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Incidence of myocarditis and pericarditis generated by immunization against covid-19

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ABSTRACT:
Introduction: individuals with cardiovascular diseases have a higher incidence of severe symptoms of COVID-19 with an incidence of acute cardiac injury in those affected, resulting in a poor therapeutic prognosis. **Objectives**: The objective of this current literature review was to verify the incidence of Myocarditis and Pericarditis generated by immunization against COVID 19. **Material and Methods**: The research was carried out through an electronic search for scientific articles published on the Scielo websites (Scientific Electronic Library Online) and Lilacs (Latin American Literature in Health Sciences) and Pubmed. The health terminologies consulted in the Health Sciences Descriptors (DeCS/BIREME) were used: Gestational Complications related to Myocarditis and Pericarditis generated by immunization against COVID 19. **Discussion**: A series of case reports and registry data suggest that myocarditis is a side effect of vaccination against COVID-19. There are case reports associating both vaccines based on viral vectors and inactivated vaccines against SARS-CoV-2 with the incidence of fulminant myocarditis. Another case report linked the mRNA-based COVID-19 vaccine to myocarditis and pericarditis in young male patients. **Conclusion**: However, one must be aware of the potential for even mild COVID-19 to cause ongoing symptoms (e.g., dysautonomia) and the infrequent presentation of myopericarditis following COVID-19 vaccination.

Keywords: Myocarditis and COVID 19; Pericarditis and COVID 19; side effects of COVID-19 vaccines.

INTRODUCTION:

Symptoms of coronavirus disease 2019 (COVID-19) can lead to serious complications, including multisystem inflammatory syndrome (CHEN et.al. 2022). To prevent COVID-19 infection and minimize the occurrence of serious complications, vaccination has been introduced along with non-pharmacological approaches, such as the application of mask policies, social distancing and school closures (DIAZ et.al, 2021).

For Goddard et.al (2022), by reducing the need for quarantine and the number of hospital admissions due to COVID-19, vaccination has had additional socio-psychological benefits, such as reducing school absences and limiting the mental health problems associated with temporary closures. According to Chen et.al (2022), it is recommended to screen patients infected with COVID-19 who have cardiovascular, kidney, lung and other chronic diseases for priority care. The symptoms of an acute myocardial infarction or decompensated heart failure may be masked by the symptoms of the new coronavirus. Although COVID-19 vaccines are effective in preventing the development of severe symptoms and death from COVID-19 infection, they have also been reported to cause myocarditis and pericarditis in rare cases (GODDARD et.al, 2022).

According to Diaz et.al (2021), in an analysis of the relationship between mRNA-based COVID-19 vaccines and myocarditis, the United States Advisory Committee on Immunization Practices reported that myocarditis or pericarditis occurred more frequently in adolescent males and young adults after the second dose. In addition, several reports have been published regarding the occurrence and characteristics of myocarditis and pericarditis following mRNA-based COVID-19 vaccination in various countries (HAUSSNER et.al, 2022).

For Gomes et.al (2023), viral infections are one of the main causes of myocarditis and pericarditis worldwide, conditions that often coexist. Myocarditis and pericarditis were some of the first comorbidities associated with SARS-CoV-2 infection and COVID-19 (ITALIA et.al, 2021). Since then, many epidemiological studies have been carried out which have concluded that SARS-CoV-2 has increased the incidence of myocarditis/pericarditis by at least 15 times compared to pre-COVID levels, although the disease remains rare (MOHAMMAD et.al, 2022). The incidence of myocarditis pre-COVID was recorded at 1 to 10 cases/100,000 individuals and with COVID it ranged from 150 to 4000 cases/100,000 individuals. Before COVID-19, some vaccines were reported to cause myocarditis and pericarditis in rare cases, but the use of new mRNA platforms has led to a greater number of reported cases than with previous platforms, providing new insight into potential pathogenic mechanisms (MOHAMMAD et.al, 2022).

For Mohammad et.al (2022), the incidence of myocarditis/pericarditis associated with the COVID-19 vaccine covers a wide range, depending on the vaccine platform, age and gender examined. Importantly, the results highlight that myocarditis occurs predominantly in male patients aged between 12 and 40, regardless of whether the cause is due to a virus such as SARS-CoV-2 or is associated with a vaccine - a demographic that was reported before COVID-19 (LI et.al, 2022). Scientists have noted that Covid-19 can trigger serious cardiovascular problems, especially among older people who have a build-up of fatty material in their blood vessels. Only now, a new study has revealed why and shown that Sars-CoV-2, the virus that causes Covid-19, directly infects the arteries of the heart (HAUSSNER et.al, 2022). According to Parodi et.al (2023), the virus can survive and grow inside the cells that form fatty plaque - the accumulation of fat-filled cells that narrow and harden the arteries, leading to atherosclerosis. If the plaque ruptures, it can block blood flow and cause a heart attack or stroke. Sars-CoV-2 infection worsens the situation by inflaming the plaque and increasing the chance of it rupturing. This may explain the long-term cardiovascular effects seen in some, if not all, Covid-19 patients. The Sars-CoV-2 virus has already been found to infect many organs outside the respiratory system. But until now it had not been shown to attack the arteries (OSTER et.al, 2022). The aim of this current literature review was to verify the incidence of myocarditis and pericarditis caused by immunization against COVID-19.

MATERIAL AND METHODS:

The methodology used was a literature review. A literature review is a meticulous and comprehensive analysis of current publications in a particular area of knowledge. This type of research aims to put the investigator in direct contact with the existing literature on a subject. The research was carried out by means of an electronic search for scientific articles published on the Scielo (Scientific Electronic Library Online) and Lilacs (Latin American Health Sciences Literature) and Pubmed websites. The health terminologies consulted in the Health Sciences Descriptors (DeCS/BIREME) were used: Gestational Complications related to Myocarditis and Pericarditis generated by immunization against COVID 19. The inclusion criteria were: original article, published in Portuguese and English, freely accessible, in full, on the subject, in electronic format and published in recent years, totaling 19 articles.

DISCUSSION:

1. The COVID-19 virus X INFLAMMATION:

A recent study of more than 800,000 people by a cardiologist at the University of Insubria in Varese, Italy, showed that Covid-19 patients develop high blood pressure twice as often as others. More worrying is the fact that the risk of heart disease can also increase for patients who have suffered only mild symptoms of COVID-19 (TSCHOPE, 2021).

For Woo et.al (2022), cardiovascular damage during Covid-19 was due to the fact that the virus directly attacked blood vessels. Their study analyzed autopsied coronary artery tissue and plaque from elderly people who died of COVID-19. They found that the virus was present in the arteries, regardless of whether the fatty plaques were large or small. According to Pimenta et.al (2021), in the arteries, the virus predominantly colonized white blood cells called macrophages.

Macrophages are immune cells mobilized to fight an infection, but these same cells also absorb excess fats, including cholesterol from the blood. When microphages carry too much fat, they turn into foam cells, which can increase plaque formation.

For Patone et.al (2022), the virus was in fact infecting and growing in blood vessel cells, the scientists obtained arterial and plaque cells including macrophages and foam cells from healthy volunteers. They then cultured these cells in the laboratory in Petri dishes and infected them with Sars-CoV-2.

Parodi et.al (2023), found that although the virus infected macrophages at a higher rate than other arterial cells, it did not replicate in them to form new infectious particles. However, when the macrophages were loaded with cholesterol and turned into foam cells, the virus was able to grow, replicate and survive for longer.

The studies by Patone et.al (2021), cite that the virus tends to persist for longer in foam cells. This suggests that foam cells may act as a reservoir for Sars-CoV-2. As more fat accumulation would mean a greater number of foam cells, plaque may increase the persistence of the virus or the severity of COVID-19.

The scientists found that when macrophages and foam cells were infected by Sars-CoV-2, they released a wave of small proteins known as cytokines, which signal the immune system to mount a response against a bacterial or viral infection. In the arteries, however, the cytokines increase inflammation and the formation of even more plaques (OSTER et.al, 2022).

Parodi et.al (2023), describes that the degree of inflammation [caused] by the virus could aggravate atherosclerosis and cardiovascular events.

These findings also confirm previous reports that measuring inflammation in the blood vessel wall can diagnose the extent of long-term cardiovascular complications after COVID-19 (MOHAMMAD et.al, 2022).

According to Li et.al (2022), plaque rupture can be accelerated and amplified by the presence of the virus.

2. Cardiac viral entry of SARS-CoV-2:

SARS-CoV-2 is a large RNA virus with an envelope that shares around 80% sequence homology with SARS-CoV and 50% homology with the respiratory syndrome coronavirus (MOHAMMAD et.al, 2022). It is important to note that ACE2 (angiotensin-converting enzyme 2) has been identified as the receptor for SARS-CoV4,5 and SARS-CoV-2.6-8 The SARS-CoV-2 spike protein binds to ACE2 and is cleaved by TMPRSS2 (human type II transmembrane serine protease-2), facilitating the entry of the virus into the cytosol (HAUSSNER et.al, 2022). TMPRSS2 is also required for viral entry of SARS-CoV and respiratory syndrome coronavirus. COVID-19 occurs predominantly in males, which can be explained, at least in part, by a greater expression of ACE2 in male cells than in female cells. Thus, these 3 coronaviruses that cause myocarditis share many similarities in the receptors they use for viral entry (LI et.al, 2022).

According to Haussner et.al (2022), ACE2 expression has been recorded in many tissues/organs, including the lung (i.e. lung type II/AT2 alveolar cells, bronchial epithelial cells), brain, kidney, small intestine, colon and heart.

Pimenta et.al (2023), examined published single-cell RNA sequencing data and found that 7.5% of heart cells expressed ACE2. In the heart, ACE2 has been reported to be expressed in cardiomyocytes, pericytes (cells present along the walls of capillaries) and macrophages, with lesser expression in fibroblasts and endothelial cells.

TMPRSS2 is also expressed in endothelial cells and pericytes. The SARS-CoV-2 genome was detected by polymerase chain reaction (PCR) in cardiac tissues from autopsies of COVID-19 patients, suggesting that the virus can infect the heart (OSTER et.al, 2022).

According to Parodi et.al (2023), cardiomyocytes and pericytes express ACE2 and TMPRSS2, as well as other accessory proteins (i.e. NRP1 [neuropilin-1 receptor], CD147, integrin α5β1 and cathepsin B/L) required for viral infection by SARS-CoV-2 (FIGURE 1).

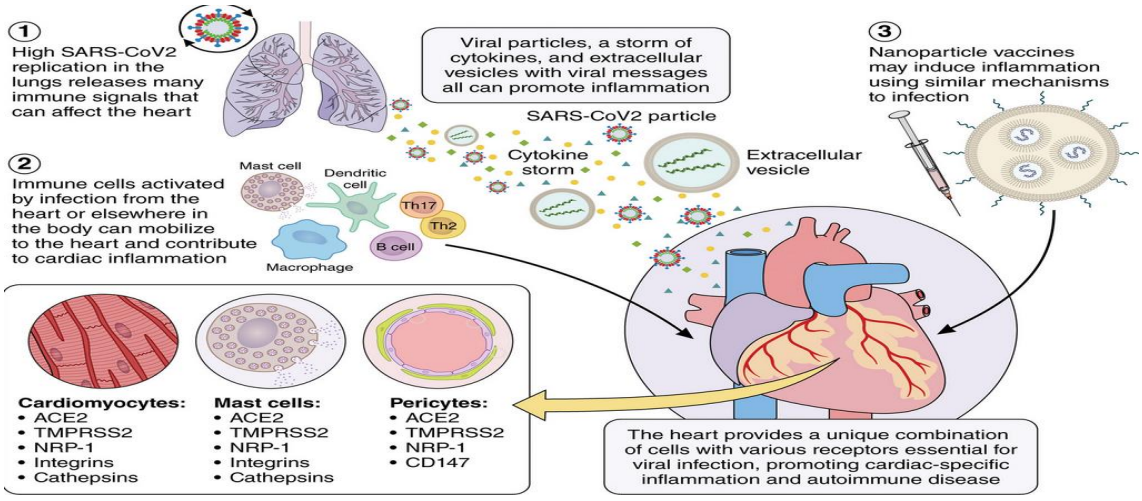

Figure 1. Potential mechanisms leading to myocarditis/pericarditis after infection or vaccination against SARS-CoV-2.

3. Cardiac damage mediated by SARS-CoV-2: Potential mechanisms:

There has been much question as to whether low levels of SARS-CoV-2 in the heart can cause myocarditis or pericarditis. Doctors usually assess myocardial damage (i.e. necrosis) by examining serum cardiac troponins (LI et. al, 2022). According to Mohammad et.al (2022), myocarditis often occurs without necrosis, so the absence of elevated troponin does not exclude the presence of myocarditis, even severe myocarditis. Potentially low SARS-CoV-2 infection can damage cardiomyocytes, leading to the release of cardiac myosin and the activation of resident APCs, such as mast cells and macrophages, to recruit inflammation to the heart (MOHAMMAD et.al, 2022). Autopsy studies carried out retrospectively to determine the number of cases of COVID-19 myocarditis often have several problems, including the requirement that histology show inflammation and necrosis and not providing or analyzing data according to gender and age. For example, a study of 277 autopsy cases of COVID-19 patients reported myocarditis in 7.2% of cases, but the average age of the individuals in the study was 75 years - both men and women, while myocarditis occurs predominantly in men under the age of 50 (HAUSSNER et.al, 2022).

FIGURE 2 shows the cardiac complications caused by COVID-19 in schematic form.

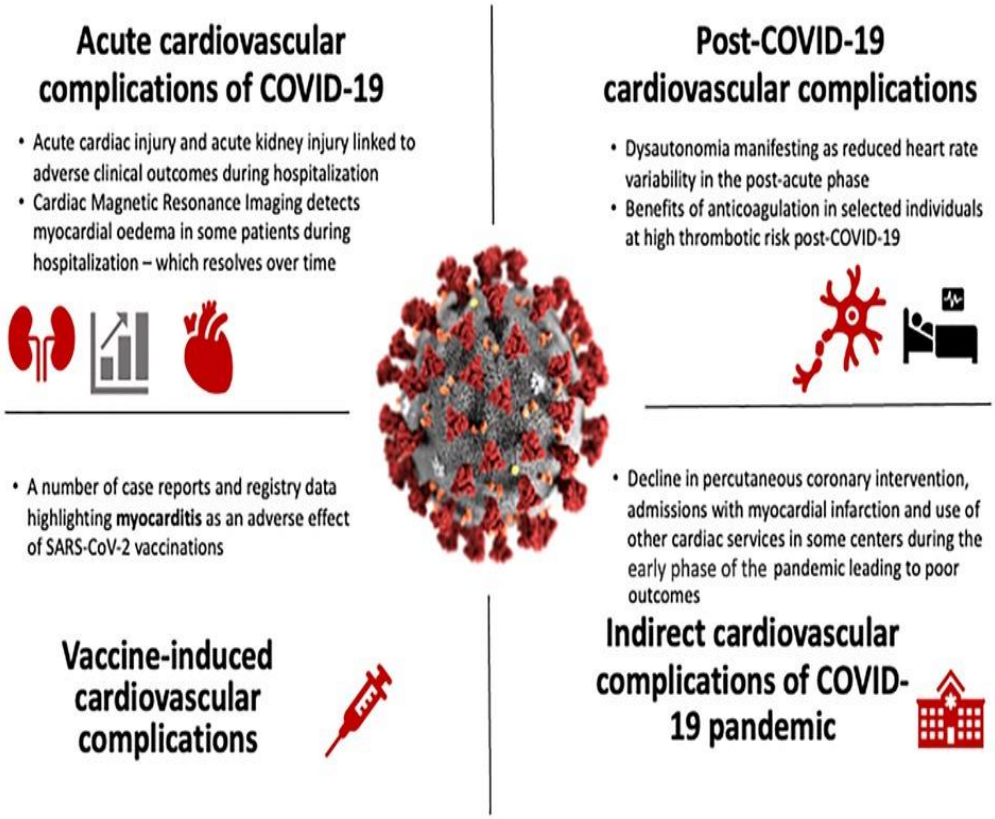

Figure 2. Cardiac complications caused by COVID-19.

According to Li et.al (2022), an important question is whether direct infection of cardiac tissues by SARS-CoV-2 can lead to myocarditis or whether other mechanisms are needed, such as cytokine storm, indirect infection from EVs or molecular mimicry. Direct infection with high viral levels is presumed to be the cause of viral myocarditis. However, several animal models of viral myocarditis have low or barely detectable levels of virus in the heart (or use Freund's complete adjuvant with inactivated Mycobacterium tuberculosis), and these autoimmune models closely resemble the time course and pathogenesis of clinical lymphocytic myocarditis. It is important to realize that the dominant immune infiltrate during COVID-19 myocarditis, acute lymphocytic myocarditis and in autoimmune models of myocarditis are macrophages (50%-80%) with fewer T and B cells (15%; FIGURE 3) and therefore the name for this most common form of myocarditis (i.e. lymphocytic) is somewhat misleading (ITALIA et.al, 2021). Thus, based on the findings in autoimmune models of myocarditis, it is not necessary for SARS-CoV-2 to replicate in the heart at a high level to cause myocarditis.

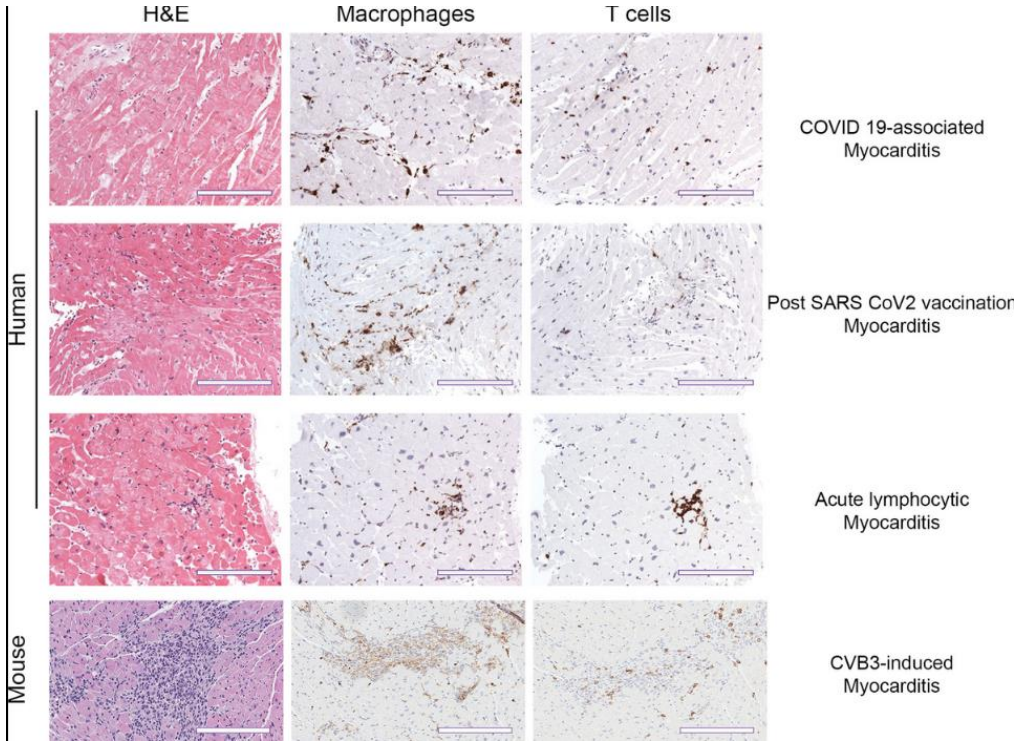

Figure 3. Similarity in the histological staining trail for macrophages and T cells during myocarditis and COVID-19 vaccination versus pre-COVID myocarditis in humans and Wistar rats.

Since COVID-19 is associated with a cytokine storm, it has been proposed that this situation can lead to myocarditis. However, there are no animal models of myocarditis in which the administration of pro-inflammatory cytokines alone induces cardiac inflammation without the use of an adjuvant (i.e. active or inactive viruses, bacteria or parasites) and damaged tissue itself (GODDARD et.al, 2022).

According to Chen et.al (2022), the fundamental question is how inflammation would be directed towards the heart, unless a heart lesion has occurred or a microbe infects the heart (even at a low level). In this context, elevated circulating cytokines could increase myocarditis, as was previously demonstrated when recombinant TNFα (tumor necrosis factor-alpha), IL (interleukin)-1β or IL-33 were administered in animal models of coxsackievirus B3 (CVB3) or autoimmune CVB3.

Similarly, Gomes et.al (2022) cites that molecular mimicry has been examined for many years as to its potential role in virus-induced myocarditis.

Patone et.al (2021), found that cross-reactivity between intestinal bacteria and cardiac myosin-specific T cells promotes myocarditis in the context of a cardiac viral infection. Thus, the simplest explanation for how SARS-CoV-2 infection leads to myocarditis is that the damage caused to the heart by the viral infection attracts inflammation to the heart and that an autoimmune response to the virus and cardiac damage is amplified by the strong circulating pro-inflammatory milieu in susceptible individuals (i.e. young men with more mast cells).

4. Myocarditis and Pericarditis due to COVID-19:

Myocardial damage, similar to myocarditis, was one of the first complications reported in COVID-19 patients in Wuhan, China, at the start of the pandemic (MOHAMMAD et.al, 2022).

According to Patone et. al (2021), although respiratory complications caused by the virus were the most frequently reported, it became clear early on that SARS-CoV-2 infection was also causing adverse cardiac events, including ventricular arrhythmias, acute coronary syndromes with obstructive coronary artery disease such as myocardial infarction, thromboembolic syndromes including stroke, acute myocardial injury with elevated troponin levels without evidence of coronary artery disease (i.e. myocarditis) and heart failure (FIGURE 4).

For Li et.al (2022), in patients with severe COVID-19, elevated biomarkers of cardiac damage that predict heart failure, including troponins and NT-proBNP (N-terminal pro-type B natriuretic peptide), were strongly and independently associated with hospital mortality.

Myocarditis is defined as inflammation of the myocardium with or without necrosis and is one of the leading causes of sudden cardiac death in children and adults worldwide.

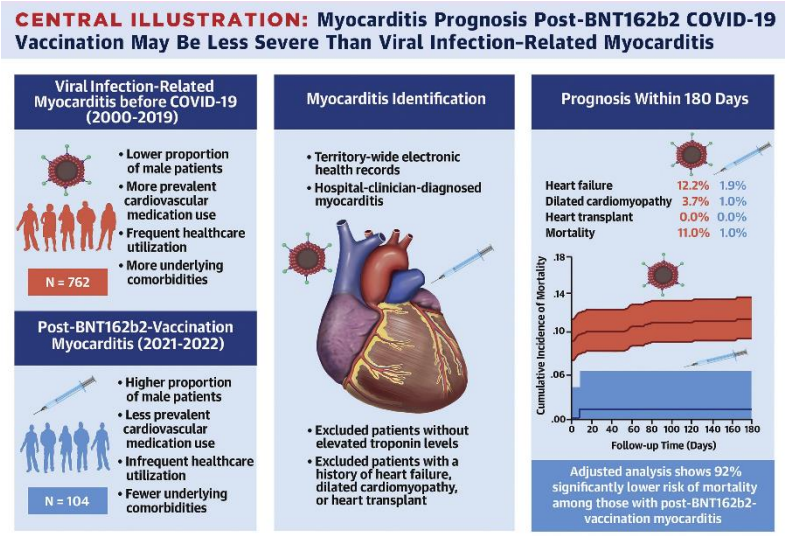

Figure 4. The prognosis of myocarditis after vaccination against COVID-19 with BNT162b2 may be less severe than myocarditis related to viral infection. Source: (OSTER et.al, 2022).

FIGURE 4 shows that the prognosis of myocarditis following BNT162b2 COVID-19 vaccination (symbolized by the virus logo) may be less severe than myocarditis related to viral infection (symbolized by the syringe logo) (OSTER et.al, 2022). Pericarditis is defined as inflammation of the pericardium and, in developed countries, is mainly caused by viral infections, while in developing countries tuberculosis is a common cause and is associated with poor outcomes. Acute myocarditis and pericarditis, referred to as myopericarditis or perimyocarditis, are often detected together in clinical practice and in animal models of myocarditis (FIGURE 5), and the terms have often been used interchangeably in the COVID-19 literature (RANARD et al. 2021).

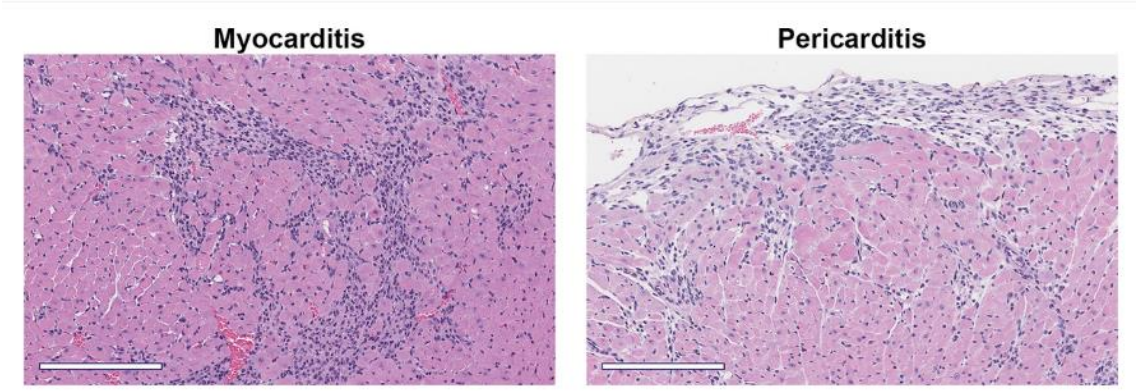

Figure 5. Myocarditis and pericarditis in the CVB3 autoimmune model Source: (RANARD et al. 2021).

5. Epidemiology of COVID-19 myocarditis/pericarditis

The most recent statistics on the global burden of disease before the COVID-19 pandemic put the worldwide prevalence of myocarditis and cardiomyopathy at between 10.2 and 105.6 cases/100,000 individuals (LI et.al, 2022).

According to Mohammad et.al (2022), a recent study estimated post-COVID myocarditis in the United States at 1 to 10 cases/100,000 individuals. The incidence of post-COVID acute pericarditis among all cardiovascular patients (n=670,409) was 3.3 cases/100,000 individuals (ITALIA et.al, 2021). Since the beginning of the pandemic, many epidemiological studies have been carried out on myocarditis in COVID-19 patients, with some of the largest studies. The overall incidence of myocarditis in England due to SARS-CoV-2 infection was estimated in a study carried out by the Centers for Disease Control and Prevention to be around 150 cases/100,000 compared to 9 cases/100,000 individuals in non-COVID cases during the same period. A separate study carried out in Europe estimated 240 cases/100,000 individuals of definite or probable myocarditis and 410 cases/100,000 individuals of possible myocarditis. These data indicate a ≥15 times higher risk of developing myocarditis due to SARS-CoV-2 infection compared to other causes (RANARD et al. 2021).

6. Cardiovascular complications following the COVID-19 vaccine:

Although the availability of vaccines heralded a new phase of the pandemic, with a reduction in the frequency of serious infections and mortality, it was also accompanied by concerns about their safety. In particular, a series of case reports and registry data (Li et.al (2022), suggest that myocarditis is a side effect of COVID-19 vaccination. In this series, two case reports associated both viral vector-based vaccines and inactivated vaccines against SARS-CoV-2 with the incidence of fulminant myocarditis. Another case report linked the mRNA-based COVID-19 vaccine to myocarditis and pericarditis in two young male patients (GODDARD et.al, 2022). The COVID-19 pandemic has had a significant impact on cardiovascular care in key areas of healthcare provision, including preventive interventions and the management of acute and chronic diseases (DIAZ et.al, 2021). ECG utilization patterns of patients with arrhythmias showed a pattern of decrease-recovery-recovery after COVID-19 lockdowns (HAUSSNER et.al, 2022).

CONCLUSION:

This study analyzed a series of articles from around the world, covering issues relevant to our understanding of the direct and indirect cardiovascular consequences of COVID-19. Although acute cardiac manifestations were reported in the initial phase of the pandemic, the decrease in virulence of the evolutionary variants of SARS-CoV-2 and the protective effects of vaccines and immunity acquired from natural infections have reduced the rates of serious complications and mortality from COVID-19. However, one must be mindful of the potential for even mild COVID-19 to cause ongoing symptoms (e.g. dysautonomia) and the infrequent presentation of myopericarditis following COVID-19 vaccination. The high cardiovascular mortality at the start of the pandemic may also have resulted from a failure of healthcare systems to adapt quickly to healthcare needs during a global health crisis and reinforces the need for greater investment in agile services in preparation for future pandemics.

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