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MYOCARDITIS AFTER COVID-19 M-RNA VACCINATION : ASYSTEMATIC REVIEW

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Abstract

One of the possible solutions to the problem of COVID-19 is vaccination against the virus. Vaccination may provide immunity by stimulating the immune system of the receiver to mount a response to the antigens that are present inside the vaccine. As part of the immunological response, a person may have both local and systemic symptoms, such as discomfort at the injection site or fever. Additional components of the vaccination have the potential to cause responses. Myocarditis that was reported to VAERS after vaccination with mRNA-based COVID-19 had demographic characteristics that were comparable to those of cases of myocarditis that were not associated with vaccination. However, the acute clinical course of myocarditis that was reported to VAERS after vaccination was different from the acute clinical course of myocarditis that was reported in cases that were not associated with vaccination. The risk of myocarditis increased after getting immunizations based on mRNA for COVID-19 in all age and gender groups, with the risk being highest after the second immunization dose in male adolescents and young men. This danger has to be assessed in light of the many positive aspects associated with the COVID-19 vaccination. One of the many possible processes is a hyperimmune or inflammatory response after exposure to spike protein, mRNA strand, or an unexplained trigger. Another possibility is a delayed onset of hypersensitivity.

Keyword: *Covid-19; Immunity; m-RNA; Myocarditis; Vaccine*

INTRODUCTION

COVID-19 is a pandemic that occurred at the end of the second decade of 2000. This disease poses a large health burden and there is still no drug that is believed to be effective in treating this disease. COVID-19 is caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2).[1,2] Vaccination against COVID-19 is one of the hopes for handling COVID-19.[3] Vaccination can trigger immunity by causing the recipient's immune system to react to the antigens contained in the vaccine. Local and systemic reactions such as injection site pain or fever may occur as part of the immune response. Other vaccine components can also trigger reactions. A quality vaccine is one that causes as few mild reactions as possible but still triggers the best immune response. The frequency of mild reactions to vaccination is determined by the type of vaccine.[4]

Myocarditis is an inflammatory illness that affects the heart muscle and has two distinct peak incidence periods: one during childhood and the other during adolescence or early adulthood.[5] Myocarditis is a heterogeneous illness that manifests itself in a variety of clinical patterns, etiologies, and treatment approaches.[6] It is characterized by inflammatory damage to cardiac tissue that occurs in the absence of ischemia. Although viral infections, which can now also be caused by SARS-CoV-2, are the most prevalent causes of the disease, some occurrences of myocarditis are connected with particular medication exposures and vaccines. Myocarditis as an adverse event following vaccination is described in rare published case reports and infrequent submissions to the Vaccine Adverse Events Reporting System.[7–9] In this study, we investigate whether there is any evidence to suggest that patients who received the m-RNA vaccine for COVID-19 experienced an increased risk of myocarditis.

METHODS

Protocol

This systematic review was created by following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist guidelines.

Eligibility Criteria

Studies with topics that discuss "myocarditis" and "COVID-19 m-RNA vaccination" are the topics analyzed in the writing of this systematic review. Writing inclusion criteria are: 1) Complete articles can be accessed; 2) Written in English; 3) Articles are published in the period above 2020 until the writing of this systematic review is carried out (November 2022). The writing exclusion criteria are: 1) Editorial letters; 2) does not have a Digital Object Identifier (DOI); 3) Article review or the like.

Search Strategy

The search for studies to be included in the systematic review was carried out from November 10-14th, 2022 using the PubMed, SagePub, and Clinical Key databases by inputting the words: "myocarditis" and "COVID-19 m-RNA vaccination". Where *("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND "m-RNA"[All Fields] AND ("vaccin"[Supplementary Concept] OR "vaccin"[All Fields] OR "vaccination"[MeSH Terms] OR "vaccination"[All Fields] OR "vaccinable"[All Fields] OR "vaccinal"[All Fields] OR "vaccinate"[All Fields] OR "vaccinated"[All Fields] OR "vaccinates"[All Fields] OR "vaccinating"[All Fields] OR "vaccinations"[All Fields] OR "vaccination s"[All Fields] OR "vaccinator"[All Fields] OR "vaccinators"[All Fields] OR "vaccine s"[All Fields] OR "vaccined"[All Fields] OR "vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields] OR "vaccins"[All Fields]) AND ("myocardic"[All Fields] OR "myocarditis"[MeSH Terms] OR "myocarditis"[All Fields] OR "myocarditides"[All Fields])* is used as search keywords.

Data retrieval

The author scanned the existing studies, by reading the title and abstract of the study, then adjusted to the inclusion and exclusion criteria, studies that met the criteria would be included in a systematic review review. Information that can be obtained in each study is in the form of title, author, time of publication, origin of study location, research study design, and research variables.

Quality Assessment and Data Synthesis

The authors independently reviewed some of the studies found from the titles and abstracts in the articles to identify potentially eligible studies. Next, the eligible studies will be read in full in order to decide which studies are eligible to serve as final inclusions for inclusion in a systematic review.

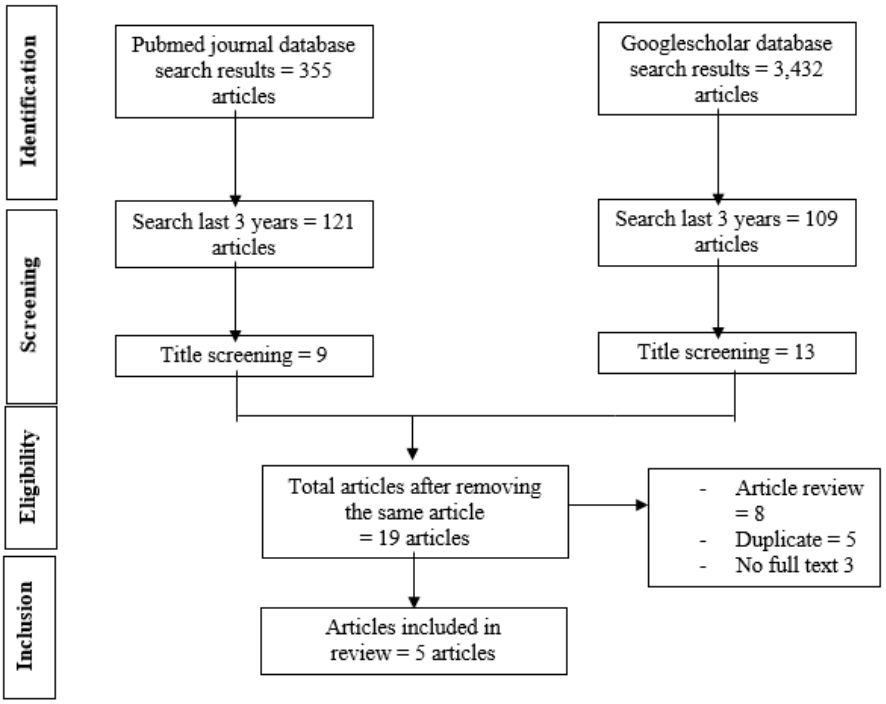

Figure 1. Article search flowchart

RESULT

Study search was carried out by utilizing PubMed, SagePub, and Clinical Key as study search database sources. From the database search results found as many as 355 articles. After elimination by removing duplicates between sources, articles were screened based on title and abstract, the number of articles screened was 32 articles. The author selected the 32 articles based on inclusion and exclusion criteria. Based on the selection the authors found that there were five studies that met the inclusion and exclusion criteria for the systematic review. The following is the PRISMA flow chart (Figure 1) which illustrates the steps for selecting studies, starting from the identification stage, to finding studies that meet the inclusion criteria. The average day interval from vaccine until the patient developed myocarditis was 4.5 days (3-9 days).

The findings of the Piras study were the first comprehensive assessment of singlecase reports, which are often excluded from systematic reviews and meta-analyses. According to the findings of the study, the majority of male cases occurred after the second injection of m-RNA immunization. Cases that were mild were able to be treated.This detrimental event affected not just teenagers but also older people, particularly women, and it was extremely destructive to them.[10]

Elhouderi showed this unfavorable occurrence happens in young guys more frequently than in any other age group. Previous COVID-19 infection may be linked to an increased risk of COVID-19-vaccine-related myopericarditis, and additional researchis required to investigate this potential connection. This ailment can be treated with supportive care, and the result is expected to be positive.[11]

Table 1. The litelature include in this study

Author	Origin	Method	Vaccine	Sample Size /Characteristic	Result
Piras, 2022[10]	Italy	Case report	Pfizer, secondshot	A 16-year-old male	This is the first major investigation of single case reports, which are generally eliminated from systematic reviews and meta-analyses. The analysis shows that most male cases occurred after the second m-RNA vaccination injection. Mild cases were treatable. This harmful occurrence harmed not just adolescents, but also older persons, especially women.
Kim, 2021[13]	US	Comparativestudy	Moderna, Pfizer	7 patients	The findings of magnetic resonance imaging were analyzed, and they were found to be consistent with acute myocarditis in seven patients. Four of these patients had previously received COVID-19 vaccination.
Montgomery ,2021[14]	US	Retrospective case series	Moderna, Pfizer	23 male patients	Within four days of receiving a COVID-19 vaccination, myocarditis was detected in this case series of 23 male patients, including 22 previously healthy service members. For the majority of patients (n = 20), the diagnosis was obtained after the second dose of mRNA COVID-19 vaccination; these incidences occurred despite the administration of 2.8 million doses of mRNA COVID-19 vaccine.
Elhouderi, 2022[11]	US	Case report	Pfizer	Male 30-yo	This unfavorable occurrence happens in young guys more frequently than in any other age group. Previous COVID-19 infection may be linked to an increased risk of COVID-19-vaccine-related myopericarditis, and additional research is required to investigate this potential connection. This ailment can be treated with supportive care, and the result is expected to be positive.
Perez, 2022[12]	US	Retrospective case series		7 patients	Myocarditis is an uncommon adverse effect linked to COVID-19 mRNAvaccinations. It is substantially more prevalent among adult men than in the general population. Myocarditis recurrence after a further mRNA vaccination dosage is still unknown.

Perez, et al (2022) study showed total incidence rate ratio (IRR) of COVID-19-related myocarditis was 4.18 (95% CI, 1.63-8.98), which was completely owing to anelevated IRR among adult men (IRR, 6.69; 95% CI, 2.35-15.52) in comparison with females (IRR 1.41; 95% CI,.03-8.45). All of the occurrences occurred within two weeks after receiving a dose of the COVID-19 mRNA vaccine, with the bulk of the casesoccurring within three days (range: 1-13) following the second dose (6 out of 7 patients, or 86%). The instances were rather minor, and all of the patients lived. Myocarditis is anextremely uncommon side effect that has been linked to the administration of COVID-19mRNA vaccinations. It is substantially more common among adult men than it is in thegeneral population, particularly in the United States. At this moment, it is unknownwhether or not myocarditis will return after receiving a repeat dose of mRNA vaccine.[12] Other study with seven individuals with acute myocarditis were discovered between February 1 and April 30, 2021, with four cases occurring within five daysfollowing COVID-19 immunization. Three were young men between the ages of 23 and36, and one was an elderly woman in her 70s. All four individuals had gotten their second dose of an mRNA vaccination (2 received mRNA-1273 [Moderna], and 2 received BNT162b2 [Pfizer]). All patients were hospitalized after presenting with significant chest discomfort with biomarker indications of myocardial damage. Testing for COVID-19 and respiratory viruses simultaneously revealed no alternate reason. Typical findings oncardiac magnetic resonance imaging for myocarditis were regional dysfunction, late gadolinium enhancement, and raised native T1 and T2.[13]

Other study showed within four days of receiving an mRNA COVID-19 vaccination, 23 male patients (22 presently serving in the military and 1 retiree; median [range] age, 25 [20-51] years) complained with sudden onset of severe chest discomfort.Prior to joining the military, each member was physically strong and in good health. Seven individuals got the BNT162b2-mRNA vaccination and sixteen individuals received the mRNA-1273 vaccine. Twenty individuals had commencement of symptoms following the second dosage of a suitably spaced 2-dose series. All individuals exhibitedconsiderably increased levels of cardiac troponin.[14]

In the acute phase of illness, all eight patients who underwent cardiac magnetic resonance imaging revealed results compatible with the clinical diagnosis of myocarditis.Other causes of myocarditis, such as acute COVID-19 and other infections, ischemia damage, or underlying autoimmune disorders, were not identified by further testing. At the time of this report, all patients had received short supportive treatment and were recovered or recovering. During this time span, the military gave almost 2,8 million doses of the mRNA COVID-19 vaccination. Although the observed number of myocarditis cases was minimal, the number of cases among male military personnel following a second vaccination dosage was greater than anticipated.[14]

DISCUSSION

Before COVID vaccination, reports of myocarditis as a possible side effect of the vaccine were limited to anecdotes; myocarditis was only scientifically proven as an effect of vaccines against smallpox, which are very different from m-RNA vaccines against COVID-19.[15] People who have cardiovascular disease are at a higher risk of developing complications from COVID-19. Physicians who care for patients who have cardiovascular disease should urge immunization and assist patients in making decisions about whether or not to get the vaccine. In one study, older persons were asked how they would go about making a decision regarding immunization, and 66 percent of those adults said that they would first consult with their primary care physician.[16]

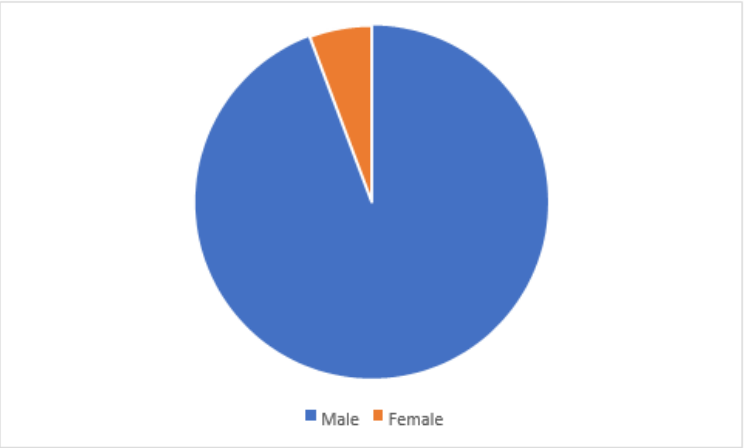

Figure 2. Comparison of the sexes of patients with myocarditis after the Covid-19mRNA vaccine

The very short amount of time that passed between m-RNA immunization and myocarditis raises the possibility of a connection between the two; nevertheless, this correlation has not yet been established by scientific research. There is a clear need for more research because it has not yet been established with absolute certainty whether or not m-RNA vaccinations cause myocarditis. There have been a few different processes proposed, but none of them are persuasive on their own.[17]

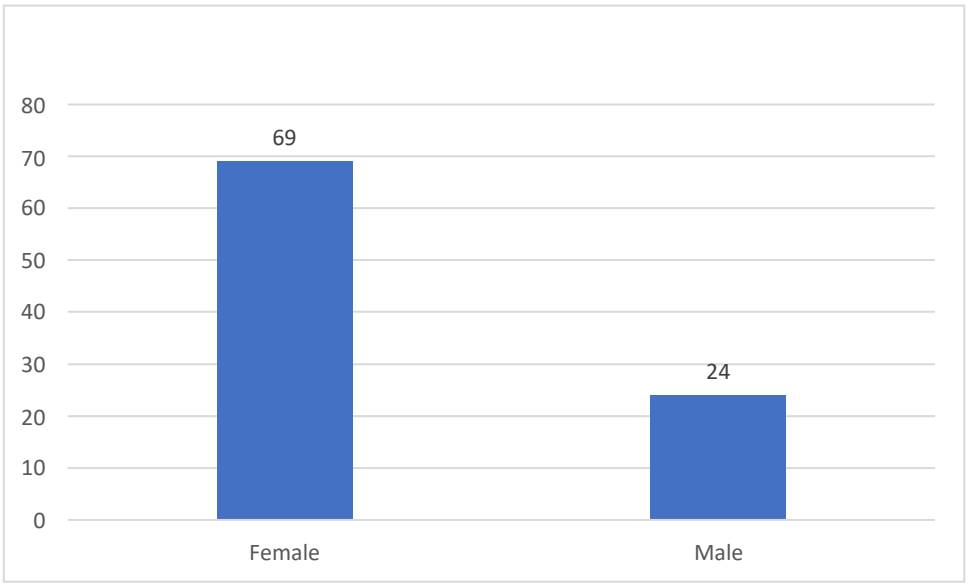

Figure 3. Comparison of the ages of patients with myocarditis after the Covid-19mRNA vaccine (years old)

Myocarditis that was reported to VAERS after vaccination with mRNA-based COVID-19 had demographic characteristics that were comparable to those of cases of myocarditis that were not associated with vaccination, but had an acute clinical course that was distinct from those of cases not associated with vaccination. First, the age distribution of vaccination recipients, which showed a larger frequency among those aged12 to 29 years compared to those aged 30 years or older, was comparable to the age distribution reported in normal instances of myocarditis.[18,19]

This trend may explain why incidences of myocarditis were not found in the United States until many months after the first Emergency Use Authorization for the immunizations (ie, until the vaccines were widely available to younger persons). Second, the sex distribution in instances of myocarditis following COVID-19 immunization was identical to that reported in ordinary cases of myocarditis; there is a high male preponderance for both illnesses. This finding was similar to what was seen in typical cases of myocarditis.[18,19]

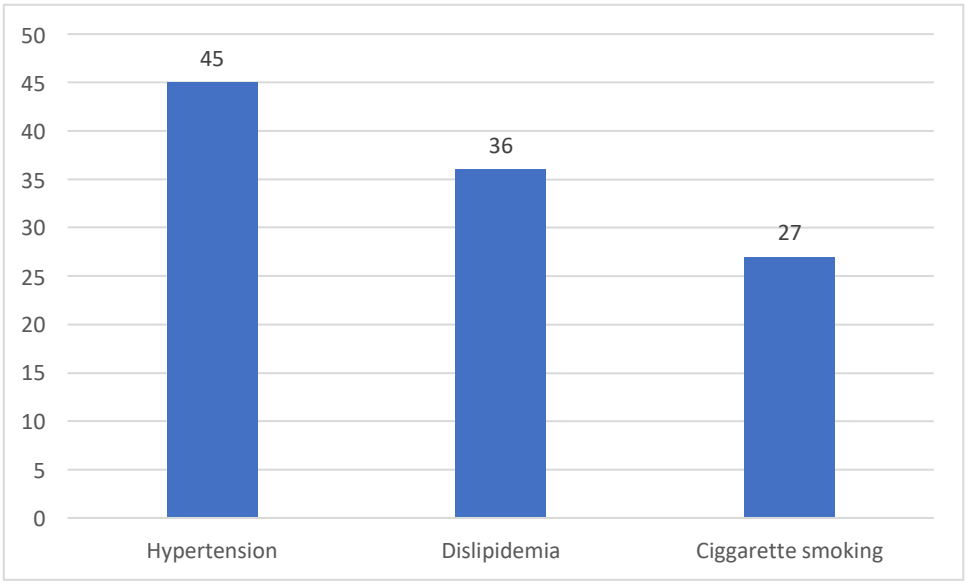

Figure 4. Comparison of the comorbidities of patients with myocarditis after theCovid-19 mRNA vaccine

The many suggested mechanisms include: hyper immune or inflammatory reaction after exposure to spike protein, mRNA strand, or unexplained trigger; late onset of hypersensitivity (serum sickness); eosinophilic myocarditis; hyperreactivity to vaccine excipients (e.g., polyethylene glycol and tromethamine or lipid nanoparticle sheath); reaction to mRNA vaccine lipid nanomolecules; self-immunity through mimicry or other pathways; low residual quantity of double strand RNA; unbalanced micro-RNA reaction; release of anti-idiotype antibodies against certain regions of antigen-specific antibodies; activation of pre-existent dysregulated immune pathways in predisposed subjects (leading to polyclonal B cell growth, immune complex development, and inflammation); antibody-dependent amplification of immunity or other forms of immune intensification with re-exposure to the virus after vaccine inoculation; direct cell invasion through the interplay of the spike protein and the angiotensin converting enzyme 2 (ACE2) widely expressed on cardiomyocytes surfaces; cardiac pericyte expression of ACE2 with disabled immune complex on the surface of pericytes along with activation of the complement system; hyperviscosity-induced cardiac problem; and demanding effort induced secretion of proinflammatory interleukin 6.[13,20]

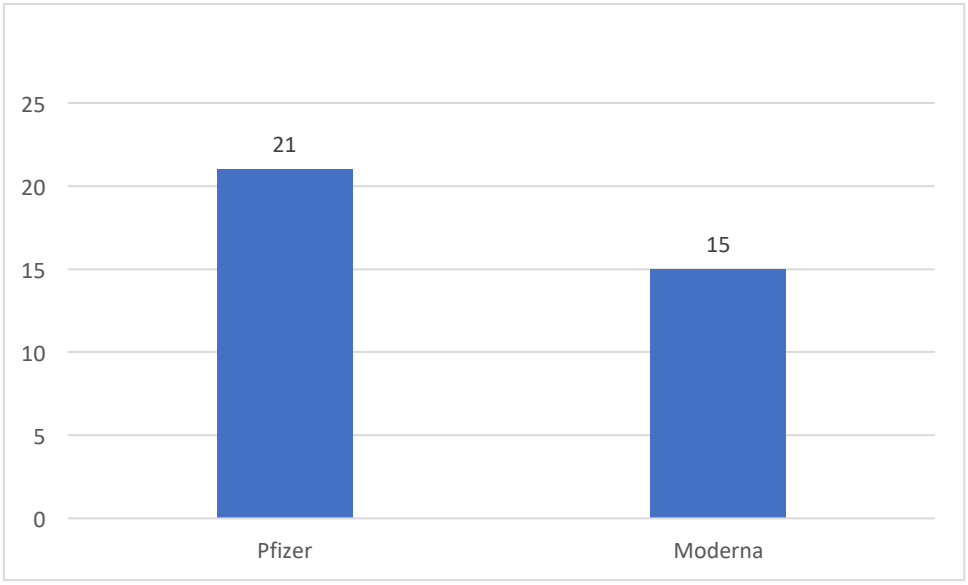

Figure 4. Comparison of the type of vaccine patients with myocarditis after theCovid-19 mRNA vaccine

On the other hand, the onset of symptoms of myocarditis after exposure to a potential immunological trigger was shorter for COVID-19 vaccine–associated cases of myocarditis than it is typically for cases of myocarditis diagnosed after a viral illness. This was a significant finding. Cases of myocarditis reported following COVID-19 immunization were often recognized within days after vaccination, while cases of normal viral myocarditis had typically indolent histories, with symptoms appearing weeks or months after a trigger, assuming the cause is ever found.[21,22]

CONCLUSION

After receiving mRNA-based COVID-19 vaccinations, the risk of myocarditis rose across different age and sex strata, with the risk being greatest after the second immunization dose in male adolescents and young men. This risk should be evaluated inlight of the advantages of the COVID-19 vaccine.

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