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Review and Meta-analysis

Global reports of myocarditis following COVID-19 vaccination: A systematic review and meta-analysis

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Abstract

Background and aims: Recent media reports of myocarditis after receiving COVID-19 vaccines, particularly the messenger RNA (mRNA) vaccines, are causing public concern. This review summarizes information from published case series and case reports, emphasizing patient and disease characteristics, investigation, and clinical outcomes, to provide a comprehensive picture of the condition.

Methods: A systematic literature search of PubMed and Google scholar was conducted from inception to April 27, 2022. Individuals who develop myocarditis after receiving the COVID-19 vaccine, regardless of the type of vaccine and dose, were included in the study.

Results: Sixty-two studies, including 218 cases, participated in the current systematic review. The median age was 29.2 years; 92.2% were male and 7.8% were female. 72.4% of patients received the Pfizer-BioNTech (BNT162b2) vaccine, 23.8% of patients received the Moderna COVID-19 Vaccine (mRNA-1273), and the rest of the 3.5% received other types of COVID-19 vaccine. Furthermore, most myocarditis cases (82.1%) occurred after the second vaccine dose, after a median time interval of 3.5 days. The most frequently reported symptoms were chest pain, myalgia/body aches and fever. Troponin levels were consistently elevated in 98.6% of patients. The admission ECG was abnormal in 88.5% of cases, and the left LVEF was lower than 50% in 21.5% of cases. Most patients (92.6%) resolved symptoms and recovered, and only three patients died.

Conclusion: These findings may help public health policy to consider myocarditis in the context of the benefits of COVID-19 vaccination.

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1. Introduction

International efforts to drive vaccinations are critical to restoring health and economic and social recovery as the SARS-CoV-2 coronavirus (COVID-19)-caused pandemic continues [1]. The COVID-19 vaccines developed by Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) were granted emergency approval by the Food and Drug Administration (FDA) of the United States in December 2020. Reports of myocarditis after the COVID-19 vaccination, notably after the messenger RNA (mRNA) vaccines, have recently received widespread media attention, causing widespread concern among the general public [1]. Myocarditis is diagnosed in about ten to twenty people per 100,000 in the general population each year, and it is more common in men and younger age groups [2]. Myocarditis following mRNA COVID-19 vaccination was first reported in Israel in April 2021, and then several case reports and case series were reported around the world.

Specifically, this report examines the current literature on myocarditis following COVID-19 vaccination, summarizing available information from previously published case reports and case series, with a strong attention on reporting patient and disease characteristics, as well as investigation and clinical outcome, in order to provide a comprehensive picture of the condition.

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2. Methods

2.1. Review objectives

The main objective is to clarify the potential occurrence of myocarditis associated with COVID-19 vaccination and elaborate on the demographic and clinical characteristics of COVID-19 vaccinated individuals who develop myocarditis and how many cases have been reported in the literature.

2.2. Protocol and registration

The review is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for the systematic review of available literature [3]. The protocol of the review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with ID CRD42022308997. The AMSTAR-2 checklist was also used to evaluate this study, and it was found to be of high quality [4]. This review article does not require ethics approval.

2.3. Search strategy

A comprehensive search of major electronic databases (PubMed and Google Scholar) was conducted on April 27, 2022, to locate all publications. The AND operator was used to connect two of the most important concepts in the search terminology (“COVID-19” AND “Myocarditis”). (“Myocarditis” and “COVID-19” OR “SARS-CoV-2” OR “Coronavirus Disease 2019” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus infection” OR “2019-nCoV” AND “vaccine, vaccination, OR vaccine” were used in the search. To make sure the search was completed, we checked the references of all relevant papers.

2.4. Eligibility criteria

All case series and case reports on post-COVID-19 vaccine myocarditis in humans were included. Individuals who develop myocarditis after receiving the COVID-19 vaccine, regardless of the type of vaccine and dose. The references of the relevant articles will also be reviewed for additional articles that meet the inclusion criteria. Narrative and systematic reviews, original and unavailable data papers were excluded from this review. Moreover, articles other than English were excluded in this review.

2.5. Data extraction and selection process

PRISMA 2020 was used to guide every step of the data extraction process from the original source. Two independent authors (SKA and RAE) used the Rayyan website to screen abstracts and full-text articles based on inclusion and exclusion criteria [5]. The discrepancies between the two independent authors were resolved by discussion. Microsoft Excel spreadsheets collected the necessary information from the extracted data. Author names, year of publication, age, gender, type of COVID-19 vaccine, dose, days to symptoms onset, symptoms, troponin level, LVEF 50% or LVEF >50%, ECG, length of hospital stay/days, treatment, and outcomes were extracted from each study.

2.6. Critical appraisal

To assess the quality of all included studies, we used the Joanna Briggs Institute’s critical appraisal tool for case series and case reports [6]. Two different authors (SKA and RAE) evaluated each article, each of whom worked independently. Paper evaluation disputes were resolved through discussion. Articles with an average score of 50% or higher were included in the data extraction process. The AMSTAR 2 criteria were used to evaluate the results of our systematic review [4]. The AMSTAR 2 tool assigned a “moderate” rating to the overall quality of our systematic review.

2.7. Data synthesis and analysis

All the articles included in the current systematic review were analyzed, and the data were extracted and pooled. This included (authors’ names, year of publication; gender; type of COVID-19 vaccine, dose, days to symptoms onset, troponin level, LVEF below or above 50%, ECG, length of hospital stay/days; treatment and outcomes). We gathered this data from the results of eligibility studies. COVID-19 vaccine recipients who developed myocarditis were included in the study.

3. Results

3.1. Selection of studies

When we searched the major databases (PubMed and Google Scholar) on April 27, 2022, we discovered 2979 articles relevant to our search criteria. A citation manager tool (Mendeley) was used to organize the references, and 397 articles were automatically removed because they contained duplicate content. Next, the titles, abstracts, and full texts of 2585 articles were checked for accuracy, and 2494 articles were rejected because they did not meet the criteria for inclusion. Besides that, 91 articles were submitted for retrieval, but twenty-seven were rejected because they did not meet our inclusion requirements. The current systematic review was limited to 62 articles in total (Fig. 1). The details of case reports and case series are shown in (Table 1).

3.2. Characteristics of the included studies

Overall, sixty-two studies, including 218 cases each, from the United States, Italy, Israel, Germany, Poland, France, Korea, Brazil, Japan, Mexico, Spain, New Zealand, Portugal, Germany, Iraq, Turkey and Iran participated in this systematic review. The median age was 29.2 years; 92.2% were male and 7.8% were female. 72.4% of patients received the Pfizer-BioNTech (BNT162b2) vaccine, 23.8% of patients received the Moderna COVID-19 Vaccine (mRNA-1273), and the rest of the 3.5% received other types of vaccines (Johnson & Johnson, AstraZeneca, Sinovac, Sputnik V vaccine).

The vast majority of cases are from the United States. All patients were diagnosed with myocarditis or myopericarditis following COVID-19 vaccination, regardless of the type of vaccine and dose.

Furthermore, most myocarditis cases (82.1%, n = 179) occurred after the second vaccine dose, after a median time interval of 3.5 days. The most frequently reported symptoms were chest pain (99.1% n = 216), fever (31.6% n = 69), myalgia/body aches (36.6% n = 80), and also variable reports of viral prodromes such as chills, headaches, and malaise. Troponin levels were consistently elevated in 98.6% (n = 215) of the cases where they were reported, consistent with myocardial injury. The admission electrocardiogram (ECG) was abnormal in 88.5% (n = 193) of cases, and the left ventricular ejection fraction (LVEF) was lower than 50% in 21.5% (n = 47) of cases. The median length of hospital stay was 5.8 days in 182 patients but unknown in 36 patients. The vast majority of patients (92.6%) (n = 202) resolved symptoms and recovered, and only three patients died (Table 2).
4. Discussion

The current systematic review summarized evidence from the original case reports and case series that explored the development of myocarditis after the COVID-19 vaccination. Throughout the selected studies, most of the participants were male, from the USA, and their mean age 29.2 years old. The vaccine-induced myocarditis mechanism is unknown but may be related to the active pathogenic component of the vaccine and specific human proteins, which could lead to immune cross-reactivity resulting in autoimmune disease, which is one cause of myocarditis [7–10]. The occurrence of myocarditis in men may be related to sex hormone variations, as testosterone hormone suppresses anti-inflammatory immune cells while promoting more aggressive T helper cells [7,11].

These findings were matched with Oster et al. (2022) [12], who found the incidence rate of myocarditis among vaccinated male people was similar to that seen in typical cases of myocarditis and there was a strong male predominance for both conditions [13]. Fatima et al. (2022) [7] found most patients who developed myocarditis were males. Moreover, Patone et al. (2022) [14] mentioned that the incidence of myocarditis was among England males younger than 40 years old. Similarly, a systematic review study found that the Incidence of myocarditis following mRNA vaccines is low but probably highest in males aged 12–29 years old [15].

Another important finding in the current systematic review is that most participants received Pfizer-BioNTech (BNT 162b2) followed by the Moderna COVID-19 vaccine (mRNA-1273), and most of the cases who complained of myocarditis received two doses of the vaccine. This indicates that mRNA vaccines are associated with a higher risk of developing myocarditis than viral vector vaccines, including Janssen, Oxford, and Sinovac. Bozkurt et al. (2021) [12], have assumed that autoantibody generation could attack cardiac myocytes in response to the mRNA vaccine, increasing the risk.
Table 1  
Characteristics and outcomes of patients with myocarditis related to COVID-19 vaccine. 

| Author/Year of publication | Country | Age | Gender | Type of COVID-19 vaccine | Dose | Days to symptom onset | Symptoms | Troponin level | LVEF <50% or LVEF >50% | Electrocardiogram (ECG) | Treatment | Length of hospital stay (days) | Outcome |
|---------------------------|---------|-----|--------|--------------------------|------|----------------------|----------|----------------|-----------------------|--------------------------|------------|--------------------------|----------|
| Abu Mouch et al., 2021 [24] | Israel | 6 cases mean age 22 years | All of them were male | BNT162b2 | 2nd in 5 cases and 1st in one case | Mean 4.5 days | Chest pain/discomfort elevated | Elevated in all cases | LVEF >50% in all cases | Normal in all cases | NSAIDs and colchicine | Mean 5.6 days | Recovered |
| Marshall et al., 2021 [25] | USA | 7 cases mean age 16.7 years | All of them were male | BNT162b2 | 2nd | Mean 2.57 days | Chest pain elevated | Elevated in all cases | LVEF >50% in 6 cases and LVEF <50% in one case | Abnormal in all cases | NSAIDs, IVlg, IV methylprednisolone, PO prednisone, famotidine, aspirin | Mean 11.57 days | Recovered |
| D'Angelo et al., 2021 [26] | Italy | 30 years | Male | BNT162b2 | 1st | 21 days | Dyspnea, constrictive retrosternal pain, nausea, and profuse sweating | Elevated | LVEF >50% in all cases | Normal in all cases | Abnormal | Bisoprolol, aspirin, and prednisolone | 7 days | Recovered |
| Nassar et al., 2021 [27] | USA | 70 years | Female | mRNA-1273 | 1st | 2 days | The patient arrived at the emergency department in severe respiratory distress | Elevated | LVEF >50% in all cases | Normal in all cases | Abnormal | Vasopressors and antibiotic therapy | 8 days | Died |
| Kim et al., 2021 [28] | USA | 4 cases mean age 38.25 years | 3 males and 1 female | mRNA-1273 in 2 cases and BNT162b2 in 2 cases | 2nd | Mean 2.75 days | Chest pain elevated | Elevated in all cases | LVEF >50% in 3 cases and LVEF <50% in one case | Normal in all cases | Corticosteroids NSAIDs and colchicine | Mean 2.5 days | Recovered |
| Montgomery et al., 2021 [10] | USA | 23 cases mean age 25 years | All of there were male | BNT162b2 in 7 cases and 16 cases mRNA-1273 | 2nd in 20 cases and 1st in 3 cases | Mean 2 days | Chest pain elevated | Elevated in all cases | LVEF >50% in 4 cases and LVEF <50% in 19 cases | Abnormal in 19 cases and normal in 4 cases | All patients received brief supportive care | Mean 7 days | Recovered |
| Verma et al., 2021 [29] | USA | 2 cases (45, 42) years Mean age 43.5 years | 1 male and 1 female | BNT162b2- mRNA-1273 | 1st in one case and 2nd in another case | Mean 12 days | Chest pain, dyspnea and dizziness, elevated | Elevated in all cases | LVEF >50% in all cases | Normal in all cases | Intravenous diuretics, methylprednisolone, lisinopril, spironolactone, and metoprolol succinate) | 7 days | Died |
| Rosner et al., 2021 [30] | USA | 7 cases Mean age 27.42 years | All of them were male | BNT162b2 in 5 cases, one case mRNA-1273 and one case Ad26.COV2 | 2nd in 6 cases and 1st in one case | Mean 3.85 days | Chest pain elevated | Elevated in all cases | LVEF >50% in 6 cases and LVEF <50% in one case | Abnormal in 6 cases and normal in one case | β-blocker and anti-inflammatory medication | Mean 2.85 days | Recovered |
| Dionne et al., 2021 [31] | USA | 15 cases mean age 15 years | 14 cases male and one case female | mRNA-1273 | 2nd in all cases | Mean 3 days | Chest pain, fever, myalgia, headache elevated | Elevated in all cases | Mean LVEF <50% in all cases | Abnormal in all cases | β-blocker therapy. | Mean 2 days | Recovered |
| Garci’a et al., 2021 [32] | Mexico | 39 years | Male | BNT162b2 | 2nd | ¼ day | Chest pain elevated | Elevated | LVEF >50% in all cases | Normal in all cases | Anti-inflammatory medication | Unknown | Recovered |
| Dickey et al., 2021 [33] | USA | 6 cases mean age 27 years | All of them were male | BNT162b2 in 5 cases and one case mRNA-1273 | 2nd | Mean 3.33 days | Chest pain, chills, myalgia, malaise, headache and fever elevated | Elevated in all cases | LVEF >50% in 5 cases and LVEF <50% in 3 cases | Abnormal in 5 cases and normal in one case | Unknown | Unknown | Recovered |
| Tano et al., 2021 [34] | USA | 8 cases mean age | All of them were male | BNT162b2 in all cases | 2nd in 7 cases and | Mean 2.37 days | Chest pain, fatigue, abdominal pain, fever, shortness of breath elevated | Elevated in all cases | LVEF >50% in all cases | Normal in 6 cases and normal in 2 cases | NSAIDs | Mean 2.36 days | Recovered |
| Study                                      | Country | Age | Gender | mRNA | Dose | Days | Symptoms                                                                 | LVEF | Other Treatments                                                                 | Recovered |
|-------------------------------------------|---------|-----|--------|------|------|------|---------------------------------------------------------------------------|------|--------------------------------------------------------------------------------|-----------|
| Larson et al., 2021 [35]                  | USA and Italy | 16.61 years | 8 males, mean age 31 years, 8 females, mean age 62 years | mRNA-1273 | 5 cases | 2nd in 7 cases and 1st in 1 case | Mean 2.75 days | Chest pain, myalgia, fever, chills, shortness of breath and cough | Elevated | NSAIDs, colchicine, prednisone | Unknown |
| Deb et al., 2021 [36]                     | USA     | 2 cases mean age 30.5 years | Male | mRNA-1273 | 2nd | ½ day | Nausea, orthopnea, fever, fatigue | Elevated | NSAIDs | Unknown |
| Abbate et al., 2021 [37]                  | USA     | 2 cases mean age 30.5 years | Male | mRNA-1273 | 2nd in one case and 1st in second case | Mean 5.5 days | Fever, cough, chest pain, nausea and vomiting | Unknown | NSAIDs | 2 days |
| Muthukumar et al., 2021 [38]              | USA     | 52 years | Male | mRNA-1273 | 2nd | 1 day | Chest pain, fever, shaking chills, myalgias, and headache | Elevated | NSAIDs | Unknown |
| Isaak et al., 2021 [39]                   | Germany | 15 years | Male | mRNA-1273 | 2nd | 1 day | Chest pain | Elevated | NSAIDs | Unknown |
| Cereda et al., 2021 [40]                  | Italy   | 20 years | Male | mRNA-1273 | 2nd | 2 days | Chest pain and shortness of breath | Elevated | NSAIDs | Unknown |
| Watkins et al., 2021 [41]                 | USA     | 3 cases mean age 37.66 years | Male | mRNA-1273 | 2nd | 1 day | Chest pain, fever, shaking chills, myalgias, and headache | Elevated | NSAIDs | Unknown |
| Mansour et al., 2021 [42]                 | USA     | 2 cases mean age 23 years | Male | mRNA-1273 in all cases | 2nd in all cases | 1 day | Chest pain, fever, shaking chills, myalgias, and headache | Elevated | NSAIDs | Unknown |
| Levin et al., 2021 [43]                   | Israel  | 7 cases mean age 20.42 years | Male | mRNA-1273 in all cases | 2nd in all cases | Mean 7 days | Chest pain, myalgia, fever and headache | Elevated | NSAIDs | Unknown |
| Schauer et al., 2021 [44]                 | USA     | 13 cases mean age 15.07 years | Male | mRNA-1273 in all cases | 2nd in all cases | Mean 2.76 days | Chest pain, shortness of breath, fever and myalgia | Elevated | NSAIDs | Unknown |
| Shumkova et al., 2021 [45]                | Poland  | 23 years | Male | mRNA-1273 | 2nd | 1 day | Chest pain, shortness of breath, fever and myalgia | Elevated | NSAIDs | Unknown |
| Minocha et al., 2021 [46]                 | USA     | 17 years | Male | mRNA-1273 | 2nd | 2 days | Chest pain, shortness of breath, fever and myalgia | Elevated | NSAIDs | Unknown |
| Hasnie et al., 2021 [47]                  | USA     | 17 years | Male | mRNA-1273 | 1st | 3 days | Chest pain | Elevated | NSAIDs | Unknown |
| Starekova et al., 2021 [48]               | USA     | 25.2 years | Male | mRNA-1273 | 2nd | 3 days | Chest pain, fatigue, nausea, fever, chills and myalgia | Elevated | NSAIDs | Unknown |
| Koizumi et al., 2021 [49]                 | Japan   | 2 cases mean age 24.5 years | Male | mRNA-1273 | 2nd | 1 day | Chest pain | Elevated | NSAIDs | Unknown |
| McLean et al., 2021 [50]                  | USA     | 52 years | Male | mRNA-1273 | 2nd | 1 day | Chest pain | Elevated | NSAIDs | Unknown |

(continued on next page)
Table 1 (continued)

| Author/Year of publication | Country   | Age       | Gender | Type of COVID-19 vaccine | Dose | Days to symptom onset | Symptoms                      | Troponin level | LVEF <50% or LVEF >50% | Electrocardiogram (ECG) | Treatment | Length of hospital stay (days) | Outcome       |
|---------------------------|-----------|-----------|--------|--------------------------|------|-----------------------|-------------------------------|----------------|-------------------------|--------------------------|-----------|-------------------------------|---------------|
| Riedel et al., 2021 [52]  | Brazil    | 16 years  | Male   | Sinovac COVID-19 vaccine  | 2nd  | Unknown               | Chest pain and myalgia        | Elevated       | LVEF <50%               | Abnormal                 | Unknown   | Unknown                        | Recovered     |
| In-Cheol et al., 2021 [53] | Korea     | 24 years  | Male   | BNT162b2                 | 2nd  | 1 day                 | Chest pain                    | Elevated       | LVEF >50%               | Abnormal                 | Unknown   | 5 days                         | Recovered     |
| Nguyen et al., 2021 [54]  | Germany   | 20 years  | Male   | mRNA-1273                | 1st  | 1 day                 | Chest pain, fatigue and myalgia | Elevated       | LVEF >50%               | Abnormal                 | Unknown   | Unknown                        | Recovered     |
| Azadiki et al., 2021 [55] | Iran      | 70 years  | Male   | ChAdOx1 nCoV-19          | 1st  | 3 days                | Chest pain                     | Elevated       | LVEF >50%               | Abnormal                 | magnesium sulfate | 7 days                         | Recovered     |
| Sokolska et al., 2021 [56]| Poland    | 21 years  | Male   | BNT162b2                 | 1st  | 3 days                | Chest pain                     | Elevated       | LVEF >50%               | Abnormal                 | Unknown   | Unknown                        | Recovered     |
| Patel et al., 2021 [57]   | USA       | 5 cases   | Male   | BNT162b2 in 4 cases and mRNA-1273 in 1 case | 2nd in 4 cases and 1st in 1 case | Mean 2.2 days | Chest pain, dyspnea, nausea, headache and chills | Elevated in all cases | LVEF >50% | Abnormal in all cases | Colchicine, Ibuprofen and aspirin | Mean 1.8 days | Recovered                      |               |
| Kim et al., 2021 [58]     | Korea     | 29 years  | Male   | BNT162b2                 | 2nd  | 1 day                 | Chest pain                     | Elevated       | LVEF >50%               | Normal                   | corticosteroids and NSAIDs, Aspirin, heparin, beta-blocker and a mineralocorticoid antagonist Unknown | 7 days | Recovered                      |               |
| Ehrlich et al., 2021 [59] | Germany   | 40 years  | Male   | BNT162b2                 | 1st  | 6 days                | chest pain and shortness of breath, and fever | Elevated       | LVEF <50%               | Abnormal                 | Unknown   | 2 days                         | Recovered     |
| Schmitt et al., 2021 [60] | France    | 19 years  | Male   | BNT162b2                 | 2nd  | 3 days                | Chest pain and dyspnea         | Elevated       | LVEF >50%               | Abnormal                 | Methylprednisolone, lisinopril, and sublingual nitroglycerin and aspirin | 6 days | Recovered                      |               |
| Kadwalwala et al., 2021 USA | USA      | 38 years  | Male   | mRNA-1273                | 1st  | 2 days                | Chest pain, fatigue and fever  | Elevated       | LVEF <50%               | Abnormal                 | Unknown   | 6 days                         | Recovered     |
| Azir et al., 2021 [62]    | USA       | 17 years  | Male   | BNT162b2                 | 2nd  | 1 day                 | Chest pain                     | Elevated       | LVEF >50%               | Abnormal                 | Unknown   | 1 day                          | Recovered     |
| Gabriel Amir et al., 2022 Israel | Israel | 15 cases | Male   | BNT162b2 in all cases    | 2nd in 14 cases and 1st in 1 case | Median 4.7 days | Chest pain and fever | Elevated in all cases | LVEF >50% in 12 cases LVEF <50% in 3 case | Abnormal in 14 cases and normal in 1 case | colchicine, aspirin | Mean 5 days | Recovered                      |               |
| Ahmed SK 2022 [64]        | Iraq      | 7 cases   | Male   | BNT162b2 in 5 cases and mRNA-1273 in 2 cases | 2nd in all cases | Median 2.14 days | Chest pain, fever, fatigue, SOB | Elevated in all cases | LVEF >50% in 6 cases LVEF <50% in 1 case | Abnormal in all cases | colchicine and NSAIDs | Mean 2.4 days | Recovered                      |               |
| Mateusz Puchalski et al., 2022 Poland | Poland | 5 cases | Male   | BNT162b2 in all cases | 2nd in all cases | Median 6.4 days | Chest pain, fever, shoulder pain | Elevated in all cases | LVEF >50% in all cases | Abnormal in all cases | ACEI | Mean 12.3 days | Recovered                      |               |
| Carolyn M. Rosner et al., 2022 USA [65] | USA | 7 cases | Male   | BNT162b2 in 4 cases and mRNA-1273 in 2 cases and Jat in 1 case | 2nd in all cases | Median 3 days | Chest pain, SOB | Elevated in all cases | LVEF >50% in all cases | Abnormal in 6 cases and normal in 1 case | NA | NA | Recovered                      |               |
| Agata Łaźniak-Pfajfer et al., 2022 Poland | Poland | 3 cases | Male   | BNT162b2 in all cases | 2nd in 1 case and 1st in 2 cases | NA | Chest pain | Elevated in all cases | LVEF >50% in all cases | Abnormal in 1 case and normal in 2 cases | Colchicine, NSAIDs | NA | Recovered                      |               |
| Study, Year, and Country | No. of Cases | Gender Details | Cause | Major Symptoms | LVEF, Abnormalities | Treatment | Time to Recovery |
|-------------------------|-------------|----------------|-------|---------------|-------------------|-----------|-----------------|
| Yoshiki Murakami et al., 2022 [67] | 2 cases | Mean age: 32.5 | All of them were male | BNT162b2 in all cases | Elevated in all cases | LVEF >50% in all cases | Abnormal in 1 case and normal in 1 case | Mean 5.5 days |
| Farah Naghashzadeh et al., 2022 [68] | 1 case | 29 years | Female | rAd26 and rAd5 (Sputnik V vaccine) | Chet pain, Elevated LVEF | Elevated LVEF <50% | Abnormal methylprednisolone, prednisolone, and mycophenolate motile | 7 days Recovered |
| Chan-Hee Lee et al., 2022 [69] | 1 case | 22 years | Male | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% | Abnormal | 5 days Recovered |
| Xavier Fosch et al., 2022 [70] | 2 cases | 24 years | Male | BNT162b2 | Elevated LVEF | Elevated LVEF >50% | Abnormal | 7 days Recovered |
| Daniel A. Gomes et al., 2022 [71] | 2 cases | 32 years | Male | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% | Abnormal | 5 days Recovered |
| Eduardo Terán Brage et al., 2022 [72] | 3 cases | 62 years | Female | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% | Abnormal | 5 days Recovered |
| Arman Sharbatdaran et al., 2022 [73] | 1 case | 29 years | Male | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% | Abnormal | 5 days Recovered |
| Julia Moosmann et al., 2022 [74] | 2 cases | Mean age: 13 years | Male | BNT162b2 in all cases | Elevated LVEF | Elevated LVEF >50% | Abnormal in all cases | Median 7.5 days |
| Carlotta Sciaccaluga et al., 2022 [75] | 2 cases | Mean age: 20.5 years | Female | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% | Abnormal in all cases | Median 9 days Recovered |
| Arianne Clare C. Agdamag et al., 2022 [76] | 3 cases | 80 years | Male | BNT162b2 | Elevated LVEF | Elevated LVEF >50% | Abnormal | 14 days Recovered |
| Samuel Nunn et al., 2022 [77] | 4 cases | Mean age: 29.5 years | 3 cases were male and 1 case was female | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% | Abnormal in all cases | Median 3 days |
| Kanak Parmar et al., 2022 [78] | 4 cases | Mean age: 29 years | 3 cases were male and 1 case was female | mRNA-1273 in all cases | Elevated LVEF | Elevated LVEF >50% | Abnormal in 3 cases and normal in 1 case | Median 7.5 days |
| Mohammad Dlewati et al., 2022 [79] | 3 cases | Mean age: 48 years | Male | BNT162b2 | Elevated LVEF | Elevated LVEF >50% | Abnormal Metoprolol succinate, spironolactone, and NSAIDs | 2 days Recovered |
| Nobuko Kojima et al., 2022 [80] | 4 cases | Mean age: 17 years | Male | BNT162b2 | Elevated LVEF | Elevated LVEF >50% | Abnormal Metoprolol succinate, ramipril, and atorvastatin | 23 days Recovered |
| Katie A. Sharff et al., 2022 [81] | 3 cases | Mean age: 6 years | 4 cases were male and 2 cases were female | BNT162b2 | Elevated LVEF | Elevated LVEF >50% in 5 cases and LVEF <50% in 1 case | Abnormal in all cases | Median 1.5 days |
| Suresh Babu Chellappandian et al., 2022 [82] | 22 years | 4 cases | 3 cases were male and 1 case was female | mRNA-1273 | Elevated LVEF | Elevated LVEF >50% in all cases | Abnormal in 3 cases and normal in 1 case | Median 2 days |
| Arthan Shiyovich et al., 2022 [83] | 4 cases | Mean age: 31 years | Male | BNT162b2 in all cases | Elevated LVEF | Elevated LVEF >50% in all cases | Abnormal in 3 cases and normal in 1 case | Median 5.7 days |

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Oster et al. (2022) [12] concluded that the risk of myocarditis after the mRNA vaccine was increased after the second dose in adolescents and young males. This finding is matched with Patone (2022) [14], who mentioned the risk of myocarditis increased within a week of receiving the first dose of both adenovirus and mRNA vaccines and after the second dose of mRNA vaccine. On the other hand, Simone et al. (2021) [16] concluded no relationship between COVID-19 mRNA vaccination and post vaccination myocarditis.

The findings extend these observations, including the median onset of symptoms after vaccine administration was 3.5 days. The most common symptoms are chest pain, followed by myalgia/body aches and fever. These findings matched with Pillay et al. (2021) [15], who reported in a systematic review that most myocarditis cases had a short symptom onset of 2–4 days after a second dose, and the majority presented with chest pain. These findings matched with Oster et al. (2022) [12], who mentioned myocarditis was diagnosed within days of vaccination.

The diagnosis is often established by heart biopsy in patients with severe myocarditis. In patients with mild myocarditis, the diagnosis is based on compatible clinical findings and confirmed by elevated levels of blood markers or an electrocardiogram (ECG) indicative of cardiac injury, with new abnormalities on echocardiography or cardiac MRI [17].

Cardiac-specific investigations revealed that troponin levels were elevated in almost all cases, consistent with myocardial injury, which is associated with autoimmune processes matched with vaccine protein and the case immune system.

In the same lines as Lee et al. (2022) [1], a systematic review to investigate myocarditis following COVID-19 Vaccination in October 2020—October 2021, mentions that all reported cases have an elevated troponin level in keeping with myocardial injury.

In our study, less than one third of cases had left ventricle ejection fraction (LVEF) was less than 50%. Compared to patients with COVID-19 illness, patients with vaccine associated myocarditis had a higher LVEF.

This finding is consistent with Fronza et al. (2022) [18], who investigated myocardial injury patterns at MRI in COVID-19 Vaccine and discovered that more than half of the cases had more than 50% LVEF. Also, Shiyovich et al. (2022) [19], who analyzed myocarditis following the third (Booster) dose of COVID-19 vaccination, found that the mean left ventricular ejection fraction was 61 ± 7% (range 53–71%). Regional wall motion abnormalities were present in one of the patients only. Global T1 values were increased in one (25%) of the patients, while focal values were increased in 3 (75%) of the patients. Global T2 values were raised in one (25%) of the patients, while focal values were increased in all of the patients (100%). Global ECV was increased in three (75%) of the patients, while focal ECV was increased in all the patients (100%). LGE was present in all the patients.

In our systematic review and meta-analysis study, 88.5% of patients had abnormal changes in the electrocardiogram (ECG) result, regardless of the vaccine type.

Vidula et al. (2021) [20] support our findings by reporting two patients with clinically suspected myocarditis who presented with acute substernal chest pain and/or dyspnea after receiving the second dose of the vaccine and were found to have diffuse ST elevations on electrocardiogram (ECG), elevated cardiac biomarkers and inflammatory markers, and mildly reduced left ventricular (LV) function on echocardiography.

Also, Puchalski et al. [21] reported the findings of a case series regarding COVID-19-Vaccination-Induced Myocarditis in Teenagers. Electrocardiogram (ECG) patterns varied, but characteristic features of acute myocardial injury, including ST segment elevation or depression, and repolarization time abnormalities, were present in all cases.

Management of myocarditis remains mainly supportive and is based on restoring hemodynamic stability and the administration.
of guideline-directed heart failure and arrhythmia treatment. According to our findings, all cases were treated with NSAIDs, beta-blockers, calcium channel blockers, and diuretics. Patients with preserved ventricular function and non-severe features were often treated with colchicine or non-steroidal anti-inflammatory drugs. The median length of hospital stay was 5.28 days in 182 patients, and the vast majority of patients resolved symptoms and recovered, and only 3 patients died.

This finding broadly supports the work of other studies in this area. Woo et al. [22] reported that many patients who received anti-inflammatory agents such as NSAIDs, colchicine, steroids, and intravenous immunoglobulin recovered without further medical treatment, with a hospital stay lasting 3–6 days.

In accordance with the present results, previous studies have demonstrated that almost all of the cases experienced a prompt recovery with no residual cardiac dysfunction. The median length of stay for all myocarditis cases was around 2–3 days, with a range of 2–10 days [23].

5. Conclusion

In conclusion, these findings may help public health policy consider myocarditis in the context of the benefits of COVID-19 vaccination and assess the cardiac condition before the choice of vaccine, which is offered to male adults. In addition, it must be carefully weighed against the very substantial benefit of vaccination. Moreover, further research is required to assess the long-term consequences and other risk factors following immunization, specifically the mRNA vaccines.

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Author agreement statement

We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We confirm that all have agreed with the order of authors listed in our manuscript. We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions, and final approval of proofs.

Data availability statement

All relevant data are within the manuscript and its supporting information files.

Authors’ contributions

Conception and design SKA acquisition of data SKA, RAE, MGM, EAA analysis and interpretation of data SKA, MGM, RAE, EEA, drafting of the manuscript SKA, RAE MGM, EAA critical revision of the manuscript for important intellectual content statistical analysis SKA, MGM, RAE, EEA, PKI, AAK, ZHW administrative SKA, technical SKA, PKI, AAK, ZHW, supervision SKA, and all authors approving the final draft.

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There is no conflict to be declared.

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Appendix A. Supplementary data

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