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Systematic Review / Meta-analysis

Development of myocarditis and pericarditis after COVID-19 vaccination in adult population: A systematic review

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ABSTRACT

Objectives: A clear temporal relationship between myocarditis and pericarditis after COVID-19 vaccination has led to the belief that the vaccine may act as a trigger for these cardiologic complications. The aim of this systematic review is to explore the incidence, clinical presentation, management, and association between them.

Methods: We conducted a systematic literature search on Cochrane, MEDLINE, and EMBASE as per guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews). A total of 41 case reports and case series describing 97 patients, and 5 original articles describing 15,585,309 participants were selected as part of this review.

Results: Of the 97 reported cases describing vaccine-associated myocarditis/pericarditis, 67 (69%) patients received Pfizer-BioNTech and 25 (25.7%) received Moderna. The mean onset of symptoms after vaccine administration was 3.8 ± 4.5 days with three-quarters developing symptoms after the second dose. Chest pain (n = 88, 90%) and fever (n = 33, 34%) were the most common presenting complaints. Out of 97, 80 (82.5%) patients recovered while 4 (4.1%) patients expired. The pooled incidence of myocarditis and pericarditis extrapolated from original studies is 0.001% and 0.0004%, respectively. In the original studies, nearly all the cases of myocarditis and pericarditis were mild. Chest pain and fever were the most common presenting symptoms.

Conclusion: Myocarditis and pericarditis after the COVID-19 vaccine have been reported more in young adult males and are most likely to occur after the second dose of mRNA vaccines. The presentation is mild and the majority of the patients recover either completely or partially.

1. Introduction

Myocarditis is the inflammation of the myocardium that occurs most commonly due to viral illnesses although non-infectious etiologies have also been reported. It is believed that myocarditis and its complications are largely immune-mediated [1]. Myocarditis usually presents with chest pain, which can result from associated pericarditis, or occasionally, from coronary artery spasm. Acute myocarditis is frequently first diagnosed as nonischemic dilated cardiomyopathy in a symptomatic patient [2]. Pericarditis (inflammation of the pericardium) commonly presents with sharp, retrosternal chest pain that is relieved by sitting or leaning forward but gets exacerbated in the supine position, by coughing, and with inspiration [3].

COVID-19, caused by the novel coronavirus SARS-CoV-2, became a public health emergency of international concern (PHEIC) in January 2020 [4]. According to the latest statistics, over 317 million global cases of SARS-CoV-2 have been reported so far. Mass immunization campaigns have been initiated throughout the world as per the World Health Organization (WHO) recommendations. Multiple coronavirus vaccines are currently being administered throughout the world which includes mRNA based vaccines, (i.e. Pfizer-BioNTech, Moderna), recombinant adenoviral vector vaccines (i.e. Johnson & Johnson/Janssen, AAbbreviations: COVID-19, coronavirus disease 19.

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Oxford-AstraZeneca and Sputnik V), and the inactivated whole viral vaccines (i.e. Sinovac Biotech and Sinopharm) [5]. Given the rapid global spread and increased associated mortality, the emergency use approval was granted to COVID-19 vaccines before the completion of conventional and robust phases of clinical trials [6]. Therefore, some concerns have been raised regarding the safety as well as the efficacy of these vaccines.

Numerous case reports, case series, and retrospective studies have now suggested a possible link between myocarditis and Covid-19 mRNA vaccination. To explore this phenomenon, we planned to conduct a systematic review in which databases would be thoroughly searched to find out all literature available on post-vaccination myocarditis and pericarditis in adults. A compilation of all such cases will alert the physicians about rare but detrimental side-effects of vaccination and enhance their knowledge regarding the likely clinical presentation, prognosis, and management. The timely diagnosis followed by prompt treatment will ultimately lead to improved patient care.

Several other reviews have reported adverse events after COVID-19 vaccination [7]. To date, only one systematic review and meta-analysis evaluating myocarditis following COVID-19 vaccination has been published in the literature [8]. However, the review included a limited number of cases, focused only on mRNA vaccines, and lacked sufficient discussion on underlying pathogenic mechanisms. This indicates the need for a more comprehensive evidence synthesis that includes original articles and updated evidence. This systematic review aims to provide a detailed account of the development of myocarditis and pericarditis following the COVID-19 vaccination, and serves as a guide for researchers for re-evaluation, who may need to take into consideration this side-effect while developing new vaccines.

2. Methods

This systematic review is compliant with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines and has been registered with The International Prospective Register of Systematic Reviews (PROSPERO: CRD42021276596) [9] (Supplementary file_3).

2.1. Search strategy

The systematic literature search was conducted on the following three databases: MEDLINE (via PubMed), Cochrane, and Embase without any restriction of language, study design, country, and year of publication. The complete search string for PubMed is given in Table 1.

| Number | Search terms |
|--------|--------------|
| #1     | sars-cov-2 [All Fields] |
| #2     | “sars-cov-2” [mh] |
| #3     | covid [All Fields] |
| #4     | covid-19 [All Fields] |
| #5     | “covid-19” [mh] |
| #6     | coronavirus [All Fields] |
| #7     | “coronavirus” [mh] |
| #8     | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 |
| #9     | vaccine [All Fields] |
| #10    | “vaccines” [mh] |
| #11    | “vaccination” [mh] |
| #12    | #9 OR #10 OR #11 |
| #13    | #8 AND #12 |
| #14    | “COVID-19 Vaccines/adverse effects” [mh] |
| #15    | #13 OR #14 |
| #16    | myocarditis [All Fields] |
| #17    | “myocarditis” [mh] |
| #18    | pericarditis [All Fields] |
| #19    | “pericarditis” [mh] |
| #20    | #16 OR #17 OR #18 OR #19 |
| #21    | #15 AND #20 |

2.2. Study selection and data extraction

We considered all the peer-reviewed published studies that included the adult population (>19 years) who developed myocarditis and pericarditis following any type (mRNA, viral vector, and protein subunit) of COVID-19 vaccine. Review articles, editorials, preprints and those original articles that reported other side effects of vaccination but did not discuss myocarditis and pericarditis specifically were excluded. This review only included articles written in English language.

Articles were searched and extracted by two reviewers (M.F and H.A. C), and a third investigator (M.H.A.K) was there to resolve any discrepancies. Identified studies were uploaded to Mendeley and duplicates were removed. Initially, the articles were screened based on title and abstract, after which the full articles were reviewed. The retrieved results are summarized in the form of two tables. One table focuses on the demographics, medical history, and outcomes, whereas the second is based on relevant medical investigations and diagnostic findings. Continuous variables are presented as means ± standard deviations, and categorical variables are presented as absolute values and percentages. Microsoft Excel was used for data extraction and calculations carried out in this study. The references were added through Mendeley.

2.3. Quality appraisal

The quality of the included articles was assessed by the Joanna Briggs Institute Critical Appraisal Tool for case reports and case series and the Newcastle-Ottawa Scale quality assessment scale for cohorts (available in Supplementary file_1) [10,11]. Three reviewers (M.F, U.H, M.H.A.K) first independently scored each article and then awarded a consensus score to each. The score report is provided in the supplementary files. The systematic review has been self-evaluated through the AMSTAR 2 checklist (available in Supplementary file_2) [12]. As no Randomized Controlled trial was included in the review, the level of compliance with AMSTAR 2 came out to be “moderate”.

3. Results

The search of three databases identified 250 articles. Seventy-one articles were removed due to duplication and 96 articles were excluded due to irrelevance to the topic. After rigorous screening, 46 articles comprising case series, case reports [2,13–52] and original articles [53–57] were included in our review (Fig. 1).

3.1. Case series and case reports

A total of 97 patients were described in 41 case series and case reports. The demographic characteristics, clinical presentation, lab investigations, radiological findings, and treatment of the 97 patients have been elaborated in the form of two tables (Tables 2 and 3).

The mean age of patients was 29.34 ± 12.94 years (range 16–68). The highest number of cases were reported in the USA (n = 67, 69%), Janssen Johnson & Johnson (n = 67, 69%), and rest of the patients received Pfizer-BioNTech (n = 67, 69%,). The majority of the cases were seen in males (n = 83, 85.5%). Only 10 patients (10.3%) had a positive history of SARS-CoV-2 infection and 6 (6.1%) had a history of some cardiovascular disease. Out of the 97, most of the patients received Pfizer-BioNTech (n = 67, 69%) and rest of the patients received Moderna 25 (25.7%) Moderna (n = 67, 69%), Johnson & Johnson (n = 4, 4.1%) and AstraZeneca (n = 1, 1.0%). A total of 79 (81.4%) patients developed acute myocarditis, 9 (9.2%) myopericarditis or perimyocarditis, 3 (3%) acute pericarditis, 4 (4.1%) fulminant myocarditis, 1 (1.0%) each with fulminant pericarditis and lymphohistiocytic myocarditis. The majority of the patients developed the...
symptoms after the second dose of the vaccine ($n = 77, 79\%$). Chest pain ($n = 88, 90\%$), fever ($n = 33, 34\%$), dyspnea ($n = 18, 18.5\%$), and myalgias ($n = 18, 18.5\%$) were the most common presentations. The mean time between the administration of the vaccine and the development of symptoms was $3.8 \pm 4.53$ days.

On investigations, $62 (63.9\%)$ patients had ST-segment elevation, $12 (12.3\%)$ had normal ECG and ECG changes of $5 (5.1\%)$ patients were not mentioned. Echocardiogram findings demonstrated that $65 (67\%)$ patients had preserved ejection fraction, $27 (27.8\%)$ had decreased ventricular ejection fraction and echocardiogram findings were not mentioned for $5 (5.1\%)$. Most of the patients ($n = 88, 90.7\%)$ had elevated levels of serum cardiac troponin while almost half ($n = 55, 56.7\%)$ also had elevated levels of C-reactive protein. CMR findings were supportive for myocarditis or pericarditis in $84 (86.6\%)$ patients. In $11 (11.3\%)$ patients, CMR was not performed, and $2 (2\%)$ patients had their diagnosis confirmed by biopsy and Swan-Ganz catheterization, respectively. The management included colchicine ($n = 29, 29.8\%)$, beta-blockers ($n = 22, 22.6\%)$, aspirin ($n = 11, 11.3\%)$ and other anti-inflammatory drugs ($n = 21, 21.6\%)$. Out of $97, 80 (82.5\%)$ patients recovered, $4 (4.1\%)$ patients expired and follow-up was not mentioned for the remaining $13 (13.4\%)$ patients.

### 3.2. Original articles

There were $15,585,309$ participants included in five original articles. Three studies were conducted in USA (United States of America) and two in Israel. Out of $15,585,309$ participants, $6,095,639 (39.11\%)$ were females and $9,489,670 (60.8\%)$ were males. A total of $9,938,097 (63.7\%)$ participants received Pfizer/BioNTech, $882,128 (5.6\%)$ received Moderna and $62,008 (0.4\%)$ received Janssen/Johnson & Johnson. Out of these patients, $235 (0.001\%)$ developed myocarditis and $64 (0.0004\%)$ developed pericarditis. The mild cases of myocarditis among these were $194 (82\%)$ whereas all $64 (100\%)$ cases of pericarditis were described as mild. Majority of the patients presented with chest pain ($n = 177, 75\%)$, fever ($n = 71, 30\%)$ and dyspnea ($n = 23, 10\%). Investigations of these patients revealed raised troponin ($n = 190, 80\%),$ ECG changes ($n = 158, 67\%),$ Late Gadolinium Enhancement (LGE) ($n = 48, 20\%)$, left ventricular dysfunction (LVD) ($n = 14, 6\%)$ and abnormal EF ($n = 8, 3.4\%$). All the participants received the first dose of the vaccine while $9,047,460 (58\%)$ participants also received the second dose of the
Table 2: Demographics of patients with myocarditis and pericarditis after COVID-19 vaccine.

| Sr No | Case report | Domain Author, Year | Country reported | Number of patients | Age(years) Gender | Medical History | Type of Vaccine administered | Myocarditis/ pericarditis | Time between vaccine administration and development of myocarditis/ pericarditis |
|-------|-------------|---------------------|------------------|--------------------|-------------------|-----------------|-----------------------------|--------------------------|-------------------------------------------------------------|
| 1     | Case report | Cimaglia et al. (2021) [30] | Portugal         | 1                  | 24, Male          | E-cigarette smoking | Pfizer-BioNTech | Myocarditis                  | 60 h after second dose                                           |
| 2     | Case report | Nguyen et al. (2021) [48] | England          | 1                  | 20, Male          | Not significant    | Moderna         | Myocarditis                  | 12 h after first dose                                            |
| 3     | Case report | Watkins et al. (2021) [14] | USA              | 1                  | 20, Male          | COVID+, Tobacco+   | Pfizer-BioNTech | Myocarditis                  | 48 h after second dose                                            |
| 4     | Case series | Vidalia et al. (2021) [44] | USA              | 5                  | Patient-No-1 19, Male | Not significant | Pfizer-BioNTech | Myocarditis                  | 4 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-2 18, Male | Not significant | Moderna         | Myocarditis                  | 24 h after second dose                                           |
|       |             |                     |                  |                    | Patient-No-3 60, Female | Stress cardiopathy | Pfizer-BioNTech | Stress Cardiomyopathy        | 4 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-4 21, Female | Not significant | Pfizer-BioNTech | Pericarditis                 | 3 weeks after first dose                                        |
|       |             |                     |                  |                    | Patient-No-5 61, Female | HTN+            | Pfizer-BioNTech | Pericarditis                 | 4 weeks after second dose                                       |
| 5     | Case report | Albert et al. (2021) [43] | USA              | 1                  | 24, Male          | Not significant    | Moderna         | Myocarditis                  | 4 days after second dose                                        |
| 6     | Case report | Shaw et al. (2021) [32]  | USA              | 4                  | Patient-No, 1 24, Male | Not significant | Pfizer-BioNTech | Myocarditis                  | 4 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-2 31, Female | A history of confirmed COVID+ 7 months ago | Moderna         | Myocarditis                  | 25 days after first dose                                         |
|       |             |                     |                  |                    | Patient-No-3 16, Female | COVID+   | Pfizer-BioNTech | Myocarditis                  | 4 days after first dose                                         |
|       |             |                     |                  |                    | Patient-No-4 17, Female | Not significant | Pfizer-BioNTech | Myocarditis                  | 2 days after second dose                                         |
|       |             |                     |                  |                    | Patient-No-5 37, Male | Ex-smoker, alcoholic, HTN + ve | Pfizer-BioNTech | Myocarditis                  | 3 days after second dose                                         |
| 7     | Case report | Habib et al. (2021) [28] | Qatar            | 1                  | 27, Male          | Downs syndrome + ve | Pfizer-BioNTech | Fulminant pericarditis       | 2 days after second dose                                         |
| 8     | Case report | Abbate et al. (2021) [34] | USA              | 2                  | Patient-No-1 20, Male | Not significant | Pfizer-BioNTech | Fulminant myocarditis        | 9 days after first dose                                           |
|       |             |                     |                  |                    | Patient-No-2 29, Female | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-3 45, Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-4 16, Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-5 17, Female | Not significant | Pfizer-BioNTech | Myocarditis/ Pericarditis    |                                                            |
| 9     | Case series | Mouch et al. (2021) [19] | Israel           | 6                  | Patient-No, 1 24, Male | Not significant | Pfizer-BioNTech | Myocarditis                  | 72 h after second dose                                           |
|       |             |                     |                  |                    | Patient-No-2 20, Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-3 29, Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-4 45, Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-5 16, Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-6 17, Male | Not significant | Pfizer-BioNTech | Myocarditis/ Pericarditis    |                                                            |
| 10    | Case report | Ammirati et al. (2021) [63] | Italy            | 1                  | 56, Male          | COVID + ve         | Pfizer-BioNTech | Myocarditis                  | 3 days after second dose                                        |
| 11    | Case report | Cereda et al. (2021) [51] | Italy            | 1                  | 21, Male          | Not significant    | Pfizer-BioNTech | Myocarditis                  | 30 h after second dose                                          |
| 12    | Case series | Chamling et al. (2021) [21] | Germany          | 3                  | Patient-No, 1 68, Female | Tobacco+, CVD+   | AstraZeneca | Myocarditis                  | 24 h after first dose                                           |
|       |             |                     |                  |                    | Patient-No-2 25, Male | Smoker +, ve,     | Pfizer-BioNTech | Myocarditis                  | 10 days after first dose                                        |
|       |             |                     |                  |                    | Patient-No-3 20, Male | Not significant | Pfizer-BioNTech | Myocarditis                  | 3 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-4 30, Male | Not significant | Pfizer-BioNTech | Myocarditis                  | 72 h after second dose                                          |
| 13    | Case report | D’Angelo et al. (2021) [52] | Italy            | 1                  | 67, Male          | HTN+, T2DM, Hyperlipidemia, CAD with CARG, CHD, COPD, GERD | Moderna         | Myocarditis                  | 6 h after second dose                                           |
| 14    | Case report | Deb et al. (2021) [18]  | USA              | 1                  | Patient-No, 1 Male | (35–40 year)       | Pfizer-BioNTech | Myocarditis                  | 4 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-2 Male (16–20 year) | Not significant | Pfizer-BioNTech | Myocarditis                  | 3 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-3 Male (20–25 year) | Not significant | Moderna         | Myocarditis                  | 4 days after second dose                                        |
| 15    | Case series | Dickey et al. (2021) [30] | USA              | 6                  | Patient-No, 1 Male | Not significant | Pfizer-BioNTech | Myocarditis                  | 2 days after second dose                                        |
|       |             |                     |                  |                    | Patient-No-2 Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-3 Male | Not significant | Moderna         | Myocarditis                  |                                                            |
|       |             |                     |                  |                    | Patient-No-4 Male | Not significant | Pfizer-BioNTech | Myocarditis                  |                                                            |

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| Sr No | Domain | Author, Year | Country reported | Number of patients | Age(years) | Gender | Medical History | Type of Vaccine administered | Myocarditis/ Pericarditis | Time between vaccine administration and development of myocarditis/ pericarditis |
|-------|--------|--------------|------------------|-------------------|------------|--------|----------------|-----------------------------|--------------------------|------------------------------------------------------------------------|
| 16    | Case report | Ehrlich et al. (2021) [36] | Germany | 1 | Male (20-25 year) | Patient 5 | Male | Not significant | Pfizer-BioNTech | Myocarditis | 4 days after second dose |
| 17    | Case report | Hanie et al. (2021) [39] | USA | 1 | Male (16-20 year) | Patient 6 | Male | Not significant | Pfizer-BioNTech | Myocarditis | 3 days after second dose |
| 18    | Case report | Hudson et al. (2021) [33] | USA | 2 | 40, Male | Patient 1 | Not significant | Pfizer-BioNTech | Myocarditis | 2 day after first dose |
| 19    | Case report | Larson et al. (2021) [17] | Italy | 8 | 22, Male | Patient no 1 | Not significant | Moderna | Myocarditis | 3 days after second dose |
| 20    | Case Report | Khogali et al. (2021) [46] | Qatar | 1 | Female | Patient no 3 | Not significant | Pfizer-BioNTech | Myocarditis | 2 days after first dose |
| 21    | Case Report | King et al. (2021) [23] | USA | 1 | Male | Patient no 1 | Not significant | Moderna | Myocarditis | 3 days after second dose |
| 22    | Case Report | Koizumi et al. (2021) [35] | Japan | 2 | 29, Male | Patient No 1 | Not significant | Pfizer-BioNTech | Myocarditis | 5 days after second dose |
| 23    | Case Report | Mannour et al. (2021) [15] | USA | 2 | 25, Male | Patient No 1 | Not significant | Moderna | Myocarditis | 2 days after second dose |
| 24    | Case Report | Matta et al. (2021) [42] | India | 1 | 21, Female | Patient No 2 | Not significant | Moderna | Myocarditis | 4 days after second dose |
| 25    | Case Report | Muthukumar et al. (2021) [27] | USA | 1 | 52, Male | Patient No 2 | Not significant | Pfizer-BioNTech | Myocarditis | 3 days after second dose |
| 26    | Case Report | Nassar et al. (2021) [26] | USA | 1 | 70, Female | Patient No 2 | Not significant | Pfizer-BioNTech | Myocarditis | 2 days after second dose |
| 27    | Case Report | Nevet et al. (2021) [38] | Israel | 3 | 20, 29, and 24 years old men | Patient No 3 | Not significant | Pfizer-BioNTech | Myocarditis | 3 days after second dose |
| 28    | Case Report | Patel et al., 2021 [31] | USA | 3 | 37, Male | Patient No 4 | Not significant | Pfizer-BioNTech | Myocarditis | 2 days after second dose |

(continued on next page)
| Sr No | Domain Author, Year Country | Number of patients | Age(years) Gender | Medical History | Type of Vaccine administered | Myocarditis/ Pericarditis | Time between vaccine administration and development of myocarditis/ pericarditis |
|-------|-------------------------------|--------------------|-------------------|-----------------|-------------------------------|--------------------------|---------------------------------|
| 30    | Case series Rosner et al., 2021 [2] USA Seven (7) | Patient no.5 20, Male Not significant | Pfizer-BioNTech | Acute myocarditis | 3 days after second dose |
|       |                               | Patient no.1 28, Male Not significant | Janssen (Ad.26. COV2.S) | Acute myocarditis | 5 days after administration of dose |
|       |                               | Patient no.2 39, Male Not significant | Pfizer-BioNTech | Acute myocarditis | 3 days after second dose |
|       |                               | Patient no.3 39, Male Not significant | Moderna | Acute myocarditis | 4 days after first dose |
|       |                               | Patient no.4 24, Male Not significant | Pfizer-BioNTech | Acute myocarditis | 7 days after second dose |
|       |                               | Patient no.5 19, Male Not significant | Pfizer-BioNTech | Acute myocarditis | 2 days after second dose |
|       |                               | Patient no.6 20, Male COVID + history | Pfizer-BioNTech | Acute myocarditis | 3 days after second dose |
|       |                               | Patient no. 7 23, Male COVID + history | Pfizer-BioNTech | Acute myocarditis | 3 days after second dose |
| 31    | Case report Singh et al., 2021 [60] USA One (1) | 24, Male Occasional alcoholic | Pfizer-BioNTech | Acute myocarditis | 3 days after second dose |
| 32    | Case report Sokolska et al., 2021 [20] Poland One (1) | 21, Male Asthma in childhood, history of appendectomy, pollen and pet allergy | mRNA COVID-19 vaccination (Comirnaty, Pfizer) | Acute myocarditis | 3 days after first dose |
| 33    | Case series Starekova et al., 2021 [25] USA Five (5) | Patient no.1 21, Male Not significant | Pfizer-BioNTech | Acute myocarditis | 2 days after second dose |
|       |                               | Patient no2 32, Female Not significant | Pfizer-BioNTech | Acute myocarditis | 3 days after second dose |
|       |                               | Patient no.3 17, Male Not significant | Pfizer-BioNTech | Acute myocarditis | 2 days after second dose |
|       |                               | Patient no.4 18, Male Not significant | Moderna | Acute myocarditis | 3 days after second dose |
|       |                               | Patient no.5 38, Male Not significant | Moderna | Acute myocarditis | 3 days after second dose |
| 34    | Case report Tailor et al., 2021 [47] USA One (1) | 44, Male Former smoker, Drug history: Albuterol, Salmetrol-fluticasone Anagrelide | Moderna | Acute myocarditis | 4 days after second dose |
| 35    | Case report Ujorta et al., 2021 [37] USA One (1) | 62, Female Medical history significant for melanoma status post-surgical resection and treatment with Pembrolizumab over one year prior as well as essential thrombocytosis currently receiving treatment with Anagrelide | Janssen Johnson & John-son (Ad.26.COV2.S) | Lymphohistiocytic myocarditis | 4 days after vaccine |
| 36    | Case series Verma et al., 2021 [41] USA Two (2) | Patient no.1 45, Female Not significant | Pfizer-BioNTech | Fulminant myocarditis | 10 days after first dose |
|       |                               | Patient no2 42, Male Not significant | Moderna | Fulminant myocarditis | 14 days after second dose |
|       |                               | 34, Male Not significant | Moderna | Perimyocarditis | 1 day after second dose |
| 37    | Case report Williams et al., 2021 [50] USA One (1) | 7 Patient | 20, Male ADHD | Pfizer-BioNTech | Myocarditis | 1 day after second dose |
|       |                               | 2 Patient No 1 | 19, Male Geliac disease | Pfizer-BioNTech | Myocarditis | 1 day after second dose |
|       |                               | 3 Patient No 2 | 19, Male Allergic asthma | Pfizer-BioNTech | Myocarditis | 1 day after second dose |
|       |                               | 4 Patient No 3 | 22, Male Not significant | Pfizer-BioNTech | Myocarditis | 5 day after second dose |
|       |                               | 5 Patient No-5 | 24, Male Not significant | Pfizer-BioNTech | Myocarditis | 2 days after second dose |
|       |                               | 6 Patient- No.6 | 21, Male Myocarditis 5 years ago | Pfizer-BioNTech | Myocarditis | 5 days after second dose |
|       |                               | 7 Patient- No.7 | 18, Male Not significant | Pfizer-BioNTech | Myocarditis | 2 days after second dose |
| 39    | Case report Patrignani et al. (2021) [22] Italy 1 | 56, Male COVID+ 5 months ago | Pfizer-BioNTech | Myocarditis | 4 days after first dose |
| 40    | Case report Sulemankhil et al.(2021) [49] USA 1 | 33, Male History of asthma and sleep apnea | Janssen Johnson & John-son (Ad.26.COV2.S) | Myocarditis | 24 h after vaccination |
| 41    | Case report Garcia et al. (2021) [13] Spain 1 | 39, Male History of asthma, autoimmune hypothyroidism, chronic atrophic gastritis, an isolated episode of | Pfizer-BioNTech | Pericarditis | 6 h after second dose |

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HTN: Hypertension, T2DM: type 2 Diabetes Mellitus.

Hyperactivity Disorder, GERD: Gastroesophageal Reflux Disease, COVID: Coronavirus Disease, CHD: Coronary Heart Disease, CABG: Coronary Artery Bypass Grafting, HTN: Hypertension, T2DM: type 2 Diabetes Mellitus.

COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, CVD: Cardiovascular Disease, CAD: Coronary Artery Disease, ADHD: Attention Deficit Hyperactivity Disorder, GERD: Gastroesophageal Reflux Disease, COVID: Coronavirus Disease, CHD: Coronary Heart Disease, CABG: Coronary Artery Bypass Grafting, HTN: Hypertension, T2DM: type 2 Diabetes Mellitus.

Table 3
Clinical Presentation, Lab investigations and Diagnostic findings in patients with myocarditis and pericarditis after COVID-19 vaccine.

| Sr No | Domain | Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|-------|--------|--------------|-------------------|--------------|------------------------|-------------------|-----------|------------------------------------------|---------------------|
| 1     | Case   | Cimaglia et al. (2021) [32] | Chest pain exacerbated by deep and aVF, mild ST elevation and supine depression in V1 to V3 | ST elevation in I, III, LVEF 45% | Normal ECG | Troponin T 1.304 ng/L, C-repressive protein 1.9 mg/dl | Anti-inflammatory therapy | Mildly dilated LV with normal EF and no regional wall motion abnormality | Discharged on beta blocker and lisinopril, recovered and discharged |
| 2     | Case   | Nguyen et al. (2021) [43] | Fever, myalgia, fatigue, and growing mid-sternal bunting chest pain without radiation 12 h after vaccine administration | LVEF = 53-56% | Not mentioned | Cardiac troponin T (333 pg/mL), C-reactive protein (19.6 mg/L) | Not mentioned | Subepicardial and intramural LGE in mid and Discharged | Subepicardial and intramural LGE in mid and Discharged |
| 3     | Case   | Watkins et al. (2021) [44] | Cardiac pain radiating to the left side | LVEF 59% | Troponin increased to a maximum of 108 ng/L | Colchicine, metoprolol, and ibuprofen. | CMR positive for myocarditis | Recovered and discharged |
| 4     | Case   | Vidula et al. (2021) [45] | Acute substernal chest pain, dyspnea | LVEF: 47%; Diffuse ST elevations | LVEF: 59%, diffuse ST sub-sternal chest pain elevations | Troponin T: 0.129 ng/mL, CRP: 74.2 mg/L | Lisinopril and metoprolol succinate | CMR revealed mild hypokinesis of the basal to mid-lateral wall with elevated corresponding T1 value, elevated T2 value and sub-epicardial delayed enhancement in the lateral wall. | Discharged |
| 5     | Case   | Albert et al. (2021) [46] | Substernal chest pain| Normal ECG with LVEF within 65% | LVEF = 44% | Not mentioned | Troponin T: 0.129 ng/mL | Cardiac MRI not performed | Discharged |
| 6     | Case   | Shaw et al. (2021) [47] | Chest pain | LVEF: 60%, pericardial effusion | Not mentioned | Not mentioned | Cardiac MRI not performed | Discharged |

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### Table 3 (continued)

| Sr Domain/Author, Year Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|------------------------------------------|--------------|------------------------|-------------------|-----------|------------------------------------------|-------------------|
| Chest pain                               | Not mentioned| ST-segment elevation    | Not mentioned     | Troponin I 4.35 ng/mL, Troponin I 5.41 ng/mL | Not mentioned | CMR demonstrated LVEF \( \geq 64\% \), epicardial edema | Discharged from the hospital after 73 days, LVEF 59%, mid myocardial LGE of the same affected walls |
| Chest pain                               | Not mentioned| ST-segment elevation    | Not mentioned     | Troponin I 4.35 ng/mL, Troponin I 5.41 ng/mL | Not mentioned | CMR demonstrated LVEF \( \geq 64\% \), epicardial edema | Discharged from the hospital after 73 days, LVEF 59%, mid myocardial LGE of the same affected walls |
| Presented with chest pain preceded by generalized body aches, fever, chills, and headache for one-day | Mild ST-segment elevation | Ejection fraction (EF) Troponin T (troponin T = 1138 ng/mL) | Not mentioned | Immunosuppressive Therapy Methylprednisolone 1000 mg | Not mentioned | CMR revealed an early and late faint subepicardial enhancement of the basal lateral myocardium | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Fever, cough, chest pain, nausea, and vomiting, hypotension and tachycardia | LVEF 20% | CRP (13.1 mg/dL), | Not significant | CRP 5.6 mg/dL | LVEF of 35%, small pericardial effusion, delayed enhancement after hospital for chest pain | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Presented in cardiogenic shock | ST-segment elevations | Normal CRP | Not significant | LVEF of 15% | Immunosuppressive Therapy Methylprednisolone | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest pain                               | Diffuse ST elevation, inverted T lead III | Normal CRP | 58.1 mg/L; NSAID and colchicine Troponin T - 589 ng/mL | T2 showed mild myocardial edema of the basal septum | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest discomfort                         | ST elevation V2-6, LVEF of 50–55% sinus tachycardia | ST depression 86.0 mg/L, NSAID and colchicine Troponin T - 876 ng/L | Not mentioned | Ibuprofen and colchicine | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest pain                               | Normal study | Diffuse PR depression | Normal CRP | Ibuprofen and colchicine | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest pain                               | ST elevation: I, aVL, V3-Slnverted T, ST depression: III, aVF | LVEF- 50–55%. | Normal CRP | Ibuprofen and troponin-1 14350 Colchicine ng/L | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest pain                               | ST elevation V2-4 | Normal | Normal CRP | Ibuprofen and troponin-1 14350 Colchicine ng/L | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest pain                               | ST elevation I II aVL, V2-6SI III | Normal | CRP - 5.47 mg/L, Ibuprofen and Troponin T 1130 Colchicine ng/L | T2 sequence showed mild myocardial edema of the basal septum | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). |
| Chest pain                               | Minimal ST elevation on | Not mentioned | Troponin T 289 ng/mL, and C-NSAIDs | LVEF (62%), There was focal subepicardial myocardial LGE of the same affected walls | Discharged from the hospital after 73 days, normal 905 ms-1050 ms, epicardial fibrosis was observed on LGE imaging and interstitial expansion by extracellular volume fraction mapping (40%–44%, normal <28%). | (continued on next page)
| Sr No | Domain/Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|-------|---------------------|-------------------|-------------|------------------------|-------------------|----------|----------------------------------------|-------------------|
| 1     | Cereda et al. (2021) | Fever and cardiac sounding chest pain, retromental pain, nausea, and profuse sweating | Diffuse ST elevation with slightly widened QRS | Normal | Troponin I: 6.53 ng/mL, C-reactive protein: 2.4 mg/dL | Biopsodiol and ramipril (beta-blocker + ACEI) | LV-EF [%]: 67 | Epicardial edema and nonischemic delayed enhancement | Discharged |
| 2     | Chamling et al. (2021) | Acute chest pain with radiation to her left shoulder | NOT significant | C-reactive protein Not mentioned | | LV-EF [%]: 57 | | No follow-up mentioned |
| 3     | D’Angelo et al. (2021) | Dyspnea, constrictive Subsegment elevation fraction, mild pericardial effusion | Preserved ejection fraction | Normal | Troponin I (12.564.80 pg/mL), C-reactive protein (39.6 mg/L), | Biopsodiol, acetylsalicylic acid, prednisolone. | LGE showed subepicardial enhancement of the myocardium | Discharged |
| 4     | Deb et al. (2021) | Dyspnea, fever, and chills, nausea, orthopnea, and increasing fatigue | Not significant | LVEP: 50%-54% | Troponin of 180.8 mg/L, CRP: supplemental oxygen therapy | | NOT mentioned | Recovered and Discharged |
| 5     | Dickey et al. (2021) | Positional and pleuritic chest pain, neck pain, chills and myalgias | Interfocalateral ST elevation | Ejection fraction: 45% | Peak cardiac troponin I (ng/mL): 5.41 | | | Recovered and Discharged |
| 6     |     | Pleuritic and positional chest pain, elevation rhinorrhea, headache and fever with 3 days into hospitalization. | Diffuse ST elevation | Ejection fraction: 53% | Peak cardiac troponin I (ng/mL): 38.3 | | | Recovered and Discharged |
| 7     |     | Pleuritic and positional chest pain, elevation rhinorrhea, headache and fever with 3 days into hospitalization. | Sinus rhythm with diffuse ST elevation | Ejection fraction: 50% | Peak cardiac troponin I (ng/mL): 18.94 | | | Recovered and Discharged |
| 8     |     | Chest pain radiating to back, myalgia, malaise and fever | Sinus rhythm with diffuse ST elevation | Ejection fraction: 48% | Peak cardiac troponin I (ng/mL): 13.4 | | | Recovered and Discharged |
| 9     |     | Pleuritic and positional chest pain, headache | NOT significant | Ejection fraction: 46% | Peak cardiac troponin I (ng/mL): 5.21 | | | Recovered and Discharged |
| 10    |     | Non-positional chest pain and myalgias | Ectopic atrial rhythm with diffuse ST elevation | Ejection fraction: 50% | Peak cardiac troponin I (ng/mL): 19.7 | | | Recovered and Discharged |

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| Sr No | Domain Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|-------|---------------------|-------------------|--------------|-------------------------|-------------------|-----------|------------------------------------------|-------------------|
| 16    | Ehrlich et al. (2021) [36] | Fever, headache, chest pain and dyspnea. | Sinus rhythm | Ejection fraction: 45% | Troponin T concentration of 952 ng/L, elevated C-reactive protein (50.9 mg/L) | Therapy with acetylsalicylic acid, unfractionated heparin, an ACE inhibitor, a beta-blocker, and a mineralocorticoid antagonist was started. | Inflammation of myocarditis Cardiac MRI revealed increased left ventricular wall thickness with a septal thickness of 16 mm at maximum and a persistent myocardial inflammation throughout the left ventricle: myocardial hyper-intensities on T2w images indicating myocardial edema were detected in the left ventricle, primarily in the basal and mid inferoseptal and anterolateral segments as well as in the apical lateral segment Normal LVEF (58%), Mild adjacent pericardial LGE Recovery and Discharged | |
| 17    | Hasnie et al. (2021) [39] | Sharp subternal non-Diffuse ST radiating chest pain, elevation. | Normal ECG | Troponin:1.05 ng/ml (<0.09), C-reactive protein: 3.6 mg/dL. | Aspirin, colchicine, metoprolol | Aspirin and colchicine, and ibuprofen | Patchy subepicardial delayed enhancements | Recovered and Discharged |
| 18    | Hudson et al. (2021) [33] | Fever, chills, myaligaDiffuse ST segment LVEF: 50%, on day +1, followed elevation with by chest pain day +3 depression in aVR | Normal | Troponin:1.5 ng/ml (<0.09), C-reactive protein: 3.6 mg/dL. | Aspirin and colchicine | Normal Troponin:1.5 ng/ml (<0.09), C-reactive protein: 3.6 mg/dL. | Patchy subepicardial and midmyocardial delayed enhancements | Recovered and Discharged |
| 19    | Larson et al. (2021) [17] | Fever, chills, myalgiaDiffuse ST segment LVEF: 50%, on day +1, chest pain, dyspnea on day +3 | Chest pain Diffuse ST segment LVEF: 47%, elevation | Troponin:5.20 ng/mL, CRP: 9.5 mg/dL. | Prednisone, colchicine | Edema, delayed enhancement, pericardial effusion | Hemodynamically stable | Recovered and Discharged |
|       |                     |                   |              |                        |                   |          |                                          |                   |
| 20    | Khogali et al. (2021) [46] | High-grade fever, fatigue, myalgia and headache, multi-organ failure, deranged liver function and DIC | Diffuse ST segment elevation and short(EP) of 27% increase in pericardial effusion, and signs of pericardial tamponade. | Troponin T concentration of 98 ng/L reaching up to 1632 ng/L, CRP = 53.7 mg/L | Dobutamine, colchicine, CMR not mentioned and aspirin | Dobutamine, colchicine, CMR not mentioned | Admitted to ICU due to hemodynamic instability and the presence of combined hypovolemic, obstructive and cardiogenic shock. However recovered after 3 weeks and was discharged. | (continued on next page) |
### Table 3 (continued)

| Sr No | Domain/Author, Year | Clinical Features | ECG Findings | Echocardiogram Findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|-------|---------------------|-------------------|--------------|-------------------------|-------------------|-----------|-----------------------------------------|-------------------|
| 21 Case Report | Kim et al., 2021 [16] | Chest pain that was not related with effort or labor; an atypical dull nature on the subternal area, and non-radiating and constant discomfort. Myalgias, fatigue | Mild ST-segment elevation in leads II,V6, and V2-6 | Minimal periocardial effusion. GLS bulls map revealed the worsened strain value in basal inferior and inferolateral segments, particularly in epicardium than endocardium. | Troponin-I 2.28 ng/ml, C-reactive protein 7.7 mg/dL | Symptomatic therapy | Abnormal findings on CMR, Recovered and the subepicardial pattern of discharged LGE in basal inferior and inferolateral segment | 
| 22 Case Series | King et al., 2021 [25] | Chest pain | Diffuse ST elevation and downslping PR depressions | LVEF = 55-60%, with basal inferior and basal inferolateral hypokinesis | Troponin of 14,045 pg/ml and an elevated CRP | Specific Treatment not mentioned | CMR revealed LGE involving the basal inferior, of hospitalization basal to mid inferolateral, mid anterolateral, apical lateral, apical septal, and apical inferolateral wall segments in a subepicardial distribution pattern, consistent with myocarditis. | Discharged on 3rd day |
| 23 Case Series | Koizumi et al., Worsening chest pain | ST-elevation leads II, III, aVF and V3-6 | Based on ECG and Labs findings | LVEF of 45% moderate hypokinesis of the apex and apical septum. | Troponin-I was 22,638 and CRP was markedly elevated | Specific treatment not mentioned | Outpatient CMR is pending Chest pain resolved the following day. He was discharged on hospital day 5. | 
| 24 Case Series | Mansour et al., Fever and chills, Six hours later, developed substernal chest pain | Mild concave ST elevations | LVEF = 55% | Based on ECG and Labs findings | Troponin-I was 2447 pg/ml and CRP was notably elevated | Specific treatment not mentioned | Endomyocardial biopsy showed no inflammatory cell infiltration | Discharged the following day. |
| 25 Case Report | Matta et al., 2021 [42] | Sharp, central, non-radiating chest pain associated with fatigue | Normal sinus rhythm without any ST-T changes. | Elevation of troponin-I Aspirin 325 mg oral once CMR not mentioned. | Elevated troponin-I of 1.3 ng/mL. The patient improved clinically and was discharged home on metoprolol. | Stabilized on same day and discharged on 3rd day | 
| 26 Case Report | Muthukumar et al., 2021 [27] | High fevers, shaking chills, myalgias, and a headache. | Sinus rhythm with LVEF = 54% | Arrhythmia with incomplete right bundle branch block | Troponin I peaked at 6770 ng/L, C-reactive protein elevated | Low-dose lisinopril and carvedilol, Midmyocardial and subepicardial linear and nodular LGE in the infarceoseptal, inferolateral, | At the time of discharge, the patient remained asymptomatic, and his high-sensitivity | (continued on next page) |

Worsening chest pain Slight ST elevation NOT significant

**Note:** ECG findings may vary and are presented as an example to illustrate the study's observations. The detailed clinical and investigative findings are provided within the table for reference.
| Sr No | Domain/Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criterias (CMR imaging findings) | Additional Comments |
|-------|---------------------|-------------------|--------------|------------------------|------------------|-----------|-------------------------------------------|-------------------|
| 27 Case | Nassar et al. 2021 [26] | Developed dyspnea | Sinus tachycardia | LVEF = 55% depression and PR segment elevation in lead AVR | Serum Tn (ng/mL) = 37 C-reactive protein (mg/l) = 50 | Aspirin and colchicine | Subepicardial LGE and myocardial edema in the basal inferior, basal inferolateral, and apical lateral LV segments. | Discharged home in stable clinical condition after 48 h of observation |
| 28 Case | Nevet et al. 2021 [38] | Acute fever and chest pain | Diffuse PR segment LVEF = 60% depression and PR segment elevation | Serum Tn (ng/mL) = 49 C-reactive protein (mg/l) = 109 | Colchicine and high-dose ibuprofen | Discharged in stable condition | | |
| 29 Case | Patel et al. 2021 [31] | Chest pain, Headache, generalized malaise | Diffuse PR segment LVEF = 55% depression and PR segment elevation in lead aVR | Serum Tn (ng/mL) = 26 ESR 32 mm/hr | None | CMR showed subepicardial LGE and myocardial edema. | Discharged in stable condition | |
| 30 Case | Rosner et al. 2021 [2] | Chest pain at rest, non-exertional | ST elevation | LVEF = 51%, mid global hypokinesis | Cardiac troponin I 17.08 ng/mL | Beta blockers, ACE inhibitors | CMR showed subepicardial LGE and myocardial edema. | Recovered and Discharged |
|       |                     | non-exertional; no fevers, cough |                        |                        |                  |                        | Patchy mid subepicardial LGE | Recovered and Discharged |
|       |                     | ing, or dyspnea |                        |                        |                  |                        |                            | |
|       |                     | Chest pain associated with dyspnea; worse when lying left transverse inversion V1 and with inspiration | PR depression in II, LVEF = 35-40% AVF, V4-V6, T | Cardiac troponin I 11.01, C-reactive inhibitor, aspirin, and protein peak, mg/clopidogrel dl = 1.3 | Cardiac troponin I mg/mL peak = 110, C-reactive protein peak, mg/dl = 5.1 | Left ventricular ejection fraction = 56% (no regional wall motion abnormalities) LGE = Subepicardial LGE, no pericardial thickening or effusion | Recovered and Discharged |
|       |                     | Fever, chills, dyspnea, and chest heaviness/pain symptoms | Not significant | LVEF = 61% | Cardiac troponin I 13 mg/mL peak = 5.7, C-reactive protein peak, mg/dl = 11.70 | Left ventricular ejection fraction = 52%, Multiblobal sub-epicardial and midmyocardial LGE | Recovered and Discharged |
|       |                     | Intermittent, positional chest pain with left arm numbness and tingling | Not significant | LVEF = 53% | Cardiac troponin I 3 days IV steroids | Left ventricular ejection fraction = 48% | Recovered and Discharged |
|       |                     | Midsternal sharp chest pain, waxing/and po- stional; | Not significant | LVEF = 55% | Cardiac troponin I mg/mL peak = 44.8, C-reactive | Left ventricular ejection fraction = 48% Midmyocardial LGE | Recovered and Discharged |

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### Table 3 (continued)

| Sr Domain/Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|------------------------|-------------------|--------------|-------------------------|--------------------|-----------|------------------------------------------|---------------------|
| 31 Case report Singh et al., 2021 [40] | Chest pain (left-sided, ST-depression in severe, constant, non-lead III radiating, was associated with headache) | Diffuse ST elevation | LVEF = 58% | Troponin-1 peak (ng/mL) peak = 8.36, C-reactive protein peak, mg/dl = 8.2 | No specific treatment mentioned | Left ventricular ejection fraction = 52%, Subepicardial LGE T2 – inferior wall myocardial edema | The patient was hospitalized for 4 days and discharged in a stable condition. He was seen in an outpatient clinic 6 weeks later, is doing well and is back at work. |
| 32 Case report Sokolksa et al., 2021 [20] | Severe chest pain | Q wave and ST-segment elevation in leads II, III and aVF | LVEF = 58% | High-sensitivity troponin (6490-6559 pg/mL, reference range <34 pg/mL), C-reactive protein (82 mg/L; reference range <5 mg/L/L), | Not mentioned | Diffuse subepicardial LGE | Recovered and Discharged |
| 33 Case series Starekova et al., 2021 [25] | Chills, headache, fever, chest discomfort and pain, dyspnea | Diffuse ST elevations | LVEF = 32% | Troponin-1 at peak (ng/mL) = 6.940–6559 pg/mL, C-reactive protein (82 mg/L), | Not mentioned | Linear, midmyocardial septum, epicardial LGE | Follow-up not mentioned |
| | Headache, body ache, fatigue, chest discomfort and pain | Nonspecific T-wave abnormality | LVEF = 64% | Troponin-I at peak (ng/mL) = 3.82 | Not mentioned | Pericardial enhancement and small effusion. | Follow-up not mentioned |
| | | diffuse ST elevations | LVEF = 53% | Troponin-I at peak (ng/mL) = 1.02BNP (pg/mL) = 75 | Not mentioned | Epicardial LV, Pericardial enhancement, no effusion. | Follow-up not mentioned |
| | Subjective Mild Fever, Chills, Malaise, Nausea, Chest pain | Nonspecific T-wave abnormality | LVEF = 57% | Troponin-I at peak (ng/mL) = 14.65 | Not mentioned | Epicardial LV | Follow-up not mentioned |
| | Myalgias, Malaise, Nausea, lightheadedness, chest pain | Inferolateral T-wave inversion | LVEF = 54% | Troponin-I at peak (ng/mL) = 4 | Not mentioned | LGE: epicardial LV, Pericardial enhancement and borderline effusion, | Follow-up not mentioned |
| 34 Case report Tailor et al., 2021 [47] | Severe chest pain radiating to both arms, associated with limb and precordial leads | ST segment elevation in lateral global hypokinesia mainly at apex | LVEF = 40% | Troponin-I at peak (ng/mL) = 12.19 | Brief course of intravenous diuretics with mild symptoms of congestion. Angiotensin-converting enzyme inhibitor and a beta-blocker therapy were commenced to treat systolic dysfunction. He was also initiated on colchicine to treat mild persistent chest pain | Patchy linear mid-myocardial enhancement in the septum and inferior wall at the base to mid-ventricle, sub-epicardial mid-myocardial enhancement of the lateral wall at the mid-ventricle and apical lateral wall | He was discharged home after 5 days of monitoring without evidence of electrical or haemodynamic instability and with NYHA Class I symptoms |
| 35 Case report Ujuea et al., 2021 [37] | Progressive body aches, weakness and worsening fatigue | Sinus tachycardia with T wave inversions in the septal leads with Biventricular cardiomyopathy with LVEF = 29%, C-reactive protein Vasopressin, 63.5 < 8.0 mg/L. Phenylephrine, and Peak troponin T, Epinephrine. Intravenous IV | | Multiple immunohistochemistry staining like CD163 supports the diagnosis of | | Patient expired after several rounds of advanced cardiovascular life (continued on next page) |
### Table 3 (continued)

| Sr. Domain/Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criteria (CMR imaging findings) | Additional Comments |
|-------------------------|-------------------|--------------|-------------------------|-------------------|-----------|---------------------------------|-------------------|
| 36 Case series Verma et al., 2021 [41] | Dyspnea and dizziness | Tachycardia; ST elevation depression | Severe biventricular cardiomyopathy with LVEF = 29%, and a small pericardial effusion | Cardiac Marker Troponin I 6.4 ng/ml, peak C Reactive protein = 49 | Troponin I level of 6.14 ng per milliliter | Methylprednisolone 60 mg bolus was administered every 8 h, Vaso-prenin, Phenytoine, and Epinephrine. Intravenous (IV) Methyl-prednisolone | Lymphohistiocytic myocarditis with sparse eosinophils | Recovered and Discharged |
| 37 Case report Williams et al., 2021 [50] | Fevers and myalgias and dull, retrosternal depression and ST elevation mirrored in aVR with PR elevation and ST depression | Lateral PR LVEF = 43% | Troponin T 1.30 ng/ml; CRP 10.2 | Ibuprofen | Slightly reduced left ventricular pump function, Discharged |
| 38 Case series Levin et al., (2021) [24] | Fatigue, headache, abdominal pain, chest pain radiating to right arm, perspiration | ST elevation LVEF = 43% | Troponin T(bs-cTnT) concentration of 4026 ng/L, and C reactive protein 111 mg/L | High dose aspirin, colchicine, bisoprolol and ramipril | LVEF to 54% with subepicardial late gadolinium enhancement, pericardial enhancement | Recovered and Discharged |
| 39 Case report Patrignani et al., (2021) [52] | Fever and malaise, squeezing chest pain radiating to the back consistent with LV hypertrophy | Sinus tachycardia LVEF = 60% | Troponin T409 ng, CRP = 58.1 mg/L (0.2-5) | Colchicine, Ibuprofen | Myocardial edema and LGE Recovered and subepicardial myocardium | Recovered and Discharged |
| 40 Case report Sulemankhil et al., (2021) [49] | Acute subendocardial chest pain followed by constant, retrosternal, non-radiating, non-exertional chest pain. | Normal ECG | Troponin T 0.041 Not mentioned | Normal range <0.014ng/ml, CRP = 40.4 mg/L | A gadolinium-enhanced cardiac magnetic resonance Discharged imaging showed a small focal area of myocarditis in the mid to apical lateral region of the left ventricle with a scar size of 2% | Recovered and Discharged |

(continued on next page)
Table 3 (continued)

| Sr No | Domain/Author, Year | Clinical features | ECG Findings | Echocardiogram findings | Lab Investigations | Treatment | Diagnostic Criterias (CMR imaging findings) | Additional Comments |
|-------|---------------------|-------------------|--------------|-------------------------|-------------------|----------|---------------------------------------------|---------------------|
| 41    | Case report (2021)  | Fever. Intermittent chest and interscapular pain | Diffuse ST-segment NOT significant elevation | Troponin T (hsTnT) of 139 ng/L. | Anti-inflammatory treatment | Subepicardial edema | Follow-up not mentioned |                        |

LGE: Late Gadolinium Enhancement
LV EF: Left Ventricular Ejection Fraction
EF: Ejection Fraction
CRP: C-Reactive Protein
TTE: transthoracic Echocardiogram
CMR: Cardiac Magnetic Resonance Imaging
ECG: Electrocardiogram
LV: Left Ventricle.

Original Article:

| Sr No | Study Design Author, Year | Country | Sample size | Age | Gender (M/F) | Follow-up | Comparator characteristics (Vaccine administered) | Outcome | Results |
|-------|---------------------------|---------|-------------|-----|--------------|-----------|-------------------------------------------------|---------|---------|
| 1     | Retrospective observational study | George A. Diaz, 2021 [54] | USA | 2000287/57(40-70) 1178619 | N/A | None | BNT162b2(Pfizer/BionTech) = 52.6%, mRNA-1273(Moderna) – 44.1%, Ad26.COV2.S (Johnson & Johnson) = 3.1%, 76.1% received more than 1 dose | Myocarditis = 20, pericarditis = 37 where 4 participants developed myocarditis after first dose and 16 developed after second dose, 15 participants developed pericarditis after first dose and 22 developed after second dose |          |
|       |                           |         |             |     |              |           | Clinical features: Mild Myocarditis = 20 (100%) | Rate Ratio: Myocarditis: (1.0 [95% CI, 0.61 – 1.54] per 100,000), Pericarditis: (1.8 [95% CI, 1.30-2.55] per 100,000) |          |
| 2     | Prospective cohort study  | Han. W. Kim, 2021 [56] | USA | Mean:38.5 ±1 | N/A | None | BNT162b2(Pfizer/BionTech) = 2, Moderna (mRNA1273) = 2, Dose = 2, Onset of symptoms 3 days after vaccination for patient 1, 5 days after vaccination for patient 2, 1 day after vaccination for patient 3, 2 days after vaccination for patient 4 | Myocarditis in all four patients |          |
|       |                           |         |             |     |              |           | Clinical features: Mild Myocarditis = 4 (100%) | Rate Ratio: Myocarditis: (1.0 [95% CI, 0.61 – 1.54] per 100,000), Pericarditis: (1.8 [95% CI, 1.30-2.55] per 100,000) |          |
| 3     | Retrospective cohort study | Guy Witberg, 2021 [57] | Israel | 2,558,421 median=44 | 1,248,433/42 days None | N/A | BNT162b2(Pfizer/BionTech) = 2,558,421, All of the participants received first dose, whereas 2,401,605 participants received second dose. | Myocarditis = 54 | Cumulative incidence: 2.13(1.56-2.70) per 100,000 |
|       |                           |         |             |     |              |           | Clinical features: Mild Myocarditis = 41(76%), Intermediate myocarditis = 12 (22%), LV EF = 14(26%) | Rate Ratio: Myocarditis: (1.0 [95% CI, 0.61 – 1.54] per 100,000), Pericarditis: (1.8 [95% CI, 1.30-2.55] per 100,000) |          |
| 4     | Retrospective cohort study | Noam Barda, 2021 [53] | USA | 1,736,832 median=38 | 1,309,988 | N/A | BNT162b2(Pfizer/BionTech)=204,828 | Myocarditis:21 | Risk Ratio: Myocarditis: 3.24 (1.55-12.44), Pericarditis:1.27 (0.68-2.31) |

(continued on next page)
vaccine. The mean follow-up reported by three articles was 89 days.

4. Discussions

This systematic review summarized evidence from the original studies, case reports, and case series which discussed the development of myocarditis and pericarditis following COVID-19 vaccination. This will keep physicians up-to-date regarding the complications and side effects of newly introduced COVID-19 vaccines. We found that males are notably more likely to develop myocarditis and pericarditis following COVID-19 vaccination than females (85% vs 15%). The majority of the patients had no significant history of COVID-19 infection or any other cardiovascular disease. The prevalence of myocarditis and pericarditis was more among the patients who received Pfizer-BioNTech (BNT162b2) than those who received other vaccines, but this may be due to the fact that more patients included in this review had received the aforementioned vaccine. Similarly, a greater percentage of patients who developed the symptoms received two doses of vaccine (compared to one). Chest pain, fever, myalgias, and dyspnoea were the most common presentations. The majority of the patients who presented with myocarditis and pericarditis had a good recovery and were discharged.

Several hypotheses have been put forward to explain the factors that might cause these complications of the COVID-19 vaccine. However, the exact pathophysiology is yet to be elaborated. One of the proposed mechanisms is the interaction between components of the vaccine and the susceptibility of the subject known as molecular mimicry. Due to the similarity between the pathogenic component of the vaccine and specific human proteins, there is immune cross-reactivity resulting in autoimmune disease [58,59]. Among other vaccines for which myocarditis has been reported as an adverse effect, only the smallpox vaccine differs from the COVID vaccine both in composition and elicitation of a specific immune response.

The higher prevalence of this condition among males can be explained based on the role played by variations in hormone signalling. Testosterone has the ability to suppress anti-inflammatory immune cells while promoting a more aggressive T helper 1 cell immunological response. Oestrogen, on the other hand, inhibits pro-inflammatory T cells, resulting in a reduction in cell-mediated immune responses [59]. However, further research is required to explore the exact phenomenon.

The incidence of myocarditis following the second dose is greater, probably because of a phenomenon called hypersensitivity myocarditis, with the first dose presenting as a sensitising dose [61]. More prevalence of myocarditis and pericarditis among the patients who received Pfizer-BioNTech (BNT162b2) and Moderna (mRNA 1273) indicates that mRNA vaccines are associated with a higher risk of developing myocarditis than the viral vector vaccines like AstraZeneca and The Janssen/Johnson & Johnson [62]. Bozkurt et al. has proposed that autoantibody generation and subsequent attack on cardiac myocytes in response to mRNA vaccine underlie this increased risk [63]. Larger scale studies have indicated myocarditis and pericarditis to be rare adverse events of the COVID-19 vaccine. The US population-based study has reported the incidence rate of myocarditis and pericarditis to be 5.73 to 26 cases per 100,000 person-year and 0.95 to 2.16 cases per 100,000 person-year, respectively [64]. Another study conducted in Israel has reported the cumulative incidence rate to be 2.13 (1.56–2.70) per 100,000 [65].

Most patients underwent CMR imaging revealing myocardial edema and hyperaemia, findings supportive of myocarditis. CMR imaging has an important role in therapeutic decision-making in patients with suspected myocarditis. It acts as a predictor of functional and clinical recovery and the CMR-visualised pattern of myocardial damage provides some insight into the underlying illness aetiology and pathogenesis [66]. As the CMR imaging of patients was performed in an acute setting, it was difficult to assess the actual degree of damage and prognosis and highlight etiological and pathological factors that may be at play [67]. NSAIDs, colchicine, and steroids were the most commonly employed treatments in the case studies, suggesting that the management of post-COVID vaccine myocarditis is in line with the current guidelines. The good prognosis and recovery of patients in most cases corroborate this fact as well. The effectiveness of anti-inflammatory drugs also backs the theory of molecular mimicry and autoimmunity in C-VAM (COVID vaccine-associated myocarditis).

Practising physicians and healthcare providers can benefit from the information included in this study by providing improved consultation on vaccine safety and potential side effects. Healthcare providers should discuss all the possible risk factors before choosing the specific type of vaccine. The viral vector vaccine can be an alternative for patients with increased risk of myocarditis/pericarditis, or for those who have a history of cardiomyopathy ...

The main limitation of this review is that no large-scale clinical trial investigating the risk factors, clinical presentation, and prognosis of

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**Table 3 (continued)**

| Sr No | Study Design | Author, Year | Country | Sample size | Age range | Gender (M/F) | Follow-up | Experimental group characteristics (Vaccine administered) | Outcome | Results |
|-------|--------------|--------------|---------|-------------|-----------|--------------|-----------|----------------------------------------------------------|---------|---------|
| 5     | Retrospective cohort study | Mevorach et al., 2021 [55] | Israel 9,289,765 | 2,668,894–183, 277,802 days | None | BNT162b2 (Pfizer/BioNTech) = 5,442,696. | Myocarditis: 136, | 1st dose: 5,442,696, 2nd After second dose: Dose: 5,125,635 | 129 (90.9%) cases: | 3.19 (2.37–4.02) risk difference |
|       |              |              |         |             |           |              |           | Chest pain = 129 (95%) | Fever = 63 (46.7%) | Standardized Incidence ratio for myocarditis according to age, sex and dose: 5.34 (4.48–6.40), Rate ratio of myocarditis within 30 days after second dose as compared to unvaccinated patients: 2.35 (1.10–5.02) |
|       |              |              |         |             |           |              |           | Elevated Troponin I or T = 136 (100%) | Elevated C-reactive protein = 118 (86.7%) | LVEF = 48 (35%) |

LVEF = Left Ventricular Ejection Fraction, EF = Ejection Fraction, LGE = Late Gadolinium enhancement, LVD = Left Ventricular Dysfunction, ECG = Electrocardiogram, RD = Risk difference.
patients developing myocarditis and pericarditis following COVID-19 vaccination has been conducted so far so only case reports, case series, and cohort studies have been included in the review. Moreover, there is inherent heterogeneity owing to the individual nature of every patient included in the case report and case series. Lastly, mild cases of myocarditis and pericarditis remain unreported and due to the recent nature of the condition, there is insufficient evidence to expound on the underlying pathogenic mechanisms. There is a significant potential for publication bias because rare events and diagnostically unique cases are more likely to be reported and published.

5. Conclusion

Myocarditis and pericarditis after the COVID-19 vaccine occur most commonly in adult males after the second dose of mRNA vaccines (Pfizer and Moderna). The presentation is usually mild, and the majority of patients have a good recovery. Cell-mediated immune responses generated by the body against the vaccine components cross-react with cardiac cells to cause myocardial and pericardial inflammation. It follows that the most effective treatment for this clinical entity are immunosuppressants and anti-inflammatory agents (e.g., colchicine, NSAIDs and steroids). Physicians should consider myocarditis and pericarditis as a probable diagnosis in patients who have received COVID-19 vaccines, especially in males who develop suggestive symptoms after a second dose of Pfizer and Moderna. Viral vector vaccines may be a better alternative for patients with a history of cardiac diseases.

Ethical approval

This is a systematic review and did not require ethical approval.

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Author contribution

MF and HAC conceived the idea established a search strategy. MF, MHAH and MSA retrieved the articles, and screened them for relevancy. After selecting relevant articles, MWM, UH and HS ran quality assessment on the included articles. Data was extracted by MF, UH, MHAH and HS. MF and MAUR proofread the extracted data and matched it with articles to eliminate errors. MF and MAUR then worked on the write up. MAUR, HF and HAC provided critical assistance in proof reading and editing of the write up. All the authors approved the final version of the article.

Registration of research studies

Name of the registry: PROSPERO.
Unique Identifying number or registration ID: CRD42021276596.
Hyperlink to your specific registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=276596.

Guarantor

I, Mauritsh Fatima, the corresponding author for this review accept my role as the Guarantor for this research.

Consent

This is a systematic review, where authors verified that proper consent was obtained from patients in all the studies included.

Provenance and peer review
Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103486.

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