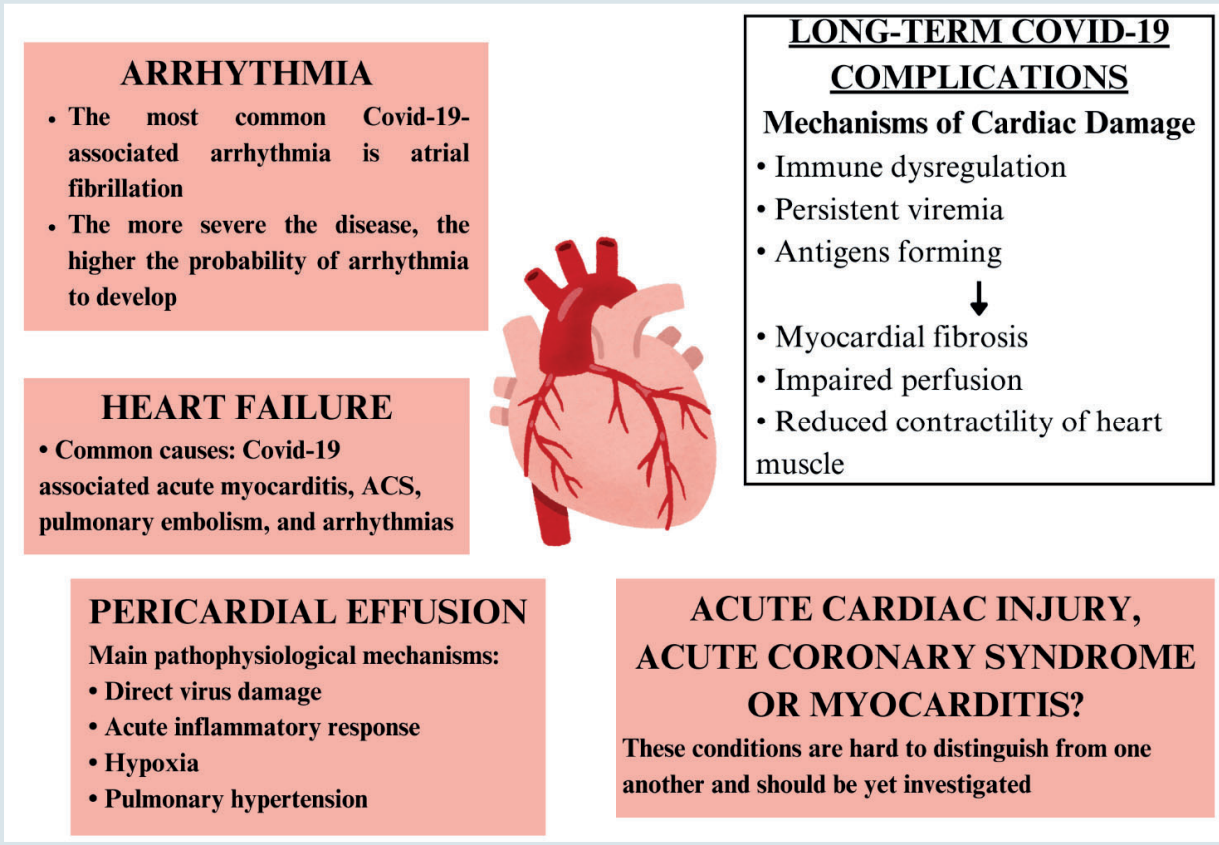


Figure. **COVID-19-associated cardiac complications**

existing comorbidities, higher levels of inflammatory markers, cardiac injury and impaired renal function.

According to the current data, not only cardiovascular comorbidities are risk factors for worse prognosis in coronavirus patients, but also different secondary cardiac pathologies due to SARS-CoV-2 infection [4]. As shown in this study, 27.8 % of 187 patients had myocardial injury. This complication had a more substantial impact on fatal outcomes compared to pre-existing cardiovascular diseases *(Figure)*.

**The aim** – to perform a literature review on COVID-19-associated cardiac complications, their role in mortality and long-term perspective, possible pathophysiological mechanisms, and future implementation opportunities.

**Material and methods.** For the analysis of the scientific literature, two independent authors selected from the international databases Scopus, PubMed, and Google Scholar 58390 articles for the period 2020–2024 using the keywords «coronavirus disease – 2019», «complications of coronavirus disease – 2019»; «cardiovascular diseases»; «myocardial infarction»; «heart failure», «arrhythmia», «cardiac injury», «troponin», «myocarditis». For the final analysis, 65 articles that met the search criteria were selected.

## Cardiac rhythm and conduction disorders

One of the most frequent complications is different cardiac rhythm disorders. Since the beginning of SARS-CoV-2 infection, they have been recognised as common disease features [5]. E.J. Coromilas and colleagues conducted a retrospective study of 4526 COVID-19 patients from 12 countries [6]. Most of them had no prior history of arrhythmia. Of 827 patients with new-onset arrhythmias, most developed atrial arrhythmias (81.8 %), 20.7 % developed ventricular arrhythmia, and 22.6 % – bradyarrhythmia. These cardiovascular complications were associated with higher morbidity and mortality. In another retrospective study, 784 patients were included; in 19 %, new-onset arrhythmias were documented [7].

Arrhythmias were diagnosed in 48 % of patients with poor outcomes and only 6 % with better survival chances. Cardiac arrhythmias occur more often in severely ill COVID-19 patients. Of 1553 patients, 349 of which presented with severe coronavirus manifestation, and 1204 were non-

severely ill, the percentage of those who developed cardiac arrhythmia was significantly higher in the first group (30.09 %), while it remained low in mild or moderate severity inpatients (2.82 %) [8]. In the study by M. Rav-Acha and colleagues in 2021, 21 of 390 COVID-19 patients were documented with new arrhythmias. There was a strong correlation between disease severity and arrhythmia prevalence ($p < 0.001$) when its prevalence in the mild-severity group was only 2 % [9].

Other studies also reported a correlation between poor outcomes and COVID-19-associated cardiac arrhythmia [10–12]. According to mentioned studies, the most common Covid-19-associated arrhythmia is atrial fibrillation. At the same time, it is still unclear if new-onset atrial fibrillation in patients with coronavirus infection can significantly impact long-term results. Thus, data from a recent observational study of 646 patients diagnosed with COVID-19 shows no correlation between new-onset atrial fibrillation and in-hospital or long-term mortality [13]. On the other hand, new-onset atrial fibrillation had an increased risk of invasive ventilation for those inpatients.

A total of 4975 patients with coronavirus disease COVID-19 were hospitalised at Saint Mykhailo Clinical Hospital in 2020–2021 years. In 490 (9.9 %) of them, atrial fibrillation was documented (138 with paroxysmal, 189 with persistent and 163 with chronic form). In-hospital mortality rate showed no significant difference: 31.9 % in the general group and 34.3 % in the atrial fibrillation group. A slightly higher mortality rate was found in patients with a paroxysmal form of atrial fibrillation (37.7 %), but further investigation should be performed.

## Acute cardiac injury, acute coronary syndromes or myocarditis?

Acute coronary syndromes, myocarditis or acute cardiac injury as specific complications of COVID-19 are being investigated and described in the literature. However, it is still challenging sometimes to distinguish these conditions from each other and manage these patients. The elevated level of high-sensitivity troponin identified as acute cardiac injury in patients with coronavirus infection seems to be a marker of poor outcomes, especially in acute settings [14]. T.J. Poterucha and colleagues analysed 887 patients with COVID-19 and found that acute cardiac injury and rhythm disturbances are associated with higher mortality [11]. Cardiac injury occurrence in COVID-19 patients was also investigated in another retrospective study, in which of 1413 inpatients, 319 were diagnosed with acute cardiac injury (22.58 %) [15]. The mortality rate was 48.28 % in patients with acute cardiac injury and 15.63 % in those without ($p < 0.001$). The significant impact of cardiac injury on mortality and outcomes is not well described in different groups of patients. Another big study shows an association between acute cardiac injury in COVID-19 patients and pre-existing chronic coronary syndromes. Elevated high-sensitivity troponin levels were found in 43.8 % of patients with CCS vs. 14.8 % without CCS [16].

According to our data in the intensive cardiac care unit of Saint Mykhailo Clinical Hospital, coronavirus disease COVID-19 was associated with worse prognosis in patients with ST-elevation myocardial infarction (STEMI) in 2020–2021. Among 795 STEMI patients who underwent early invasive percutaneous coronary reperfusion, coronavirus disease COVID-19 was diagnosed in 68 (8.6 %). COVID and non-COVID patients were comparable in terms of cardiovascular risk factors, comorbidities and the frequency of significant complications of myocardial infarction, but not in in-hospital mortality: 26.5 % and 9.2 %, respectively ($p < 0.001$).

Observing the precise occurrence of myocardial infarction in COVID-19 patients is challenging. Many other complications, such as coronary spasm, myocarditis or cardiomyopathy, may be presented as an ST-elevation myocardial infarction [2]. Some studies have reviewed potential COVID-19-associated plaque-disrupting mechanisms that may lead to type 1 myocardial infarction, but the data is limited. The other feasible way of myocardial infarction developing in SARS-CoV-2 infection, especially in patients with pneumonia and respiratory failure, is an imbalance between myocardial oxygen demand and supply (known as myocardial infarction type 2) [17]. It has also been reported that a patient developed acute myocardial infarction due to coronary thrombosis, left ventricular thrombus and acute ischemic cerebral infarction secondary to COVID-19 infection [18].

Although SARS-CoV-2 infection may affect myocardial muscle cells leading to myocarditis, the exact mechanisms are still unclear [19]. According to some studies, the risk of myocarditis in patients has grown since the beginning of the COVID-19 pandemic. A comprehensive survey of patients from more than 900 hospitals in the United States shows a 42 % higher occurrence of myocarditis in 2020 compared to 2019, and 40 % of all patients were diagnosed with

COVID-19 [20]. The correct incidence of COVID-19-associated myocarditis is difficult to know because of possible increased troponin levels due to myocardial injury. The ability of instrumental testing such as magnetic resonance imaging is low, and therefore, diagnosing is challenging [21]. The risk of myocarditis is lower in vaccinated individuals compared to unvaccinated [22].

Non-ischemic Takotsubo cardiomyopathy in the setting of COVID-19 infection is associated with a more severe course of the disease and higher mortality rates, although the diagnostic process may be challenging [23]. In the study of M.G. Davis and colleagues, of all 1659040 COVID-19 patients, the number of described stress cardiomyopathy cases was 1665 (0.1 %) [24]. Stress cardiomyopathy was associated with the higher in-hospital mortality rate in COVID-19 patients (32.8 %), while mortality in non-cardiomyopathy patients was 14.6 % (p = 0.01). The need for mechanical ventilation and inotropes or vasopressors administration was higher in patients with diagnosed stress cardiomyopathy.

## Heart failure

Heart failure is a quite common state in the general population, and it may also be a severe complication of coronavirus infection. Like other comorbidities, heart failure may increase the risk of severe COVID-19 course. COVID-19-associated acute myocarditis, acute coronary syndromes, pulmonary embolism, and arrhythmias are possible causes of new heart failure development. Patients with pre-existed heart failure were more likely to decompensate and stay longer in hospital in the acute settings of COVID-19 disease [25]. Twenty-two percent of patients with no cardiovascular disease risks were diagnosed with new-onset heart failure during hospitalisation. In comparison, the total amount of those with new heart failure was only 0.6 % of 6439 enrolled patients [25]. The occurrence of new-onset heart failure was almost one-third of critically ill patients who were admitted to the intensive care units [26, 27]. Elevated natriuretic peptides are usually a marker of worse outcomes in patients with COVID-19 and heart failure. Therefore, proper management should be assessed [28].

## Pericardial effusion

Pericardial effusion may also result from virus infection due to COVID-19. Main possible mechanisms for pericardial involvement are direct virus damage, acute inflammatory response, hypoxia due to respiratory distress syndrome or pulmonary hypertension [29, 30]. Pericardial effusion in hospitalised COVID-19 patients is associated with a higher risk of poor outcomes and may be a marker of severe infection course [31].

In the recent retrospective study of 211619 patients with COVID-19 infection, the number of those with a secondary diagnosis of acute pericarditis was 983 (0.43 %). Its occurrence was more common in younger patients, patients with cancer, chronic kidney disease and anemia. The risk of mortality was almost twice as high in patients with acute pericarditis (21.3 %) compared to patients without (11.3 %). Acute pericarditis has also been associated with some complications, such as cardiogenic shock, ventricular arrhythmias, and congestive heart failure, which may prolong the hospital stay [32]. Another study in which 100 patients with severe COVID-19 course were enrolled reported a higher mortality rate in the group of patients with pericardial effusion (33.3 %) compared to 20.8 % in the group without [33]. The development of pericardial effusion in these patients wasn't associated with comorbidities or lung involvement severity.

There is a possible correlation between the size of pericardial effusion and prognosis. Thus, in the study of İ. Saraç et al. (2023), 9182 patients with COVID-19 infection and 405 patients with pericardial effusion were detected [34]. 149 patients with pericardial effusion died during hospitalisation (39.2 %), and the other 256 patients were followed up after discharge. The rate of hospitalisation and mortality increased with the increase in pericardial effusion size. It is also important to mention that the correlation between the size of pericardial effusion and the severity of lung damage was statistically significant in all groups. The authors believe excessive inflammation to be an important cause for the development of pericardial effusion in COVID-19 patients. There was no difference in treatment patients with steroids, non-steroid anti-inflammatory drugs or colchicine for pericardial effusion incidence and chronicity.

## Long-term COVID-19 cardiovascular complications

The «post-COVID-19» or «long-COVID-19» syndrome is now used to describe a system of pathological events and symptoms in patients who suffered from COVID-19 previously [35]. While cardiovascular complications in the settings of acute COVID-19 courses are being reported and studied frequently, information about cardiac involvement in the long-term implications in patients

who were discharged home or were not hospitalised at all is still a little bit more complicated to deal with. The most commonly reported symptoms and signs of post-acute COVID-19 complications are fatigue, dyspnea, sleep disorders, effort intolerance and others [36, 37].

A significant study compared a cohort of COVID-19 patients with 5.8 million historical and 5.6 million contemporary controls and found a higher risk for ischemic and non-ischemic heart disease, heart failure, arrhythmias, pericarditis, myocarditis and thromboembolic complications in COVID-19 individuals [38]. The retrospective study in the Post-COVID Cardiology Clinic at Washington University included one hundred patients presenting with cardiovascular symptoms after COVID-19 infection [39]. The most common symptoms reported were chest pain (66 %), palpitations (59 %) and dyspnea (56 %). It was also noted that median systolic and diastolic arterial pressure were increased. Different laboratory markers involved in the examination didn't show any correlation to symptoms or post-COVID severity. Cardiac injury, assessed by elevated levels of troponin or cardiac magnetic resonance, was reported in patients recovered from COVID-19 infection, and even in some cases, mild infection led to persistent myocardial injury [40–42].

Another large study shows a much higher rate of hospital readmission compared to the control group over a period of 8 months in post-COVID patients due to major cardiovascular events [43]. According to the literature review made in the study of C.M. Terzic and B.J. Medina-Inojosa, the prevalence of long-term cardiac complications of COVID-19 varies from 1 to 30 % for pericardial effusion, 4–60 % for myocarditis, 17–23 % for myocardial infarction, 10–52 % for heart failure, 18 % for atrial fibrillation, 15–21 % for thromboembolism [2]. A recently published observational study showed a high prevalence of new cardiac events in patients who recovered from COVID-19 infection from a long-term perspective [44]. Of 502 enrolled patients, new cardiac alterations were found in 138 (27.49 %) and 60 cases of pericardial effusion. Patients with cardiovascular complications in the described group were older (median 60 years) and had a higher prevalence of smokers and coronary artery disease. Different cardiovascular complications due to COVID-19 have seemed to be significant not only in patients who were hospitalised but also in non-hospitalized groups [45]. In this retrospective cohort study, doctors have examined mortality, hospitalisation, cardiovascular disease and stroke outcomes after non-hospitalized COVID-19 in a group of 944 371 individuals. As a result, COVID-19 has a strong effect on all-cause mortality, hospitalisation, and cardiovascular disease outcomes. The effects were time-dependent and reduced after a 3-month follow-up; mortality risks returned to baseline after six months.

Possible mechanisms of post-acute cardiac damage, such as immune dysregulation, persistent viremia, and the formation of antigens, may further lead to myocardial fibrosis, impaired perfusion, and reduced heart muscle contractility [46–48].

## Possible pathophysiological mechanisms of COVID-19 associated cardiovascular complications

Different possible pathways for cardiovascular complications due to SARS-CoV-2 infection are proposed, but data is still limited. The direct viral myocardium invasion may probably be a mechanism for cardiac complications due to the high affinity of the SARS-CoV-2 spike protein to the angiotensin-converting enzyme 2 receptor [49]. After binding to these receptors and entering the cell using host transmembrane protease serine 2, the virus intervenes in the cell genetic system and provides its ribonucleic acid replication [50, 51]. After synthesising proteins, the new virus exits the cell, while the host cell may be destroyed by an immune response.

Biopsy reports, especially in the first years of the pandemic, found SARS-CoV-2 virus ribonucleic acid in human myocardium while confirming cases of COVID-19-associated myocardial injury [52–59]. Despite a significant number of mentioned papers, more recent data doesn't support this mechanism. Thus, in the study of Ammirati E. and colleagues, only 4 out of 15 patients with histologically proven acute myocarditis had the SARS-CoV-19 genome in the myocardium [60].

The other possible direct mechanism is myocardium damage due to a cytokine storm, which is proved by inflammatory myocardial changes, including macrophage infiltration, in the study by C. Basso in 2020 [61]. On the other hand, other mechanisms, such as ischemia, inflammation, and acute respiratory distress syndrome leading to oxygen demand-supply mismatch, are discussed [52, 62–65]. The exact pathophysiological impact of SARS-CoV-2 is still not fully understood to date.

## Conclusions

According to the data from accumulated studies, cardiovascular complications are common manifestations of acute and post-acute COVID-19. The most known pathologies are myocarditis, acute cardiac injury, arrhythmias, heart failure, myocardial infarction and pericardial effusion. Despite growing evidence from different studies and case reports, the effect on the cardiovascular system due to COVID-19 infection is still not fully understood.

Few possible mechanisms of cardiac involvement due to SARS-CoV-19 infection are described, but managing them remains challenging. Different observational papers study in-hospital and long-term outcomes for COVID-19 patients with new-onset cardiac pathology. According to studies, many inpatients who developed new-onset cardiac pathology in the acute settings of COVID-19 have worse prognoses and higher mortality rates.

The number of cardiovascular complications from COVID-19 is higher in critically ill patients. Observational data about long-term complications of COVID-19 are insufficient. Extensive observational studies for each cardiac complication and its effects on prognosis are important to achieve evidence-based management recommendations.

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ОГЛЯДИ

# Вплив кардіальних ускладнень, асоційованих із COVID-19, на найближчий та віддалений прогноз

В огляді обговорюються кардіальні ускладнення в пацієнтів із коронавірусною хворобою (COVID-19). Розглянуто дані 65 статей, опублікованих у період 2020–2023 рр., за винятком одного дослідження щодо патофізіології коронавірусу, опублікованого в 2015. Проаналізовано поширеність, ймовірні механізми розвитку кардіальних ускладнень COVID-19, близький та віддалений прогноз захворювання. Найчастіше з COVID-19 асоціювались порушення серцевого ритму і провідності, гострий коронарний синдром, міокардит, серцева недостатність та ураження перикарда. Серцево-судинні захворювання є загальними чинниками ризику для різних інфекційних хвороб, зокрема й COVID-19, і є також провісниками несприятливого прогнозу в госпітальному і віддаленому періоді. Можливими механізмами ураження серця є висока спорідненість спайкового білка SARS-CoV-2 з рецепторами ангіотензинперетворювального ферменту 2, цитокіновий шторм, ішемія, запалення та гострий респіраторний дистрес-синдром. Накопичені дані повинні бути систематизовані та використані з метою створення доказових рекомендацій та клінічних протоколів.

**Ключові слова:** COVID-19, захворювання серцево-судинної системи, гострий коронарний синдром, інфаркт міокарда, перикардіальний випіт, серцева недостатність, міокардит, аритмія, пошкодження міокарда.