Volume 19 • Issue 1 • June 2023

AMJ

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AL-ANBAR MEDICAL JOURNAL

College of Medicine - University of Anbar

E-ISSN: 2664-3154

P-ISSN: 2706-6207

doi Crossref

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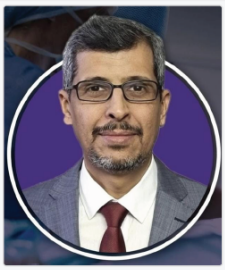

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REVIEW ARTICLE

AL-ANBAR MEDICAL JOURNAL
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Myocarditis Related-COVID-19 mRNA Vaccination: A Narrative Review

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(Received : 13 April 2023; Accepted : 30 May 2023; First published online: 1 June 2023)

ABSTRACT

The unprecedented impact of the coronavirus disease-19 (COVID-19) pandemic on society and the global economy has highlighted the urgent need for an effective and safe vaccine. One of the very rare side effects of this vaccine is myocarditis, which was realized to be a terrible complication of the COVID-19 mRNA vaccine. A recent study showed an increase in 1824 events of myocarditis reported to VAERS, 383 (21.00%) reported after receiving a single dose of vaccine, then 956 (52.41%) after injection of the second dose. The most common complaint is chest pain that appears within 1 week after the injection. Young and male patients have a high incidence. The pathophysiology of post-mRNA vaccination myocarditis remains unclear, with one study hypothesizing it to be due to hypersensitivity myocarditis and another study suggesting another possible mechanism is molecular mimicry. The main aim of this literature review is to improve knowledge, prevention, and management, as well as determine the incidence between the COVID-19 mRNA vaccine and myocarditis.

Keywords: COVID-19; Myocarditis; COVID-19 mRNA vaccine.

DOI: 10.33091/amj.2023.139728.1106

INTRODUCTION

The worldwide pandemic coronavirus disease-19 (COVID-19) was announced by the World Health Organization (WHO) On March 11, 2020 [1]. All nations around the world struggle to maintain the spread of the virus due to the direct impact and absence of effective treatment, starting from organizing a call to quarantine and lockdown, socially distancing, and self-protecting by using a face mask [2, 3].

As of January 12, 2022, there are some vaccines released by WHO that possess the WHO Emergency Use Listing Procedure (EUL), such as Moderna, PfizerBioNTech, Sinovac Biotech, Johnson and Johnson, AstraZeneca-University of Oxford, Sinopharm, Nuvaxovid, and covovax [4]. In addition to being quite widespread, useful, and safe, vaccination administration is faced with unexpected and rare side effects. Beyond the usual of peri-injection symptoms of fatigue, myalgias, and fevers, tracked in clinical trials, vaccine-related myocarditis has emerged as an exceedingly rare adverse event [5, 6].

The most widely recognized incidence of myocarditis is related to the mRNA vaccine following the second dose, nonetheless, these were generally a very rare occurrence, at less than 10 for every 100,000 individuals [7]. The exact mechanism of this event is still not well known and must be investigated again, but the most likely is the binding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike proteins to angiotensin-converting enzyme 2 (ACE2) and then expressed on host cells in rhythm with host transmembrane serine protease 2 (TMPRSS2), this can lead to cell entry and viral infection [8].

The use of the SARS-CoV-2 spike protein to elicit an immune response is of greater concern because it can cause vaccine-associated myocarditis [9]. The risk factors for developing myocarditis post COVID-19 vaccination are still unclear, but it is suspected to be linked with gender, age, and genetic factor. Myocarditis is particularly seen in young adult and adolescent males aged 16 – 40 years, present with the symptoms present mostly within 1 week post-vaccination

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[7, 9, 10]. Through June 11, 2021, 1226 probable myocarditis/pericarditis cases were reported to the Advisory Committee on Immunization Practices with 67% occurring after the second dose of the mRNA vaccine. The predominant gender was male, with a percentage of 79%, and commonly appeared in people < 30 years [9]. Here we provide further details on the data, prevention, and management of events leading to myocarditis after vaccination with the COVID-19 mRNA vaccine.

METHODS

We conducted a literature review based on the relevance of this topic. All databases were searched on Google Scholar, PubMed, and ReseacrhGate using the following keywords: 'COVID-19, myocarditis, COVID-19 mRNA vaccine'. Overall, eight case reports related to COVID-19 mRNA vaccine-induced myocarditis as well as several systematic reviews and literature reviews were found.

MYOCARDITIS

The occurrence of inflammation that causes weakness of the heart muscle, or cardiomyopathy, is said to be myocarditis associated with decreased cardiac function and ventricular remodelling, diagnosed by established histological, immunological, and immunohistochemical criteria [11–13].

Myocarditis can occur due to both non-infectious and infectious agents. According to the last 4 decades, viral infection is considered the most frequent etiology, and examples of other etiologies can be infection (bacteria, spirochetes, parasites), autoimmune disturbance (autoimmune disease, sarcoidosis), and drug toxicity [13]. Coxsackie and Parvovirus B19 are the major causes of myocarditis in the United States and Europe [14]. The incidence of myocarditis in the world reaches 10 to 20 cases per 100,000 population, with Coxsackie B virus as the most common etiology, endomyocardial biopsy results show that 25% to 40% of patients have the virus, but in recent years coronaviruses have become a frequently discussed etiology [11, 15].

Myocarditis conditions affect all ages, ethnicities, and genders, sufferers are dominated by young people, adults, and middle-aged people, and the rate is also very high in men [11]. Symptoms such as fever, respiratory symptoms, gastroenteritis, and myalgia are the most common non-specific systemic symptoms. Chest pain (36.5%), heart failure (30.5%) and a combination of dyspnea, palpitations, and transient fatigue (24.1%) were the most common symptoms with biopsy-proven myocarditis. Early manifestations, such as ventricular tachycardia, were rare and occurred in only 5% of patients [14].

The diagnosis of myocarditis can be difficult, it is usually done by excluding other diseases. Electrocardiography (ECG) is used as a screening tool, and it shows various non-specific anomalies [16]. Frequently, it appears as ST-segment elevation, often in the inferior and lateral leads. Moreover, it show up as T-wave inversions, PR-segment depressions, widespread ST-segment depressions, pathological Q waves, bundle branch block (new-onset), QT prolongation, bradycardia, tachycardia, atrioventricular block, or ventricular arrhythmias [16–18]. In addition to the ECG, cardiac markers can be performed. Troponin I and T (TnI, TnT), creatine kinase, and CK-MB are usually assessed in suspected patients [18]. Since the vast majority of TnI is associated with the myocyte contractile apparatus, it shows a higher sensitivity and specificity for the diagnosis of myocarditis and can be identified up to 14 days after, even though it is not specific for inflammatory-mediated myocyte injury [19]. Markers of inflammation such as white blood cells, C-reactive protein, and erythrocyte sedimentation rate are also inflated in many cases of myocarditis [20]. Echocardiography can be utilized as a routine investigation to eliminate non-inflammatory cardiac disease and might be helpful in recognizing fulminant acute myocarditis [14, 20, 21]. Echocardiographic findings that may occur in myocarditis include reduced left ventricular ejection fraction (LVEF), diastolic dysfunction, segmental wall motion abnormalities, increased cardiac wall thickness, abnormal echogenicity in the myocardium, or pericardial effusion [21]. Endomyocardial biopsy (EMB) is a gold standard test in diagnosing myocarditis, yet it appears to be insensitive, it is reported to diagnose myocarditis in just 25% of the cases [18]. Cardiac magnetic resonance (CMR) imaging is used as a non-invasive diagnostic tool based on the Lake Louise Criteria (LLC): the original LLC and the 2018 LLC. The latest criteria have a higher sensitivity than the original version [22].

COVID-19 VACCINES

Though still based on the same principles, vaccine development has continued into the modern era, and the techniques for introducing antigens have changed [23]. There are several types of vaccines currently available, for now, the most modern platforms; are mRNA vaccines, but other types exist, toxoid, recombinant, live attenuated, inactivated, subunit, polysaccharide, and conjugate [24].

The foundation of an mRNA vaccination is the idea that mRNA is an intermediary messenger that must be converted into an antigen after being introduced into host cells through a variety of mechanisms [25]. There are some vaccines that are in clinical trials as well, such as ARCT-021 (Arcturus, USA), ARCoV (Abogen, China), LNP-nCoVsaRNA (Imperial College London, England), CVnCoV (CurVac, Germany), and ChulaCoV19 mRNA vaccine [26]. WHO released the vaccines that have obtained the WHO Emergency Use Listing Procedure (EUL), including Sinovac Biotech, PfizerBioNTech, Moderna, Sinopharm, AstraZeneca, Johnson and Johnson, Nuvaxovid, and covovax [4]. Two mRNA COVID-19 vaccines have been given a path to commercialization, taking advantage of their rapid adaptability and development, namely mRNA-1273 and BNT162b2 [26].

Frequent side effects include heat, discomfort, edema, and erythema at the injection site, fever and chills, weariness, headaches, decreased appetite, myalgia, arthalgia, significant adverse reactions anaphylaxis/anaphylactic shock, Bell's palsy, and there are also unconfirmed issues such as infertility, preterm labor, and autoimmune diseases [23, 27]. Myocarditis and pericarditis incidents have been linked to the two COVID-19 mRNA vaccines from Moderna and PfizerBioNTech, according to recent reports from several studies [9, 28–30].

MYOCARDITIS ASSOCIATED COVID-19 MRNA VACCINES

Prior to the implementation of COVID-19, myopericarditis was the cause of 0.1% of the 620.195 reports submitted to the Vaccine Adverse Event Reporting System (VAERS) between 1990 and 2018 [9]. Between December 14, 2020, and August 31, 2021, there have been 1991 cases of myocarditis (391 of which also included pericarditis) post mRNA vaccination re-

http://doi.org/10.33091/amj.2023.139728.1106

ported to VAERS [9]. Of these cases, 1626 met the criteria for probable or confirmed myocarditis, 208 did not meet the criteria, and 157 others needed more information [31]. Those aged 12-39 years who received the second dose of the COVID-19 mRNA vaccine were projected to have 12.6 cases of myocarditis per million doses [28]. Another Israeli study with around 5.4 million vaccine recipients found that the second-dose vaccination-related myocarditis had an incidence ratio of 5.34 per 100,000 people, with diagnosis primarily occurring in younger males [30]. Consequently, for every million vaccines that had at least one dose of Comirnatym, there were roughly 48.09 occurrences of myocarditis and pericarditis. Around 1.6 million first doses and 1.5 million second doses of Spikevax have been given up to this point [15]. There were 203.13 incidences of myocarditis and pericarditis recorded per million people who had taken at least one dose of Spikevax in the UK. Although most cases are common after mRNA vaccines and increased up to 4 times compared to the others [32, 33].

Myocarditis typically presents with symptoms of dyspnea, orthopnea, and chest discomfort, which are similar to those of heart failure [34]. Relatively minor symptoms including cough, fever, and dyspnea might be brought on by COVID-19 by itself rather than myocarditis [34]. Patients with COVID-19 myocarditis might, however, presents in a variety of clinical ways. Many research studies have shown that data from myocarditis associated with mRNA vaccines mostly presents with chest pain [6, 9, 28, 35, 36]. Patients were presented with cardiac symptoms such as chest pain or palpitations [35]. The COVID-19 vaccine's most often reported local side effects were pain at the injection site, swelling, and redness. Symptoms of the systemic response included chills, myalgia, fatigue, and fever [9, 28, 37]. A total of 1824 myocarditis occurrences were reported to VAERS; 956 (52.41%) occurred after the second dose and 383 (21.00%) occurred after the first [38]. According to research, the second dose was documented more often in numerous works of literature, with an onset time range of one to two days [6, 29, 39]. Table 1 shows some summary data related to the incidence of myocarditis and immunization with the COVID-19 mRNA vaccine.

The pathophysiology of myocarditis post-mRNA vaccination is still unclear, but it may be hypothesized due to myocarditis hypersensitivity [40]. There was a study with military soldiers in the United States with a total of 23 subjects who were people with good fitness levels but contracted myocarditis after receiving the COVID-19 mRNA vaccine, from the results of the study discussion said that the clinical course showed eosinophilic hypersensitivity myocarditis, which may be related to drug use or also to vaccines [41]. The COVID-19 mRNA vaccines contain nucleoside-modified mRNA that can lessen innate immunogenicity; nevertheless, in people with certain genetic predispositions, the immune response to the mRNA may not be diminished and may instead result in aberrant activation of innate and acquired immunological responses. The dendritic cells recognize the vaccine's mRNA as an immunizing agent, activating Toll-like receptors, and starting pro-inflammatory cascades and immunological pathways to release cytokines [9, 42]. Another potential mechanism is the cross-reactivity of the SARS-CoV-2 antibodies and myocardial myosin caused by the molecular mimicry between the spike (S) protein of SARS-CoV-2 and cardiac antigens. This may result in tan increase in polyclonal B cells, the production of immunological complexes, and an inflammatory response in people who already have dysregulated immune pathways due to predisposition factors [9, 42, 43]. The S glycoprotein of SARS-CoV-2 also plays a role in the mechanism of myocarditis. It enters the cells through the mRNA vaccines and binds to ACE2 causing a buildup of angiotensin II, a protein associated with inflammation, which therefore initiates myocardial inflammation [42].

In the United States, patients with myocarditis after receiving COVID-19 vaccines can report to the VAERS and are categorized as probable and confirmed cases based on their symptoms and lab findings [9, 44]. A study was conducted on 74 patients with myocarditis post-vaccines, abnormal ECG findings were seen in 87,8% of patients with the highest abnormality in the ST-segment, all patients presented with an increased levels of cardiac enzyme, 86,4 % of patients had elevated C-reactive protein levels, and 67,8% of patients had CMR suggesting myocarditis based on LLC [28].

PREDISPOSING FACTORS

Starting the attack against the COVID-19 with vaccinations, the mortality rate and severity have drastically decreased. On the other hand, there are many reports of side effects, such as myocarditis as a cardiovascular complication. The ratio of the incidence of myocarditis in men and women reaches 1.7:1 [29]. Other data shows the majority of reported cases in males (90%) compared to females (10%) [45]. This is also found in other regions such as America with 72.92% data and 60.75% in the EU [38]. Male predominance has been discussed in previous studies, and the reason is still unknown. Sex hormones are a widely discussed theory which are the factors that influence the differences that occur through their receptors in both immune cells and host cardiac tissues [9, 29, 45]. A key player in this process is the male hormone testosterone, which has a strong inhibitory effect on anti-inflammatory cells and a commitment to a Th1-type immune response. Another factor that increases the prevalence is under diagnosis in women. Estrogen also inhibits proinflammatory T cells, which results in a reduction in cell-mediated immune responses. Hence, sex hormones may help to explain both the predilection for men and the cardioselective nature of the autoimmunity caused by the COVID-19 vaccination [9, 29, 45].

In addition to gender, myocarditis after vaccination is more common at a young age which is the highest according to the data at the age of 18-24 years [46, 47]. There have been case reports reporting young male patients who died with histological findings suggestive of myocarditis after the COVID-19 mRNA vaccine but on the other hand, there are also reports of death at an older age [48, 49]. In contrast with men, the incidence of myocarditis in women is more stable with age and without an increase in incidence during adolescence [50]. Due to testosterone, post-vaccination myocarditis is more common in teenage boys, the same thing happens to post-menopausal women because of low estrogen levels at the age of 55-60 years. Progesterone is considered as a protective factor against myocarditis [50, 51].

MANAGEMENT AND PREVENTION

Recommendations from the National Advisory Committee on Immunization (NACI) from Canada to minimize side effects with recommended doses of the Pfizer 30 mcg mRNA vaccine at ages 12 to 29 years and for ages 12-17 years related to the risk of myocarditis NACI recommends a gap of 8 weeks between the first

http://doi.org/10.33091/amj.2023.139728.1106

Table 1. Overview of the reviewed sources.

Authors	Country	Purpose	Design study	Summary
M.E Oster et al. (2022) [31]	US	Report on cases of myocarditis after COVID-19 mRNA vaccine injection	Descriptive study	Data shows that of the 192,405,448 people who received a total of 354,100,845 mRNA-based COVID-19 vaccines in this study, there were 1991 reports of myocarditis to VAERS and 1626 of these reports met the criteria for myocarditis cases. Most of these cases occurred in males, and most occurred after the injection of the second dose of the vaccine. The overall incidence of myocarditis after vaccination is still quite infrequent.
W. Woo et al. (2022) [28]	Korea	Provide comprehensive information on complications that do not often occur after the COVID-19 vaccine, and also provide people with information before they get vaccinated.	Systematic review	This study obtained 74 patients from a total of 24 sources who shows signs of myocarditis after COVID-19 mRNA vaccination. The authors found that the majority of patients (49.5%) were less than 20 years old and the majority were male. Symptoms usually appear within a few days after vaccination, with chest pain being the most common. An excerpt from one of the source articles reported 148 cases of myocarditis among 10.4 million vaccinated people, with symptoms appearing within 30 days of receiving the mRNA vaccination.
J Montgomery et al. (2021) [34]	US	To explain myocarditis that occurs after COVID-19 vaccination in the health System.	Retrospective case series	The military stated that there have been more than 2.8 million doses of the COVID-19 mRNA vaccine during the making of this study. A total of 23 male patients and previously healthy military members with high fitness levels showed symptoms of myocarditis. The largest percentage of events occurred after the second dose of the COVID-19 mRNA vaccine.
S. Lane (2022) [35]	UK	To summarize the data reported by several countries to estimate the reporting rate, and better understand the risk factors for myocarditis and pericarditis after COVID-19 mRNA vaccine injections.	Systematic review	This study used 32 sources that met the criteria. A total of 18,204 myocarditis and pericarditis events were submitted to UK, US, and EU/EEA regulators within the study timeframe. Males had a high rate of 62.24%. In the UK and US, the rate was high at age < 40 years and after the second dose at 47.1%.

and second doses of the mRNA vaccine [Canada Goverment, "COVID-19 vaccine: Canadian Immunization Guide-Canada.ca," 2022. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html (accessed Jan. 14, 2023)].

Another recommendation from Singapore for COVID-19 vaccination recommends avoiding strenuous exercise for 2 weeks after vaccination [Ministry of Health Singapore, "MOH | News Highlights," Singapore, 2021. https://www.moh.gov.sg/news-highlights/details/expert-committee-on-covid-19-vaccination-statement-on-skin-reactions-after-vaccination-and-refraining-from-strenuous-physical-activity-after-vaccination (accessed Jan. 14, 2023).]. People who experience chest pain within a week after vaccination, especially considering the prevalence, namely young people and men, should be suspicious of complications of myocarditis. Seeing that there are reports of complications of myocarditis, it is recommended that people who have risk factors have another examination 3 to 6 months after vaccination. In addition, patients diagnosed with myocarditis should not engage in strenuous activities or competitive sports [31]. Examination with cardiac MRI may be able to help with the evaluation of the progression or improvement of myocarditis in patients, but it is still not known for sure.

Angiotensin-converting enzyme inhibitor, β-blocker, intravenous immunoglobulin (IVIG) and aspirin have been applied to some patients, this is due to left ventricular systolic dysfunction that occurs [47]. In patients with good resolution of symptoms and normal cardiac biomarkers, therapy can be deferred. If there are persistent mild symptoms in the absence of hemodynamic instability, heart failure, and arrhythmia, then the administration of non-steroidal anti-inflammatory drugs, colchicine, and steroids may be considered. In more severe conditions the use of intravenous steroids and IVIG along with other cardiac or circulatory support measures may be considered in patients with hemodynamic instability, heart failure, new onset arrhythmias, and left ventricular dysfunction. Cardiologists should be involved for initial assessment, evaluation, treatment, and follow-up, as well as infectious disease specialists for consideration of subsequent immunizations [9].

http://doi.org/10.33091/amj.2023.139728.1106

Diagnosis is important as myocarditis associated with the COVID-19 mRNA vaccine and common myocarditis are very similar, which is important for future treatment. Initial evaluation, cardiac troponin levels and ECG should be performed, and examination of erythrocyte sedimentation rate and C-reactive protein may be helpful. Clinical findings and course, patient age, hemodynamic stability, heart rhythm, comorbidities, and other potential causes, determine the type of evaluation and management [31]. There are neither guidelines nor specific treatment data for myocarditis related to the COVID-19 mRNA vaccine. There is a meta-analysis showing the use of IVIG as a management of acute myocarditis shows positive results and low mortality rates, this is attributed to IVIG and steroids are immunosuppressive agents as well as immunomodulators and can reduce the specific immune response to SARS-CoV-2 triggered by the vaccine, along with improvements in left ventricular ejection fraction. Other conditions, such as fulminant myocarditis, in which patients given IVIG are even more noticeable where it is shown to significantly increase the survival rate of this dangerous condition [52, 53]. Corticosteroids such as prednisolone, may be considered in treating viral myocarditis in the absence of viral replication [34]. Other management options, such as colchicine, NSAIDs, favipiravir and tocilizumab, have been used by different studies, so further research is needed [40, 47, 54]. A condition that can worsen myocarditis associated with the COVID-19 mRNA vaccine is cytokine storm, if this occurs, the combination therapy of favipiravir, and tocilizumab should be administered. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, was tested in combination with the anti-viral, favipiravir, to treat COVID-19 patients with cytokine storm, which had a positive effect on patients and can be given to reduce inflammation due to cytokine storm [54].

CONCLUSION

Myocarditis associated with the COVID-19 mRNA vaccine appears to be a very rare side effect. Clinical manifestations of this illness vary widely, while some research indicate that chest pain is the most common symptom. Data show high rates in young adults and adolescents. Further surveillance is initiated 3 to 6 months after vaccination to assess health, functional status, and cardiac outcomes. Although there are no definitive evidence-based recommendations for the management of myocarditis caused by mRNA vaccination, much data suggests that the initial evaluation and treatment of COVID-19 mRNA vaccine-associated myocarditis cases is similar to that of myocarditis cases in general. Health coworkers should take into account the possibility of post-vaccination myocarditis so they can adequately treat and avoid it. With a low incidence rate and the vaccination's advantages above risks in avoiding COVID-19, monitoring and more study must still be done to identify the other advantages and possible risks.

ETHICAL DECLARATIONS

Acknoweldgements

None.

Ethics Approval and Consent to Participate

No needed.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

This is a minireview article.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

No funding.

Authors' Contributions

All the authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Myocarditis Related-COVID-19 mRNA Vaccination: A Narrative Review

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Submission date: 18-Aug-2024 02:32PM (UTC+0700)
Submission ID: 2433631468
File name: Final_Draft-AMJ-2304-1106_Proofread.docx (353.99K)
Word count: 5499
Character count: 32276

Myocarditis Related-COVID-19 mRNA Vaccination: A Narrative Review

Running title: Myocarditis Related-COVID-19 mRNA Vaccination

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Received date: 13-4-2023

Accepted date: 30-5-2023

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Abstract

The unprecedented impact of the coronavirus disease-19 (COVID-19) pandemic on society and the global economy has highlighted the urgent need for an effective and safe vaccine. One of the very rare side effects of this vaccine is myocarditis, which was realized to be a terrible complication of the COVID-19 mRNA vaccine. A recent study showed an increase in 1824 events of myocarditis reported to VAERS, 383 (21.00%) reported after receiving a single dose of vaccine, then 956 (52.41%) after injection of the second dose. The most common complaint is chest pain that appears within 1 week after the injection. Young and male patients have a high incidence. The pathophysiology of post-mRNA vaccination myocarditis remains unclear, with one study hypothesizing it to be due to hypersensitivity myocarditis and another study suggesting another possible mechanism is molecular mimicry. The main aim of this literature review is to improve knowledge, prevention, management, and also determine the incidence between the COVID-19 mRNA vaccine and myocarditis.

Keywords: COVID-19; Myocarditis; COVID-19 mRNA vaccine

Introduction

Worldwide pandemic coronavirus disease-19 (COVID-19) announced by World Health Organization (WHO) On 11 March 2020 [1]. All nations around the world struggle to maintain the spread the virus due to direct impact and absence of effective treatment, starting from organizing a call to quarantine and lockdown, socially distancing, and self-protecting by using a face mask [2], [3]

As of 12 January 2022, there are some vaccine released by WHO released the vaccines that have possess the WHO Emergency Use Listing Procedure (EUL), such as Moderna, Pfizer–BioNTech,

Sinovac Biotech, Johnson and Johnson, AstraZeneca–University of Oxford, Sinopharm, Nuvaxovid, and covovax [4] In addition being quite widespread in the world, useful, and safe, vaccination administration is faced with unexpected and rare side effects. Beyond usual symptom peri-injection fatigue, myalgias, and fevers, tracked the clinical trials, vaccine related myocarditis has emerged as an exceedingly rare adverse event [5], [6].

The most widely recognized incidence of myocarditis is related with mRNA vaccine following the second dose, nonetheless, these were generally a very rare occurrence at less than 10 for each 100,000 individuals [7]. The exact mechanism of this event is still not well known and must be investigated again, but the most likely is the binding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike proteins to angiotensin-converting enzyme 2 (ACE2) and then expressed on host cells in rhythm with host transmembrane serine protease 2 (TMPRSS2), this can lead to cell entry and viral infection [8]

The use of the SARS-CoV-2 spike protein to elicit an immune response is of greater concern because it can cause vaccine-associated myocarditis [9] The risk factors for developing myocarditis post COVID-19 vaccination is still unclear, it is suspected to be linked with gender, age, and genetic factor. Myocarditis is particularly seen in young adult and adolescent males aged 16 - 40 years present with the symptoms mostly within 1 week post vaccination [7], [9], [10]. Through June 11, 2021, 1226 probable myocarditis/pericarditis cases were reported to the Advisory Committee on Immunization Practices with 67% occurring after second dose mRNA vaccine. Predominant gender was male with a percentage of 79% and commonly appeared in people < 30 years [9]. Here we provide further details on the data, prevention, and management of events leading to myocarditis after vaccination with the COVID-19 mRNA vaccine.

Methods

We conducted a literature review based on relevance to this topic. All databases were searched on Google Scholar, PubMed, and ReseacrhGate using the following keywords: 'COVID-19, myocarditis, COVID-19 mRNA vaccine'. Overall, 8 case reports related to COVID-19 mRNA vaccine induced myocarditis as well as several systematic reviews and literature reviews were found.

Myocarditis

The occurrence of inflammation that causes weakness of the heart muscle or cardiomyopathy is said to be myocarditis associated with decreased cardiac function and ventricular remodeling diagnosed by established histological, immunological, and immunohistochemical criteria [11]–[13].

Myocarditis can occur due to non-infectious and infectious agents. Data since the last 4 decades, viral infection is considered the most frequent etiology, and examples of other etiologies can be infection (bacteria, spirochetes, parasites), autoimmune disturbance (autoimmune disease, sarcoidosis), and drug toxicity [13]. Coxsackie and Parvovirus B19 are the major causes of myocarditis in the United States and Europe [14] The incidence of myocarditis in the world reaches 10 to 20 cases per 100,000 population, Coxsackie B virus as the most common etiology, endomyocardial biopsy results show that 25% to 40% of patients have the virus, but in recent years coronaviruses have become a frequently discussed etiology [11], [15]

Myocarditis conditions affect all ages, ethnicities, and genders, sufferers are dominated by young people and adults and middle-aged people, and is also very high in men [11]. Symptoms such as fever, respiratory symptoms, gastroenteritis, and myalgia are the most common non-specific systemic symptoms. Chest pain (36.5%), heart failure (30.5%) and a combination of dyspnea, palpitations and transient fatigue (24.1%) were the most common symptoms with biopsy-proven myocarditis. Early manifestations such as ventricular tachycardia were rare and occurred in only 5% of patients [14]

Diagnosis of myocarditis can be difficult, it is usually done by excluding other diseases. Electrocardiography (ECG) is used as a screening tool and it shows various non-specific anomalies [16] Frequently appears as ST-segment elevation often in the inferior and lateral leads. Moreover, it shows as T-wave inversions, PR-segment depression, widespread ST-segment depressions, pathological Q waves, bundle branch block (new-onset), QT prolongation, bradycardia, tachycardia, atrioventricular block or ventricular arrhythmias [16]–[18] In addition to ECG, cardiac markers can be performed. Troponin I and T (TnI, TnT), creatine kinase, and CK-MB are usually assessed in suspected patients [18] Since the vast majority of TnI is associated with the myocyte contractile apparatus, it shows a higher sensitivity and specificity for diagnosis myocarditis and can be identified up to 14 days after, even though it is not specific for inflammatory-mediated myocyte injury [19] Markers of inflammation such as white blood cell, C-reactive protein, and erythrocyte sedimentation rate are also inflated in many cases of myocarditis [20]. Echocardiography can be utilized as a routine investigation to eliminate non-inflammatory cardiac disease and might be helpful while recognizing fulminant from acute myocarditis [14], [20], [21]. Echocardiographic findings that may occur in myocarditis include reduced left ventricular ejection fraction (LVEF), diastolic dysfunction, segmental wall motion abnormalities, increased cardiac wall thickness, abnormal echogenicity in the myocardium or pericardial effusion [21] Endomyocardial biopsy (EMB) is a gold standard test in diagnosing myocarditis yet appears to be insensitive, it is reported to diagnose myocarditis in just 25% of the cases [18] Cardiac magnetic resonance (CMR) imaging is used as a non-invasive diagnostic tool based on the Lake Louise Criteria (LLC): original LLC and 2018 LLC. The latest criteria has higher sensitivity than the original version [22]

COVID-19 Vaccines

Though still based on the same principles, vaccine development has continued into the modern era, and the techniques for introducing antigens have changed [23] There are several types of vaccines currently available, for now the most modern platforms; mRNA vaccines, and other types exist, toxoid, recombinant, live attenuated, inactivated, subunit, polysaccharide, and conjugate [24]

The foundation of an mRNA vaccination is the idea that mRNA is an intermediary messenger that must be converted into an antigen after being introduced into host cells through a variety of mechanisms [25] There are some vaccines that in clinical trial as well such as ARCT-021 (Arcturus, USA), ARCoV (Abogen, China), LNP-nCoVsaRNA (Imperial College London, England), CVnCoV (CurVac, Germany), and ChulaCoV19 mRNA vaccine [26] WHO released the vaccines that have obtained the WHO Emergency Use Listing Procedure (EUL), including Sinovac Biotech, Pfizer–BioNTech, Moderna, Sinopharm, AstraZeneca, Johnson and Johnson, Nuvaxovid, covovax [4] Two mRNA COVID-19 vaccines have been given a path to commercialization, taking advantage of their rapid adaptability and development, namely mRNA-1273 and BNT162b2 [26]

Frequent side effects include heat, discomfort, edema, and erythema at the injection site, fever and chills, weariness, headaches, decreased appetite, myalgia, arthalgia, significant adverse reactions anaphylaxis/anaphylactic shock, Bell's palsy, and there are also unconfirmed issues such as infertility, preterm labor, and autoimmune diseases [23], [27] Myocarditis and pericarditis incidents have been linked to the two COVID-19 mRNA vaccines from Moderna and Pfizer-BioNTech, according to recent reports from several studies [9], [28]–[30].

Myocarditis Associated COVID-19 mRNA Vaccines

Prior to the implementation of COVID-19, myopericarditis was the cause of 0.1% of the 620.195 reports submitted to the Vaccine Adverse Event Reporting System (VAERS) between 1990 and 2018 [9] Around December 14, 2020 and August 31, 2021 there have been 1991 cases of myocarditis (391 of which also included pericarditis) post mRNA vaccination reported to VAERS [9]. Of these cases, 1626

met the criteria for probable or confirmed myocarditis, 208 did not meet the criteria and 157 others that needed more information [31] Those aged 20-39 years who received the second dose of the COVID-19 mRNA vaccine were projected to have 12.6 cases of myocarditis per million doses [28] Another Israeli study with around 5.4 million vaccine recipients found that second-dose vaccination-related myocarditis had an incidence ratio of 5.34 per 100,000 people, with diagnosis primarily occurring in younger males [30] Consequently, for every million vaccines that had at least one dose of Comirnatym, there were roughly 48.09 occurrences of myocarditis and pericarditis. Around 1.6 million first doses and 1.5 million second doses of Spikevax have been given up to this point [15] There were 203.13 incidences of myocarditis and pericarditis recorded per million people who had taken at least one dose of Spikevax in the UK. Although most cases are common after mRNA vaccines and increased up to 4 times compared to the others [32], [33]

Table 1: Overview of the reviewed sources.

Authors	Country	Purpose	Design study	Summary points
M.E Oster et al. (2022) [31]	US	Report on cases of myocarditis after COVID-19 mRNA vaccine injection	Descriptive study	Data shows that of the 192,405,448 people who received a total of 354,100,845 mRNA-based COVID-19 vaccines in this study, there were 1991 reports of myocarditis to VAERS and 1626 of these reports met the criteria for myocarditis cases. Most of these cases occurred in males, and most occurred after the injection of the second dose of the vaccine. The overall incidence of myocarditis after vaccination is still quite infrequent.
W. Woo et al. (2022) [28]	Korea	Provide comprehensive information on complications that do not often occur after the COVID-19 vaccine, and also provide people with information before they get vaccinated.	Systematic review	This study obtained 74 patients from a total of 24 sources that showed with myocarditis after COVID-19 mRNA vaccination. The authors found that the most patients (49.5%) were less than 20 years old and the majority were male. Symptoms usually appeared within a few days after vaccination, with chest pain being the most common. An excerpt from one of the source articles reported 148 cases of myocarditis among 10.4 million vaccinated people, with symptoms appearing within 30 days of receiving the mRNA vaccination.
J Montgomery et al. (2021) [34]	US	To explain myocarditis that occurs after COVID-19 vaccination in the health System.	Retrospective case series	The military stated that there have been more than 2.8 million doses of the COVID-19 mRNA vaccine during the making of this study. A total of 23 male patients and previously healthy military members with high fitness levels showed symptoms of myocarditis. The largest percentage of events were after the second dose of the COVID-19 mRNA vaccine.
S. Lane	UK	To summarize	Systematic	This study used 32 sources that met the

(2022)[35]	the data reported by several countries to estimate the reporting rate, and better understand the risk factors for myocarditis and pericarditis after COVID-19 mRNA vaccine injections.	review	criteria. A total of 18,204 myocarditis and pericarditis events were submitted to UK, US, and EU/EEA regulators within the study timeframe. Males had a high rate of 62.24%. In the UK and US, the rate was high at age < 40 years and after the second dose at 47.1%.

Myocarditis typically presents with symptoms of dyspnea, orthopnea, and chest discomfort, which are similar to those of heart failure [36] Relatively minor symptoms including cough, fever, and dyspnea might be brought on by COVID-19 by itself rather than myocarditis [36] Patients with COVID-19 myocarditis might, however, present in a variety of clinical ways. Many research studies have shown that data from myocarditis associated with mRNA vaccines mostly presented with chest pain [6], [9], [28], [37], [38] Patients were presented with cardiac symptoms such as chest pain or palpitations [37] The COVID-19 vaccine's most often reported local side effects were pain at the injection site, swelling, and redness. Symptoms of the systemic response included chills, myalgia, fatigue, and fever [9], [28], [39] A total of 1824 myocarditis occurrences were reported to VAERS; 956 (52.41%) occurred after the second dose and 383 (21.00%) occurred after the first [35] According to research, the second dose was documented more often in numerous works of literature, with an onset time range of one to two days [6], [29], [40] **Table 1** shows some summary data related to the incidence of myocarditis and related to immunization with the COVID-19 mRNA vaccine.

The pathophysiology of myocarditis post-mRNA vaccination is still unclear but it may be hypothesized due to myocarditis hypersensitivity [41] There was a study with military soldiers in the United States with a total of 23 subjects who were people with good fitness levels, but contracted myocarditis after receiving the COVID-19 mRNA vaccine, from the results of the study discussion said that the clinical course showed eosinophilic hypersensitivity myocarditis, which may be related to drug use or also to vaccines [34] The COVID-19 mRNA vaccines contain nucleoside-modified mRNA that can lessen innate immunogenicity; nevertheless, in people with certain genetic predispositions, the immune response to the mRNA may not be diminished and may instead result in aberrant activation of innate and acquired immunological responses. The dendritic cells recognize the vaccine's mRNA as an immunizing agent, activating Toll-like receptors, and starting pro-inflammatory cascades and immunological pathways to release cytokines [9], [42] Another potential mechanism is the cross-reactivity of the SARS-CoV-2 antibodies and myocardial myosin caused by the molecular mimicry between the spike (S) protein of SARS-CoV-2 and cardiac antigens. This may result in the increase of polyclonal B cells, the production of immunological complexes, and an inflammatory response in people who already have dysregulated immune pathways due to predisposition factors [9], [42], [43] The S glycoprotein of SARS-CoV-2 also plays a role in the mechanism of myocarditis. It enters the cells through the mRNA vaccines and binds to ACE2 causing a buildup of angiotensin II, a protein associated with inflammation, therefore initiate myocardial inflammation [42]

In the United States, patients with myocarditis after receiving COVID-19 vaccines can report to the VAERS and were categorized as probable and confirmed cases based on their symptoms and lab findings [9], [44] A study was conducted at 74 patients with myocarditis post vaccines, abnormal ECG

findings are seen in 87,8% of patients with the highest abnormality in the ST-segment, all patients present with an increase levels of cardiac enzyme, 86,4 % of patients had elevated C-reactive protein levels, and 67,8% of patients had CMR suggesting myocarditis based on LLC [28]

Predisposing Factors

Starting the attack against the COVID-19 disease with vaccinations, the mortality rate and severity have drastically decreased. On the other hand, there are many reports of side effects, such as myocarditis as a cardiovascular complication. The ratio of the incidence of myocarditis in men and women reaches 1.7:1 [29]. Others data shown the majority of reported cases in males (90%) compared to females (10%)[45] This is also found in other regions such as America with 72.92% data and 60.75% in the EU [35]. The male predominance has been discussed in previous studies, and the reason is still unknown. Sex hormones are a widely discussed theory which are the factors that influence the differences that occur through their receptors in both immune cells and host cardiac tissues [9], [29], [45] A key player in this process is the male hormone testosterone, which has a strong inhibitory effect on anti-inflammatory cells and a commitment to a Th1-type immune response. Another factor that increases the prevalence is under diagnosis in women. Estrogen also inhibits proinflammatory T cells, which results in a reduction in cell-mediated immune responses. Hence, sex hormone may help to explain both the predilection for men and the cardioselective nature of the autoimmunity caused by the COVID-19 vaccination [9], [29], [45]

In addition to gender, myocarditis after vaccination is more common at a young age which is the highest according to the data at the age of 18-24 years [46], [47] There have been case reports reporting young male patients who died with histological findings suggestive of myocarditis after COVID-19 mRNA vaccine but on the other hand there are also reports of death at an older age [48], [49]. In contrast with men, the incidence of myocarditis in women is more stable with age and without an increase in incidence during adolescence [50] Due to testosterone, post-vaccination myocarditis is more common in teenage boys, the same thing happens to post-menopausal women because of low estrogen levels at the age of 55-60 year. Progesterone is a protective factor against myocarditis [50], [51]

Management and Prevention

Recommendations from the National Advisory Committee on Immunization (NACI) from Canada to minimize side effects with recommended doses of the Pfizer 30mcg mRNA vaccine at ages 12 to 29 years and for ages 12-17 years related to the risk of myocarditis NACI recommends a gap of 8 weeks between the first and second doses mRNA vaccine [33], [52] Another recommendation from Singapore for COVID-19 vaccination recommends avoiding strenuous exercise for 2 weeks after vaccination [33], [53] People who experience chest pain within a week after vaccination, especially considering the prevalence, namely young age and men should be suspicious of complications of myocarditis. Seeing that there are reports of complications of myocarditis, it is recommended that people who have risk factors have another examination 3 to 6 months after vaccination. In addition, patients diagnosed with myocarditis should also not engage in strenuous activities and competitive sports [31] Examination with cardiac MRI may be able to help the evaluation of the progression or improvement of myocarditis in patients, but it is still not known for sure.

Angiotensin-converting enzyme inhibitor, β-blocker, intravenous immunoglobulin and aspirin have been applied to some patients, this is due to left ventricular systolic dysfunction that occurs [47] In patients with good resolution of symptoms and normal cardiac biomarkers, therapy can be deferred. If there are persistent mild symptoms in the absence of hemodynamic instability, heart failure, and arrhythmia, then administration of non-steroidal anti-inflammatory drugs, colchicine, and steroids may be considered. In more severe conditions the use of intravenous steroids and intravenous immunoglobulin along with other cardiac or circulatory support measures may be considered in

patients with hemodynamic instability, heart failure, new onset arrhythmias, left ventricular dysfunction. Cardiologists should be involved for initial assessment, evaluation, treatment, and follow-up, as well as infectious disease specialists for consideration of subsequent immunizations [9]
Diagnosis is important as myocarditis associated with COVID-19 mRNA vaccine and common myocarditis are very similar, which is important for future treatment. Initial evaluation, cardiac troponin levels and ECG should be performed, and examination of erythrocyte sedimentation rate and C-reactive protein may be helpful. Clinical findings and course, patient age, hemodynamic stability, heart rhythm, comorbidities, as well as other potential causes, determine the type of evaluation and management [31] There are no guidelines nor specific treatment data for myocarditis related to the COVID-19 mRNA vaccine. There is a meta-analysis showing the use of Intravenous Immunoglobulin (IVIG) as a management of acute myocarditis shows positive results and low mortality rates, this is attributed to IVIG and also steroids are immunosuppressive agents as well as immunomodulators and can reduce the specific immune response to SARS-CoV-2 triggered by the vaccine along with improvements in left ventricular ejection fraction. Other conditions such as in fulminant myocarditis patients given IVIG are even more noticeable where it is shown to significantly increase the survival rate of this dangerous condition [54], [55] Corticosteroids such as prednisolone, may be considered in treating viral myocarditis in the absence of viral replication [36] Other management options such as colchicine, NSAIDs, favipiravir and tocilizumab, have been used by different studies, so further research is needed [41], [47], [56] A condition that can worsen myocarditis associated with the COVID-19 mRNA vaccine is cytokine storm, if this occurs, the combination therapy of favipiravir and tocilizumab should be administered. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, was tested in combination with the anti-viral, favipiravir, to treat COVID-19 patients with cytokine storm, which had a positive effect on patients and can be given to reduce inflammation due to cytokine storm [56]

Conclusion

Myocarditis associated with the COVID-19 mRNA vaccine appears as a very rare side effect. There is considerable variation in the clinical findings of this condition, with some studies suggesting that the majority present with chest pain. Data shows high rates in young adults and adolescents. Further surveillance is initiated at 3 to 6 months after vaccination to assess health and functional status and cardiac outcomes. Although there are no definitive evidence-based recommendations for the management of myocarditis caused by mRNA vaccination, many data suggest that the initial evaluation and treatment of COVID-19 mRNA vaccine-associated myocarditis cases is similar to that of myocarditis cases in general. The presence of post-vaccination myocarditis should be considered by health workers so that they can prevent and manage it properly. In addition, with a low incidence rate and the benefits of vaccination in preventing COVID-19 outweighing the risks, but monitoring and further research must still be carried out to determine other benefits and potential risks.

Ethical Declarations

Acknoweldgements

None.

Ethics approval and consent to participate

No needed.

Consent for publication

Not applicable (no individual personal data included).

Availability of data and material

This is a minireview article.

Competing interests

The authors declare that there is no conflict of interest

Funding

No funding

Author contributions

All the authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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