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COVID-19 AND HEART INVOLVMENT IN ADULTS AND PEDIATRIC PATIENTS: AN UP-TO-DATE COMPRHENSIVE REVIEW

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Abstract. *Introduction.* Cardiovascular system seems to be one of the most common organ systems affected by COVID-19 both in adults and children. Myocardial injury is an independent predictor of in-hospital mortality. The SARS-CoV-2 virus is known to cause myocardial injury in some individuals and, when present, is associated with a fourfold increased risk of mortality

Aim. This comprehensive review of the current literature aims to provide primary care physicians and pediatricians with detailed information on possible cardiovascular complications in COVID-19 to better understand their nature and choose the right strategy for timely diagnosis in adult and pediatric patients.

Materials and methods. An exhaustive literature review was conducted on major databases: PubMed, WHO COVID-19 Database, Embase, China National Knowledge Infrastructure (CNKI) Database, Google Scholar, manual searches of leading medical journals, and a pre-print servers, to determine publications published from January 1, 2020 to December 15, 2021. The websites of World Health Organization, Centres for Disease control and Prevention, and the Johns Hopkins Coronavirus Resource Centre, European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) were reviewed to provide up to date information in the context of cardiovascular complications in COVID-19.

Results. Myocardial injury was associated with a mortality rate of 51.2%, compared with 4.5% without cardiac injury, and was present in 59% of non-survivors. Any associated cardiac complication is considered detrimental to the survival of COVID-19 patients. 46% of patients with COVID-19 had echocardiographic abnormalities including myocardial infarction, myocarditis, and Takotsubo cardiomyopathy. 50% of COVID-19 patients had electrocardiographic abnormalities, and 42% experienced chest pain, palpitations, or dyspnea. In the same study, 75% of cases in the same study had cardiac magnetic resonance (CMR) abnormalities.

Conclusion. The overall incidence of cardiac injury caused by COVID-19 varies from 7-64%. There is still limited data about the role of cardiovascular involvement in COVID-19 in children. Based on our review, children with acute COVID-19 requiring hospital admission should undergo a cardiac workup and close cardiovascular monitoring to identify and treat timely life-threatening cardiac complications. To date, we have few data on the Omicron variant and studies must be quickly carried out to better define the threat that this variant represents, including risk factors, mechanisms, and long-term outcomes of cardiovascular involvement, especially in children.

Key words: COVID-19, SARS-CoV-2, cardiovascular system, myocarditis, myocardial infarction, cardiomyopathy, arrhythmias, heart failure, Omicron.

COVID-19 та ураження серця у дорослих і дітей: комплексний огляд сучасної літератури

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Резюме. *Вступ.* Ураження серцево-судинної системи при COVID-19 серед ускладнень з боку внутрішніх органів і систем є найчастішими як у дорослих, так і у дітей. Пошкодження серця вірусом SARS-CoV-2 призводить до підвищення летальності в чотири рази.

Мета дослідження. Даний комплексний огляд сучасної літератури має за мету надати лікарям загальної практики та педіатрам детальну інформацію про можливі серцево-судинні ускладнення при COVID-19, щоб краще зрозуміти їх сутність та вибрати правильну стратегію своєчасної діагностики у дорослих і педіатричних пацієнтів.

Матеріали та методи. Ретельний аналіз літератури проведено за основними базами даних: PubMed, WHO COVID-19 Database, Embase, China National Knowledge Infrastructure (CNKI) Database, Google Scholar, а також пошук статей, опублікованих у провідних медичних журналах та на серверах попереднього друку, в часі від 1 січня 2020 року до 15 грудня 2021 року. Також були проаналізовані веб-сайти Всесвітньої організації охорони здоров'я, Центру контролю та профілактики захворювань, Ресурсного центру Джона Хопкінса щодо коронавірусу, Європейського агенції з лікарських засобів (EMA) та Управління з контролю за продуктами і ліками США (FDA), для з'ясування актуальних даних у контексті серцево-судинних ускладнень при COVID-19.

Результати досліджень. Пошкодження міокарда при COVID-19 корелює з 51,2% рівнем летальності проти 4,5% у випадках без ушкодження серця. Ускладнення з боку серцево-судинної системи знаходять у 59% тих, хто не вижив. Будь-які супутні серцеві ускладнення погіршують надію на виживання пацієнтів із COVID-19. У 46% хворих на COVID-19 виявляють ехокардіографічні відхилення, включаючи ознаки інфаркту міокарда, міокардиту чи кардіоміопатії Такоцубо. У 50% пацієнтів із COVID-19 виявляють патологічні зміни на ЕКГ, а 42% мають біль у грудях, серцебиття або задуху. В 75% випадків COVID-19 наявні патологічні зміни під час МР обстеженні серця.

Висновки. Загалом вважається, що частота ускладнень з боку серцево-судинної системи внаслідок захворювання COVID-19 коливається від 7% до 64%. На сьогодні маємо лише обмежені дані про значення та важливість серцево-судинних ускладнень при COVID-19 у дітей. Немає жодних сумнівів, що госпіталізовані діти з COVID-19 повинні пройти ретельне обстеження серця та потребують довготривалий моніторинг для своєчасного виявлення та успішного лікування можливих серцево-судинних ускладнень, котрі можуть загрожувати життю. Поки що маємо обмежені відомості щодо варіанту вірусу SARS-CoV-2 Омікрон. Тому існує велика потреба у невідкладному проведенні досліджень, спрямованих на визначення загрози, яку несе даний варіант вірусу SARS-CoV-2, включаючи можливі фактори ризику появи серцево-судинних ускладнень, механізми їх прогресування та довготривалий прогноз, особливо у дітей.

Ключові слова: COVID-19, SARS-CoV-2, серцево-судинна система, міокардит, інфаркт міокарда, кардіоміопатія, аритмії, серцева недостатність, Омікрон.

Aim

In this up-to date review, potential mechanisms, incidence, and clinical manifestation for cardiac involvement in COVID-19 adult and pediatric patients is provided by performing a literature research to summarize the current knowledge about the potential cardiovascular involvement in COVID-19 in order to give a perspective on how to take care of them during the current pandemic situation.

Methods

An exhaustive literature review was conducted on major databases: PubMed, WHO COVID-19 Database, Embase, China National Knowledge Infrastructure (CNKI) Database, Google Scholar, manual searches of leading medical journals, and a pre-print server, medRxiv. Multiple searches were performed using the search terms "COVID-19" or "SARS-CoV-2" were used in combination with "cardiovascular involvement" or "heart disease" "myocardial injury" or "myocarditis» or "cardiomyopathies" or «arrhythmia» or „heart failure" or "multisystem inflammatory syndrome in children (MIS-C)» or «thromboembolism" to identify articles published from January 1st, 2020 until December 15, 2021. The websites of World Health Organization, Centres for Disease control and Prevention, and the Johns Hopkins Coronavirus Resource Centre, European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) were reviewed to provide up to date numbers and infection control recommendations. Reference lists from the articles were reviewed to identify additional pertinent articles. Retrieved manuscripts concerning the subject were reviewed by the authors, and the data were extracted using a standardized collection tool. For MIS-C temporally associated with COVID-19, multiple meta-analyses were conducted to summarize the pooled mean proportion of different cardiovascular variables in this population.

Introduction

This up-to-date review intends to provide the primary care physicians and pediatricians with concise knowledge of potential cardiovascular complications in COVID-19 patients to understand the disease course better and decide how to manage adult and pediatric patients. The aim is to ensure physicians are up to date on the cardiovascular complications that can arise from COVID-19 infection. Cardiovascular system seems to be one of the most common organ systems affected by COVID-19 [122]. The clinical features of heart involvement can vary from one individual to another [137]. In some patients it can be asymptomatic, while in others it can result in life-threatening heart and lung failure. Myocardial injury is an independent predictor of in-hospital mortality. The SARS-CoV-2 virus is known to cause myocardial injury in some individuals and, when present, is associated with a fourfold increased risk of mortality [35].

Myocardial injury was associated with a mortality rate of 51.2%, compared with

4.5% without cardiac injury, and was present in 59% of non-survivors [38]. Any associated cardiac complication is considered detrimental to the survival of COVID-19 patients. 46% of patients with COVID-19 had echocardiographic abnormalities including myocardial infarction, myocarditis, and Takotsubo cardiomyopathy (TCM) [82, 135]. Another study showed 50% of COVID-19 patients had electrocardiographic abnormalities, and 42% experienced chest pain, palpitations, or dyspnea. In the same study, 75% of cases in the same study had cardiac magnetic resonance (CMR) abnormalities. The overall incidence of cardiac injury caused by COVID-19 varies from 7-64%, depending on the parameter used, among hospitalized patients in various reports [38, 39, 75, 78, 126]. There is still scarce data about the role of cardiovascular involvement in COVID-19 in children.

Cardiovascular involvement of COVID-19 in adults

Myocardial injury

Analyses of prior coronavirus outbreaks and COVID-19 data suggest several potential mechanisms of COVID-19 myocardial injury. Acutely, SARS-CoV-2 may directly infect and damage cardiac cells, triggering severe cellular and organ-wide pathology and dysfunction, although fulminant myocarditis is relatively uncommon in COVID-19.Factors associated with myocardial injury include age, presence of comorbidities, ferritin and fibrinogen levels and kidney, liver or other organ dysfunction, especially kidney injury. Thus, optimisation of organ dysfunction is a key point in the treatment of COVID-19 with myocardial injury. Several theories have been put forward to explain the mechanism of myocardial injury including the complex interaction between hypoxaemia, ischaemia and the procoagulant state in the setting of pneumonia. The cytokine storm that results from uncontrolled viral infection can lead to acute coronary syndrome. Prior coronary disease leads to higher endothelial inflammation and can even cause plaque rupture. Viral infection can even activate the coagulation process and endanger the anticoagulant property of endothelium to form thrombus. Thus, by blocking the compromised cardiac blood flow, it further exacerbates the injury [138].

While the direct cardiovascular manifestations of COVID19 detailed above stem from unique aspects of SARS-CoV2 virology and may be specific to coronaviruses, indirect pathological mechanisms have been reported, including hypoxia-induced myocardial injury due to hypoxic respiratory failure and hypoxemia, small vessel ischemia due to microvascular injury and thrombosis, or acute RV failure due to pulmonary embolism or in situ pulmonary artery thrombosis. Cardiac injury may also stem from a dysfunctional immune response. Hypo- and hyper-immune responses may contribute to severity of COVID-19 disease. Systemic inflammatory responses or cytokine storm may lead to cell death and multiorgan dysfunction, and late autoimmune phenomena have been postulated to contribute to autonomic dysfunction. The remarkable variety of symptoms, clinical severity, and manifestations after SARS-CoV2 exposure underscores our limited understanding of the heterogeneity of immune dysfunction in COVID-19. A deeper understanding of the pathways that account for immune success or failure in COVID19 would inform our understanding of the mechanisms that account for cardiovascular disease in more generalizable settings.

Clinical Evidence for Acute Myocardial Injury

The underlying mechanisms of cardiac injury are still not clearly understood, but it has been hypothesized that they are most likely multifactorial. Direct cardiotoxicity of SARS-CoV-2 can occur due to the ACE2 expression on myocardial cells and cardiac pericytes inducing capillary endothelial and microvascular dysfunction. Hypoxemia, as a consequence of lung involvement, can contribute to direct cardiac injury [25, 27].

Among hospitalized patients with COVID-19, evidence of acute cardiac compromise is common and includes acute heart failure (3%–33%), cardiogenic shock (9%–17%) [105], myocardial ischemia or infarction (0.9%–11%), ventricular dysfunction (left ventricular [10%–41%], right ventricular [33%–47%], biventricular [3%–15%]) [38, 61, 79], stress cardiomyopathy (2%–5.6%) [38, 61], arrhythmias (9%–17%) [126], venous thromboembolism (23%–27%) [63], and arterial thrombosis secondary to viral-mediated coagulopathy [74].

Pre-existing cardiovascular disease (coronary heart disease, heart failure, cerebrovascular disease), cardiovascular risk factors (male sex, older age, hypertension, diabetes), and other comorbidities (chronic obstructive pulmonary disease, chronic renal failure, and cancer) predispose patients with COVID-19 to more severe disease and mortality. The mortality rate is higher among patients with vs without cardiac injury (42 [51.2%] vs 15 [4.5%]; P < .001). The mortality rate increased in association with the magnitude of the reference value of high-sensitivity troponin-I (hs-TnI). Multivariable adjusted Cox proportional hazard regression model showed a significantly higher risk of death in patients with cardiac injury than in those without cardiac injury [106].

Biomarker Evidence for Cardiac Injury

Elevation of cardiac biomarkers, particularly high-sensitivity cardiac troponins and/or creatinine kinase MB, is a marker of myocardial injury. Elevation of cardiac biomarkers is common in patients with COVID-19 infection. In a review of clinical studies with at least 100 COVID-19 patients, there was found that in 26 studies including 11,685 patients, the overall prevalence of acute myocardial injury ranged from 5% to 38% depending on the criteria used. The overall crude prevalence of acute myocardial injury was 21.4% (1961/9164) [15].

Biomarker evidence of cardiac injury is strongly associated with worse COVID-19 outcomes. Elevation of cardiac biomarkers, such as NT-proBNP, troponins, or D-dimer [98] predict poor clinical outcomes. In hospitalized patients with COVID-19, the prevalence of elevated high-sensitivity troponin-T (hs-TnT) is 20% to 30%. Elevated hs-TnT levels were rare in COVID-19 survivors with an uncomplicated course (1%–20%), common in severely ill patients (46%–100%), and nearly universal in the critically ill and nonsurvivors. Among 2736 hospitalized patients with COVID-19 in New York City, even small elevations of hs-TnI were associated with higher mortality [109]. Furthermore, the greater the hs-TnI elevation, the higher the mortality risk. Compared with those without hs-TnI elevation, patients with COVID-19 with hs-TnI elevation have higher risks of acute respiratory distress syndrome (58%–59% versus 12%–15%), need for mechanical ventilation (22%–60% vs 4%–10%), malignant arrhythmias (17% versus 2% VT/VF), and death (51%–95% versus 5%–27%) [107, 138].

Recent reports have demonstrated TCM as a complication of COVID-19. A review of the literature has yielded 10 cases of TCM in patients with COVID-19 [102]. 90% of the cases occurred in women with a mean age of 64.6 years. Apical involvement was the most common form TCM, which is induced by cytokine storm and elevated levels of cortisol and other stress-related hormones. TCM is previously known as a self-limiting and benign cardiac manifestation, but it has been uncovered that TCM can be associated with fatal cardiac outcome due to cardiogenic shock and life-threatening arrhythmia [101, 125]. Vascular integrity is compromised by virus action and causes myocardial alteration. Treatment is still controversial. However, ACE inhibitors, beta-blockers and diuretics are used in the treatment of such patients [5].

Imaging Evidence for Myocardial Injury

Biomarker evidence of myocardial injury with associated echocardiographic abnormalities correlate with higher risk of in-hospital mortality. Echocardiographic abnormalities commonly reported in hospitalized patients with COVID-19 include right ventricular (RV) dysfunction (26.3%), LV wall motion abnormalities (23.7%), global LV dysfunction (18.4%), grade II or III diastolic dysfunction (13.2%), and pericardial effusion (7.2%) [48].

Abnormalities suggesting injury on cardiac magnetic resonance imaging (CMR) have also been reported commonly. CMR findings can indicate cardiac pathologies associated with COVID-19. In a systematic review comprising 199 patients from 34 acute or postrecovery CMR studies in patients with COVID-19 CMR diagnoses included myocarditis in 40.2%, myopericarditis in 1.5%, TCM in 1.5%, ischemia in 2.5%, and dual ischemic and nonischemic changes in 2.0%. Regional wall motion abnormalities were reported in 13/32 (40.6%) [87]. Additionally, perfusion and extracellular volume mapping abnormalities were described in 18/21 (85%) and 21/40 (52%) patients, respectively. In summary, the most common CMR diagnosis was myocarditis, and imaging findings included evidence of diffuse myocardial edema, and myocardial fibrosis.

Acute Cardiac Injury and Acute Coronary Syndrome

According to a cohort study on 416 patients with COVID-19, acute myocardial injury was found in 19.7% of patients during hospitalization, and it was an independent risk factor for in-hospital mortality [107]. A study on 187 patients with COVID-19 showed a significant increase in mortality during hospitalization in those who had elevated hs-TnI (37.5%), especially when combined with underlying CVD (69.44%). Patients with elevated troponins levels had more frequent malignant arrhythmias, and indications for mechanical ventilation [54]. In an early study from China that enrolled 101 cases, the acute myocardial injury was present in 15.8% of

COVID-19 patients who were older, with a higher prevalence of pre-existing cardiovascular disease [123, 127]. Because of the higher prevalence of myocardial injury than that of underlying CVD, it can be speculated that SARS-CoV-2 affects the cardiovascular system, not only through exacerbation of the pre-existing state but also directly causing myocardial inflammation due to extensive release of proinflammatory cytokines, which, in some cases, leads to fulminant myocarditis [60]. According to the current European Society of Cardiology Guidance for the Diagnosis and Management of CV Disease, during the COVID-19 pandemic admission and peak troponin appear to be predictors for outcomes in COVID-19 patients.

Although COVID-19 has a great potential to cause acute coronary syndrome (ACS) or exacerbate previous chronic conditions, there are reports from Italy, Spain, and the USA showing a significant reduction in hospitalization for ACS (40–48%), and also a reduction in percutaneous coronary intervention (38–40% for STEMI, 57% for diagnostic procedures) [10, 20, 33]. The report from Italy also showed a 26.5% reduction in STEMI admissions and a 65.4% reduction in NSTEMI admissions with a disproportionately greater decrease in STEMI reductions for women (41.2%), than for men (25.4%). The STEMI case fatality rate increased to 13.7% from 4.1% in 2019 and the rate of major complications increased to 18.8% from 10.4% in 2019. In central Germany, comparing lockdown in 2020 to 2019 cardiac death, pulmonary embolism, and stroke rose about 8%; however, fatal pulmonary embolism was about 11% higher [85]. Some of the reasons for this trend could be avoidance of medical facilities because of social distancing, concerns of contracting COVID-19 in healthcare settings, and less physical activity. Conversely, the rate of out-of-hospital cardiac arrest increased. A study from Italy showed a 58% increase in out-of-hospital cardiac arrest compared with the pre-COVID-19 period. The cumulative incidence of out-of-hospital cardiac arrest in 2020 was strongly associated with the cumulative incidence of COVID-19 [11]. Interestingly, there was a decrease of 15.6% in cardiopulmonary resuscitation from bystanders possibly showing the side effects of social distancing [12]. The even greater difference was found in a population-based cross-sectional study from New York City with the number undergoing resuscitation 3-fold higher during the 2020 COVID-19 period compared with the non-COVID-19 period in 2019 [9]. Patients suffering an out-of-hospital cardiac arrest during 2020 were older, and more likely to have specific comorbidities, such as diabetes and hypertension. There was a significant increase in non-shockable presenting rhythms and a substantial reduction in return of spontaneous circulation [2, 67].

Cardiogenic shock due to cardiac tamponade, acute decompensated heart failure, acute myocardial infarction and fulminant myocarditis can be observed. Haemodynamic assessment including right heart catheterisation is very important in the recognition of cardiogenic shock [3, 45]. Cardiac catheterisation is both therapeutic and diagnostic in cardiogenic shock following acute myocardial infarction in COVID-19 patients [104].

In COVID-19, viral myocarditis is a common and important cause of myocardial injury and presents similarly to myocardial infarction with a rise of cardiac biomarkers, cardiomyopathy features on echocardiography and normal coronary arteries. Diagnosis of viral myocarditis is most commonly a clinical one but may require endomyocardial biopsy (EMB) and histopathological examination. The largest study to date regarding acute myocarditis in COVID-19 is a systematic review of 38 reported cases which does not reflect the true incidence of myocarditis in COVID-19. It is a challenge to differentiate between myocardial injury in severe/critical COVID-19 and acute myocarditis, especially because of the lacking availability of diagnostic procedures, such as EMB or CMR, during the COVID-19 pandemic [23].

The possible mechanism of myocardial damage is the pathway via ACE2 receptors and a hyperimmune response. Early studies from China reported five cases of myocardial damage resulting in circulatory failure as a possible consequence of fulminant myocarditis, although the diagnosis of myocarditis was not confirmed [99]. Sala *et al.* [101] report the first direct evidence of myocardial inflammation by EMB in a COVID-19 patient. EMB revealed diffuse T-lymphocytic inflammatory infiltrates with significant interstitial oedema and limited focal necrosis

Suspicion of acute myocarditis should be raised when the levels of troponins do not correlate with the hyperinflammatory state. High levels of hs-TnT and NT-proBNP accompanied with a generalized increase in inflammatory markers are a sign of multiorgan failure rather than acute myocarditis [58]. There are no pathognomonic electrocardiographic (ECG) changes in COVID-19 myocarditis. The most common ECG changes in COVID-19 are ST-segment abnormalities (40%), followed by cardiac arrhythmias (38%) including sinus tachycardia, sinus bradycardia, conduction blocks, atrial premature complex, atrial tachycardia, atrial fibrillation, and ventricular premature complex [71].

Echocardiographic features of COVID-19 myocarditis are global and regional hypokinesia with a decreased left ventricular ejection fraction, and an increase in wall thickness suggesting edema. Right ventricular strain was decreased in patients with poor outcomes and left ventricular strain was decreased regardless of outcome [16]. Right ventricular strain measurements may be important for risk stratification and prognosis [32]. Further studies are needed to confirm these findings. A normal echocardiographic exam is possible, especially in the early stages. CMR imaging can show hypokinesis, left ventricular dysfunction and pericardial effusion [87].

In a cohort study including 39 consecutive autopsy cases from patients positive for SARS-CoV-2, the virus RNA was confirmed in 24 of 39 patients (61.5%). None of the patients in the study were diagnosed with fulminant myocarditis, and there were no massive cell infiltrates or necrosis [73]. A study including 104 EMB of patients with suspected myocarditis or unexplained heart failure detected SARS-CoV-2 genome in 5 cases, and only 2 of them met the Dallas criteria for myocarditis [40]. In an international multicentre study assessing cardiac tissue from the autopsies of 21 COVID-19 patients, lymphocytic myocarditis was present in 3 (14%) and increased interstitial macrophage infiltration was present in 18 (86%) of the cases [14]. There is still not enough evidence supporting the direct destruction of cardiomyocytes through virus-mediated lysis. Other mechanisms involving direct entry of the virus into endothelial cells in the heart or hyperactivation of the immune system have been proposed. Some authors suggest EMB should not be routinely performed due to scarce evidence of histological evidence typical for myocarditis, and actual virus RNA in cardiac tissue together with unclear therapeutic implications [65].

In Israel, 62 cases of myocarditis were reported after COVID vaccine administration in five million individuals [118]. In most cases these occurred after the second dose of mRNA vaccines [116]. Young men are more affected, with two deaths in total. Fourteen cases of myocarditis were also reported in the United States Defense Department after administration of Pfizer-BioNTech and Moderna vaccines [36, 68, 117].

Arrhythmias

Mechanisms for arrhythmogenicity in COVID-19 infection include altered intercellular signalling, ion channel dysfunction, electrophysiological and structural remodelling due to interstitial edema and cardiac fibrosis resulting in repolarization abnormalities and action potential conduction abnormalities [105, 117]. A recently published study compared COVID-19 ICU patients with ICU patients who were COVID-19 negative and showed that atrial tachyarrhythmia is associated with increased mortality in critically ill patients with COVID-19 [31]. The incidence of arrhythmias has been associated with disease severity. According to a study from Wuhan, China, patients with severe/critical COVID-19 had more atrial arrhythmias compared with those with non-severe symptoms. When they compared COVID-19 ICU patients with patients who were admitted to the ICU due to bacterial pneumonia in the pre-COVID era, those with COVID-19 had higher total, mean, and minimum heart rates, and no significant difference in the incidence of arrhythmias, including premature atrial/ventricular contractions, atrial fibrillation, nonsustained ventricular tachycardia, and atrioventricular block [56]. Studies from China, the USA and Europe showed that non-specifical arrhythmia was the most common in COVID-19 patients. To be more precise, the overall incidence was about 17%, non-specifical arrhythmia were 12%, atrial fibrillation 8%, conduction abnormalities 11%, premature contractions 9% and about 3% ventricular tachycardia/fibrillation [72].

Cardiac arrhythmias are frequent and may remain even after recovery from COVID-19. Arrhythmias such as AF, ventricular tachycardia and supraventricular tachycardia and complete heart block can appear in any phase of the disease (infective, recovery or post-recovery phase) and individualised care seems to be the best approach for these patients [34].

In a study of 1053 hospitalized patients followed for a median of 7 days on telemetry, arrhythmia was reported in 25.6% of patients [90]. The presence of arrhythmias correlated with disease severity, elevated markers of myocardial injury, inflammation, and fibrinolysis and was independently associated with 30-day mortality. Very similar results were recently reported in a large multicentre Italian study with 21.7% incidence of sustained tachyarrhythmias in 414 hospitalized patients [100]. Based on these studies, it seems that tachyarrhythmias are a marker of COVID-19 severity occurring more frequently in patients with more severe disease and are associated with higher mortality.

In general, the acute treatment of arrhythmias should not be significantly different from their management in non-COVID-19 patients and should be in line with the current ESC, European Heart Rhythm Association and related guidelines [19, 21, 22].

Another mechanism of arrhythmias in COVID-19 is multi-drug usage and their interactions. The pro-arrhythmic state - dysfunction and altered drug clearance also increases arrhythmogenicity. Additionally, some drugs used for treatment for viral replication prolong the QT interval [88]. Thus, torsades de pointes may occur in susceptible patients treated with chloroquine/hydroxychloroquine, lopinavir/ritonavir, macrolides (especially azithromycin) and fluoroquinolones. The latter two drugs are commonly used to treat bacterial superinfections in COVID-19 patients. Also, several of these patients have additional risk factors such as prior heart diseases, electrolyte abnormalities and usage of other QT-prolonging drugs such as anti-emetics, proton pump inhibitors, sedatives [64]. Patients with COVID-19 receiving those agents should be closely monitored, especially when combining more agents at a time or having congenital long QT, electrolyte imbalances, pre-existing heart disease, and renal or hepatic dysfunction [83].

The most common arrhythmias in COVID-19-affected individuals are atrial arrhythmias which can be found in up to 17.7% of mechanically ventilated patients. The cause of death in most of these patients is asystole or pulseless electrical activity secondary to pulmonary embolus or lung failure [94]. AF is a poor prognostic factor in those with acute respiratory illness. For rate control, diltiazem is preferred in COVID-19 patients as beta-blockers may precipitate bronchospasm in respiratory disease [34].

A global survey of a total of 1197 electrophysiology professionals from 76 countries and 6 continents reported atrial fibrillation as the most common tachyarrhythmia in COVID-19 patients (in 21% of the reports), and severe sinus bradycardia and complete heart block as the most common bradyarrhythmias (in 8% and 5.9% of the reports, respectively). Regarding life-threatening arrhythmias, ventricular tachycardia/ventricular fibrillation arrest and pulseless electrical activity were reported by 4.8% and 5.6% of respondents, respectively [50].

A higher incidence of out-of-hospital cardiac arrest has been noted in patients suspected of or with a confirmed diagnosis of COVID-19 [24]. Even in patients on whom emergency personnel attempted resuscitation, out-of-hospital cardiac arrest occurred at 14.9% points more in 2020 as compared to 2019 [46]. In Paris, France, the rise of cardiac arrest was partly attributed to COVID-19 infection and indirectly related to lockdown and health care services-related adjustments [80]. When the number of COVID-19 cases peaked in New York City, a three-fold higher number of out-of-hospital cardiac arrest underwent resuscitation compared to the same period in 2019 and most were older, more likely to have specific comorbidities [2, 67].

Postrecovery cardiac involvement

The potential for long-term cardiac sequelae of COVID-19-associated myocardial injury has been highlighted by CMR studies in recovered patients with evidence of myocardial fibrosis or myocarditis reported in 9% to 78% of patients recovered from acute COVID-19. Among 100 post-COVID-19 patients who underwent CMR 2 to 3 months after the diagnosis, cardiac involvement was reported 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 exhaustion (36%). Recovered patients had lower left ventricular ejection fraction and higher left ventricle volumes compared with risk factor–matched controls. In 3 patients with severe CMR findings, endomyocardial biopsy revealed active lymphocytic infiltration but without detectable viral genome [95].

CMR findings were also reported in 26 patients who had recovered from COVID-19 but with cardiac symptoms after discharge, including chest pain, palpitations, or chest distress [59].

Such CMR findings of myocarditis and myocardial fibrosis raise concerns regarding potential long-term cardiac sequelae, including increased risk for heart failure and arrhythmias based on prior experience with myocarditis. The presence of myocarditis often implies myocardial necrosis in addition to myocardial edema and has previously been associated with adverse outcomes in multiple non-COVID related myocarditis CMR studies [51, 110]. This risk has been shown to be further modulated by left ventricle dysfunction [6] and persistent of myocardial edema [7]. At this time, the actual risk of complication in patients with abnormal CMR findings remains undefined, whether it's due to capillaritis, microthombi, or endothelial dysfunction secondary to a systemic inflammatory response, or histologically defined myocarditis remains undiscerned [98, 105].

Heart failure

Approximately a quarter of hospitalised COVID-19 individuals were diagnosed with new-onset heart failure, especially in intensive care admissions (one third of admissions) [8, 138]. An increase in natriuretic peptides is indicative of a worse prognosis. Heart failure in COVID-19 can be the consequence of myocardial injury, acute coronary syndrome, acute myocarditis, and arrhythmias [139]. Moreover, heart failure can be caused by deterioration of pre-existing myocardial dysfunction or unmasking of subclinical heart failure in individuals with underlying risk factors. It is a relatively common complication noted in 49% of patients who had severe/critical COVID-19 [26]. Similarly, in a retrospective, multicentre cohort study including 191 COVID-19 hospitalized patients, heart failure was developed in 23% of patients, 52% of non-survivors and 12% of survivors [138]. It seems that in COVID-19 heart failure with preserved ejection fraction is more common than heart failure with reduced ejection fraction, both in the acute phase and chronic recovery phase [44]. Echocardiography study showed that in COVID-19 left ventricular systolic function is preserved in the majority of the patients (90%). Right ventricular abnormalities (dilatation and dysfunction) were found in 39%, and left ventricular diastolic dysfunction in 16% of patients [112].

NT-proBNP is a biomarker of hemodynamic myocardial stress and heart failure. It is frequently elevated among patients with severe/critical COVID-19, and according to some authors related to poor prognosis and increased mortality [54].

Current European Society of Cardiology Guidance for the Diagnosis and Management of CV Disease during the COVID-19 pandemic suggests a careful interpretation of NT-proBNP levels. They should be seen as the combination of the presence or extent of pre-existing cardiac disease and/or the acute hemodynamic stress related to COVID-19. It should also be taken into account that NT-proBNP levels can be associated with the right ventricular hemodynamic stress, especially in the setting of venous thromboembolism VTE [41]. The increased risk of venous thromboembolism poses a considerable challenge to caring for 31% - 40% of critically ill COVID-19 patients [66, 126]. Disseminated intravascular coagulation occurred in 71.4% of patients who died of severe COVID-19. These patients had high venous thromboembolism rates, elevated d-dimer levels, high fibrinogen levels, low antithrombin levels, and pulmonary congestion with microvascular thrombosis and occlusion [126]. The hypercoagulable changes of microthrombi are noted in pulmonary capillary vessels, and are thought to represent megakaryocytes' overexpression and platelet adhesion. Thus, current recommendations are favoring platelet inhibitors. In Italy, anti-platelet therapy including acetylsalicylic acid, clopidogrel, tirofiban, and fondaparinux showed effective in improving hypoxemia and successful in weaning ventilator in COVID-19 patients with severe respiratory failure, bilateral pulmonary infiltrates and elevated/upper limit of normal levels of d-dimer [89, 121, 124]. A lower 28-day mortality level from heparin use than non-users in COVID-19 patients with a d-dimer more than 6 times the upper limit of normal (32.8% vs 52.4%, p = 0.017) have been reported [53, 115].

Diagnostic approach for the cardiovascular complications of COVID-19

According to ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 pandemic [41], the levels of troponins and NT-proBNP correlate with disease severity and mortality but should be interpreted as quantitative variables. Mild elevations (<2–3 times the times the upper limit of normal) should be seen as a consequence of pre-existing cardiac disease, acute injury or stress related to COVID-19, and do not require any additional workup or treatment if there are no symptoms such as chest pain or ECG changes. Pre-test probability assessment and serial measurements of D-dimers may be useful in the selection of patients who would benefit from the use of higher than prophylactic doses of anticoagulation. Routine measurements of troponins and BNP/NT-proBNP are discouraged [41]. NT-proBNP as a biomarker of hemodynamic myocardial stress is more often elevated in COVID-19 patients with a cardiac injury who have a higher risk of in-hospital mortality [107].

There are no specific ECG characteristics in COVID-19 patients that were found so. Because of that, the ECG diagnostic criteria for cardiac conditions should be the same in COVID-19 patients and the general population. Atrial fibrillation is the most common tachyarrhytmia. Severe sinus bradycardia and complete heart block are the most common bradyarrhythmias. Monitoring-higher risk for prolonged QT and torsades de pointes when on COVID-19 drug therapy [19]. According to a study from Wuhan, China, the most common ECG features found in COVID-19 patients were ST-T abnormalities (40%) and arrhythmias (38%) [13, 29]. They were also associated with increased odds of ICU admission [71].

Transthoracic echocardiography (TTE) is the most used imaging modality for cardiac evaluation in COVID-19 as it is can be easily performed at the patient's bedside, providing information about cardiac structure and function [49, 91]. One survey showed that the most common indications for TTE among 1216 examined COVID-19 patients were suspected heart failure, cardiac biomarker elevation and right-sided heart failure [38]. An abnormal finding on TTE together with myocardial injury, rather than the myocardial injury alone, is associated with higher mortality [120]. Among patients with biomarker evidence of myocardial injury and COVID-19 who underwent TTE, cardiac structural abnormalities were present in nearly two-thirds of patients with myocardial injury. Myocardial injury was associated with increased in-hospital mortality particularly if echocardiographic abnormalities were present. According to a study that included 120 COVID-19 patients right ventricular longitudinal strain is a strong predictor of higher mortality in patients with COVID-19 [70]. In addition to that, right ventricular ejection fraction measured by three-dimensional echocardiography showed an even higher predictive value over standard RV function parameters and RV free wall longitudinal strain that may help to identify patients at higher mortality risk [69, 70].

The role of computed tomography (CT) in COVID-19 patients is important, especially for evaluation and progression of lung pathology but can also be useful in helping differentiate COVID-19 pneumonia and acute decompensated heart failure [49, 139]. Cardiac CT should be used to rule out cardiac thrombus and in acute chest pain to rule out obstructive coronary disease and in cases of left ventricle dysfunction. CT-pulmonary angiography enables detection of pulmonary embolism, a common finding in COVID-19 infection with incidence ranging from 2.6 to 24% according to some studies. Cardiac CT angiography may be used instead of TEE for the exclusion of left atrial appendage thrombus, evaluation of endocarditis and paravalvular complications. Coronary CT angiography can be an alternative to invasive coronary angiography [108].

CMR imaging is a very sensitive tool for identifying COVID-19-related myocardial injury, but also for detection of post-COVID-related long-term cardiovascular consequences [49, 59]. CMR can help distinguish between ischemic and non-ischemic myocardial injury and is useful for the diagnosis of myocarditis showing myocardial edema with late gadolinium enhancement, inflammation, and fibrosis. The most common diagnosis made by CMR in COVID-19 patients was myocarditis (40%). On the other hand, approximately 20% of patients with "cardiac" symptoms had a normal CMR [87]. Another study showed that 78% of recently recovered COVID-19 patients had abnormalities on CMR, and 60% had evidence of myocardial inflammation, even in asymptomatic patients, indicating the need for investigation of possible long-term cardiovascular consequences of COVID-19 [59, 95]. A similar study reported evidence of myocardial inflammation or prior myocardial injury on CMR after either asymptomatic or mildly symptomatic COVID-19 in competitive athletes [30, 96]. Therefore, CMR can be potentially used for making exercise recommendations post-COVID-19 [49, 111].

Nuclear imaging requires longer acquisition times and exposure of both patients and health care providers. The use of positron-emission tomography can be an alternative to TEE for patients with suspected endocarditis of prosthetic valves or intracardiac devices [41, 49].

Exercise testing is discouraged in the COVID-19 pandemic because of its serious limitations such as wearing a mask during the performance. Still, it remains the method of choice for the indication to heart transplantation in patients with heart failure and for the diagnosis of heart failure with preserved ejection fraction [109].

Cardiovascular complications of COVID-19 in pediatric population

Although respiratory illness is the dominant clinical manifestation of COVID-19, cardiovascular issues are emerging as one of the most significant complications of SARS-CoV-2 infection in pediatric patients. As described above, patients with pre-existing cardiovascular diseases and with PMIS accounted respectively for 18%

and 12% of pediatric deaths associated with COVID-19. Remarkably, Multisystem Inflammatory Syndrome in Children (MIS-C) has approximately a ten-fold mortality rate regarding the rest of pediatric COVID-19 cases. These data indicate that prognosis is worse when the cardiovascular system is impaired during SARS-CoV-2 infection in children.

The Chinese Center for Disease Control reported that <1% of the patients with COVID-19 were under the age of 10 years [132]. In another large pediatric-only cohort in China, authors reported that children tend to have a less severe form of COVID-19 with the majority presenting with mild symptoms. However, infants with COVID-19 were in a critical condition compared to older children [136]. The reason behind milder disease presentation in children is not yet clear. Some theories support the notion that children have a less functional ACE2 receptor compared to adults; thus, the infectivity of the virus is decreased. Another theory argues that children have higher levels of ACE2 which in its turn reduces angiotensin II plasma levels. Angiotensin II is recognized to correlate strongly with the clinical course of COVID-19 disease [114]. Indeed, children infected with COVID-19 have low hospital admission rates and an estimated mortality rate of less than 5% [76]. However, a minority of children tend to exhibit serious disease manifestations, especially cardiovascular injury.

MIS-C was reported as a new combination of atypical Kawasaki disease and toxic shock syndrome with multiorgan involvement under the umbrella of severe COVID-19. Later, the WHO and the United States Center for Disease Control and Prevention set criteria for diagnosis with overlapping features [128]. The pathophysiology involves a sequela of events. The first one is denoted by acute necrotizing arteritis characterized by neutrophils infiltrating the vessel walls. This is followed by the formation of an aneurysm within the coronary artery. Macrophages and T cell lymphocytes infiltrate the damaged vessel wall to begin a chronic form of vasculitis. Over the years, myofibroblast proliferation leads to coronary artery stenosis. In the early acute phase, myocardial edema can develop leading to myocarditis before evidence of an aneurysm. A transient left ventricular dysfunction may occur and lead to cardiovascular shock in some patients [57]. MIS-S affects mostly previously healthy school-aged children and adolescents presenting with Kawasaki disease-like features and multiple organ failure with a focus on the heart, accounting for most cases of pediatric COVID-19 mortality. They frequently presented cardiogenic shock (53%), ECG alterations (27%), myocardial dysfunction (52%), and coronary artery dilation (15%). Most cases required pediatric intensive care unit admission (75%) and inotropic support (57%), with the rare need for extracorporeal membrane oxygenation (4%). Almost all of these children wholly recovered in a few days, although rare deaths have been reported (2%) [1].

Patients who develop MIS-C amidst their SARS-CoV-2 infection are usually older than patients who develop Kawasaki disease alone with the median age being 9 years in the former. The presentation tends to begin around 4–6 weeks after contracting the virus, and they are usually PCR-negative. They commonly report fever and a spectrum of respiratory symptoms ranging from cough to dyspnea. 70% of patients with MIS-C also report gastrointestinal symptoms such as abdominal pain and diarrhea. Other signs and symptoms that are related to the Kawasaki-like features are rash, fissured lips, and conjunctivitis. The cardiac abnormalities common in MIS-C are arrhythmia, conduction abnormalities, ventricular dysfunction, coronary artery dilatation or aneurysm, and pericarditis. According to multiple reports, the most common cardiac abnormality is left ventricle dysfunction manifested by a depressed ejection fraction. While most patients are managed with inotropic support, a large cohort study revealed that around a third of the pediatric patients presenting with MIS-C required extracorporeal membrane oxygenation [4]. In a large case series, the majority of patients required inotropes but all of them recovered their left ventricle function within a median of 2 days [52]. In another large pediatric-exclusive study including patients who developed MIS-C, the authors reported that 80% of them had cardiac involvement. The majority had elevated cardiac biomarkers (73%), and 8% developed coronary artery aneurysms [42]. Patients with MIS-C may develop coronary artery abnormalities such as dilatations and aneurysms. Reports have demonstrated an array of descriptions ranging from small aneurysms to giant ones. While it has been hypothesized that a mechanism similar to that observed in Kawasaki disease occurs with MIS-C, the true pathophysiology behind coronary artery abnormalities has not been elucidated yet [28].

In addition to coronary artery abnormalities, the second most common cardiac abnormality in MIS-C is arrhythmia. First-degree heart block is the most common presentation of arrhythmia. It has been commonly reported in children presenting with left ventricle dysfunction. Electrocardiogram reveals QT prolongation, ST-segment changes, or T-wave abnormalities [93]. Laboratory workup reveals elevated troponin, NT-proBPN, D-dimer, and inflammatory markers such as ferritin, erythrocyte sedimentation rate, interleukin-6, procalcitonin, and C-reactive protein. A complete blood count reveals neutrophilia, lymphopenia, and thrombocytopenia [4]. Chest X-ray displays cardiomegaly with possible hilar and mediastinal abnormalities. More than 50% of these patients will have a degree of left ventricular dysfunction or failure noted on echocardiography. Global or wall hypokinesis has been documented as well. While right ventricular function is preserved in all patients, pericardial effusion is present in the minority of patients [37, 62]. The natural course of MIS-C is not yet known. Ventricular dysfunction tends to improve over time [17]. More studies are needed to elucidate the long-term manifestations of MIS-C. Kawasaki disease is associated with left ventricular systolic dysfunction in 20% of patients, coronary artery dilation in 29%, and mitral regurgitation in 27%, suggesting shared mechanisms between Kawasaki disease, cardiac complications and abnormalities, and myocarditis. Despite having a milder clinical course, children should be monitored for cardiac complications and, upon presenting with any Kawasaki-like disease, should be tested for COVID-19 [93].

The incidence of myocarditis is currently unknown in patients with COVID-19, as the evidence in the literature is limited to case reports [18, 45, 77]. In a cohort with small sample size, cardiac MRI performed at a median of 71 days after the SARS-CoV-2 infection revealed myocarditis in 80% of the patients [52, 57, 95]. In the pediatric population, myocardial dysfunction has also been described. In a large prospective study in France, more than half of the children enrolled had evidence of myocarditis with depressed ejection fraction and elevated inflammatory and cardiac biomarkers. There was evidence of pericardial effusion as well. Echocardiographic findings include a large left ventricular volume, left ventricular diastolic dysfunction, and low left ventricular ejection fraction. MRI findings often include a late gadolinium enhancement, and pericardial enhancement [95]. In a large pediatric cohort study, myocarditis was noted in 71% of the admitted patients [119]. This suggests that SARS-CoV-2 induces myocarditis, myocardial ischemia, and heart failure in a significant proportion of the infected patients.

The severe systemic inflammation in COVID-19 can precipitate cardiotoxicity and lead to cardiovascular dysfunction. The incidence of cardiomyopathy was reported to reach 33% in patients infected with the virus [114]. In a large cohort, up to 10% of patients hospitalized for COVID-19 were reported to have tricuspid, aortic, or mitral regurgitation leading to hemodynamic changes [134]. Moreover, cardiac dysfunction was reported in 41.2% of patients hospitalized for COVID-19 in a large cohort study. While less commonly reported in the pediatric population, in several cohort studies, the authors reported the presence of left ventricular dysfunction in patients under the age of 20 years. Left ventricular dilatation, trace mitral regurgitation, and hypokinesia of the inferior left ventricular wall were particularly reported in these patients [47, 103].

There are different types of arrhythmias described in the setting COVID-19 infection in children. The long list includes but not limited to sinus tachycardia, atrial arrhythmia, first-degree atrioventricular block, nonsustained ventricular tachycardia and fibrillation, premature atrial and ventricular beats, and incomplete right bundle branch blocks [87, 113, 133]. The estimated incidence rate of arrhythmia in COVID-19 patients is around 17% [133]. The Heart Rhythm Society has recently pointed out that in addition to the direct myocardial injury and ensuing arrhythmia, electrolyte disturbances are quite common and can induce arrhythmias themselves. Despite these hypotheses, the exact mechanism behind the initiation of any kind of arrhythmia in the setting of COVID-19 infection is still unclear. In another large cohort, atrioventricular block occurred in 28.7% of adult patients hospitalized for COVID-19. Sinus tachycardia was reported in 19.6%. In general, arrhythmia was reported in more than 50% of the patients in one cohort [133]. On the other hand, in a larger case series, only 16.7% of the hospitalized patients developed arrhythmia [55]. In a more recent large prospective study, pediatric SARS-CoV-2 positive patients had an incidence rate of arrhythmias of 12% [42].

Heart failure in pediatric patients commonly presents with tachycardia, which later leads to impaired diastolic filling and subsequent systolic and diastolic dysfunction. Eventually, mortality increases when patients present with hypotension and heart failure [97]. A large cohort study reported that up to 7% of patients with SARS-CoV-2 had an element of left ventricular diastolic dysfunction with ensuing low cardiac output. On the other hand, in this same cohort, left ventricular systolic dysfunction was reported in more >50% of patients [134].

In one of the largest cohort studies in China limited to the pediatric population, 13 out of the 2135 patients who tested positive for SARS-CoV-2 had cardiac involvement [136]. Depressed ejection fraction is reported in most studies that assessed the cardiac function of the involved children. An ejection fraction as low as 10% was reported in one of the prospective studies in France [119]. In a large prospective study in pediatric patients with SARS-CoV-2, the authors reported that severe heart failure with ejection fraction <30% was present in 5% of the patients. Moreover, while the majority had an ejection fraction above 55%, ejection fraction declined to 30%–55% in a third of the children [42]. Another large prospective cohort study reported a degree of heart failure in the pediatric population. The mean of the left ventricular ejection fraction was found to be between 10 and 57%, with a median of 38% [119]. This suggests that SARS-CoV-2 may result in both diastolic and systolic myocardial failure not only in adults but also in pediatric patients.

After the initial signals from Israel, European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) alerted on the risk of pericarditis and/or myocarditis with mRNA COVID-19 vaccines [36, 92]. In August 2021, the US Centers for Disease Control and Prevention (CDC) published data suggesting a higher rate of vaccination-related myocarditis in young men, but no stratification was made on adolescent age group [130]. Recently, two observational studies from Israel estimated the incidence of myocarditis around 0.64 and 1.42 per 100,000 persons after the first dose of Tozinameran (Pfizer-BioNTech BNT162b2) and 3.83 per 100,000 after the second dose [81, 131]. The risk difference between the first and second doses of Tozinameran (Pfizer-BioNTech BNT162b2) was evaluated to 1.76 per 100,000 persons, with a great difference among boys between 16 and 19 years. Among these cases, patients were mostly boys (205, 85%) and with a mean 15.8±1.4 age of years. Most of reports were serious (229, 95%) including 191 (79%) leading to hospitalization. The evolution was fatal in only one case. Reports of pericarditis and/or myocarditis came mostly from Germany (59; 24 %), followed by France (40, 17 %) and Italy (24; 10%) and from physicians in 150 cases (62%). The most frequent co-reported symptoms were chest pain, pyrexia or dyspnea.The time onset was 4 days for dose 1 and 3 days for dose 2 (3 days for NA). Recently published retrospectively collected data from 26 centres across the USA and Canada on patients <21 years-old presenting with suspected myocarditis within 30 days of COVID-19 vaccination revealed a mild clinical course of it with rapid resolution of symptoms. Abnormal findings on cardiac MRI were frequent. Future studies should evaluate risk factors, mechanisms, and long-term outcomes [116, 130].

Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic?

On November 25, 2021, about 23 months since the first reported case of COVID-19 and after a global estimated 260 million cases and 5,2 million deaths, a new SARS-CoV-2 variant of concern, Omicron [129], was reported. The principal concerns about Omicron include whether it is more infectious or severe than other variants and whether it can circumvent vaccine protection. The impact of Omicron variant on transmissibility is a concern. If the overlapping omicron mutations maintain their known effects, then higher transmissibility is expected. Although omicron is likely to be highly transmissible, it is not yet clear whether it has greater transmissibility than delta variant.

We await knowledge of how Omicron variant will impact clinical presentation. At this stage, the available data from clinicians at the front lines in South Africa suggest that patients with Omicron are younger people with a clinical presentation similar to that of past variants [84]. Although no alarming clinical concerns have been raised thus far, this information should be treated with caution given that severe COVID-19 cases typically present several weeks after the initial symptoms associated with mild disease, including hear involving. In terms of diagnostics, the Omicron variant is detectable on widely used PCR platforms in South Africa. There is no reason to believe that current COVID-19 treatment protocols and therapeutics would no longer be effective, with the possible exception of monoclonal antibodies, for which data on the omicron variant's susceptibility are not yet available. Importantly, existing public health prevention measures (mask wearing, physical distancing, avoidance of enclosed spaces, outdoor preference, and hand hygiene) that have remained effective against past variants should be just as effective against the Omicron variant. The question of an increase or decrease in the severity of COVID-19 arises with each new variant. It is common to hear some say, before any published data, that the new variant will lead to less severe cases while others say that it will lead to more severe cases, especially in children [43].

Data released on December 10, 2021, showed that vaccine efficacy against symptomatic infection was substantially reduced against Omicron with just two doses, but a third dose boosted protection up to over 70%. In an analysis of 581 people with confirmed Omicron, two doses of AstraZeneca or Pfizer-BioNTech, vaccines provided much lower levels of protection against symptomatic infection compared with what they provide against Delta. However, when boosted with a dose of Pfizer vaccine, there was around 70% protection against symptomatic infection for people who initially received AstraZeneca, and around 75% protection for those who received Pfizer-BioNTech [140].

Conclusions

It is known that SARS-CoV-2 viral infection may involve the heart, inducing myocardial inflammation or other cardiovascular complications, testified by an increase in cardiac enzymes, as well as a structural and functional damage. Studies confirm that also SARS-CoV-2 can cause direct or indirect myocardial injury, myocarditis, cardiomyopathies, heart arrhythmias, congestive heart failure, cardiogenic shock etc. The higher the levels of cardiac enzymes and troponin, the higher the coronavirus mortality.

Although the specific mechanisms are still a matter of concerns, an abnormal immune system response is likely to be the underlying cause of myocardial injury during coronavirus infection. The pandemic spread of the virus and its rapid modification suggests that potential cardiac involvement should be identified early in view of a prompt diagnosis capable of improving patients' outcome. In this respect, imaging - in particular echocardiography with advanced tool — spackle tracking imaging, and cardiac MRI play a crucial role. According to the International Guidelines, the involvement of a Heart Team made up of Radiologists and Cardiologists is critical in releasing a timely diagnosis, whose accuracy may help to save many lives threatened by such an aggressive disease. There is still limited data about the role of cardiovascular involvement in COVID-19 in children. Based on our review, children (previously healthy or with pre-existing heart disease) with acute COVID-19 requiring hospital admission should undergo a cardiac workup and close cardiovascular monitoring to identify and treat timely life-threatening cardiac complications.

To date, we have few data on the Omicron variant and studies must be quickly carried out to better define the threat that this variant represents, including risk factors, mechanisms, and long-term outcomes of cardiovascular involvement, especially in children.

Зі списком літератури, використаної при написанні статті, можна ознайомитися в редакції журналу.

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