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REVIEW

Cardiac complications following mRNA COVID-19 vaccines: A systematic review of case reports and case series

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Abstract

There have been several local and systemic adverse events associated with mRNA COVID-19 vaccines. Pericarditis, myocarditis and myocardial infarction are examples of cardiac complications related to these vaccines. In this article, we conducted a systematic review of case reports and case series to identify the clinical profile, investigations, and management of reported cardiac complications post-mRNA COVID-19 vaccines. We systematically searched PubMed, Scopus, Web of Science, and Google Scholar, as well as the medRxiv preprint server, with terms including: 'SARS-CoV-2', 'COVID-19', 'messenger RNA vaccine*', 'mRNA-1273 vaccine', 'BNT162 vaccine', 'myocarditis', 'pericarditis', 'stroke' and 'Myocardial Ischemia' up to 25 September 2021. Studies were excluded if they were not case reports or case series, or reported cases from non-mRNA vaccines. Case reports and case series were included that investigated the potential cardiac complications associated with mRNA COVID-19 vaccines. The JBI checklist was used to assess quality and data synthesis was conducted using a qualitative methodology called narrative synthesis. Sixty-nine studies, including 43 case reports and 26 case series, were included. Myocarditis/myopericarditis and pericarditis were the most common adverse events among the 243 reported cardiac complications, post mRNA COVID-19 vaccination. Males with a median age of 21 years had the highest frequency of myocarditis. Almost three quarters (74.4%) of cases with myocarditis had received the BNT162b2 vaccine and 87.7% had received the second dose of the vaccine. Chest pain (96.1%) and fever (38.2%) were the most common presentations. CK-MB, troponin, and NT-proBNP were elevated in 100%, 99.5% and 78.3% of subjects, respectively. ST-segment abnormality was the most common electrocardiogram feature. Cardiac magnetic resonance imaging, which is the gold-standard approach for diagnosing myocarditis, was abnormal in all patients diagnosed with

Abbreviations: ACE, angiotensin-converting enzyme; COVID-19, Coronavirus disease 2019; CK-MB, creatinine kinase-myocardial band; C-MRI, CARDIAC magnetic resonance imaging; CRP, C-reactive protein; DOI, Digital object identifier; ECG, electrocardiogram; EMB, endomyocardial biopsy; ESR, Erythrocyte sedimentation rate; IVIg, intravenous immunoglobulin; JBI, Joanna Briggs Institute; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; mRNA, messenger ribonucleic acid; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal-prohormone brain natriuretic peptide; PMH, past medical history; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TTE, trans-thoracic echocardiography; PCR, polymerase chain reaction; PCI, percutaneous coronary intervention; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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myocarditis. Non-steroidal anti-inflammatory drugs were the most prescribed medication for the management of myocarditis. Apart from inflammatory conditions, some rare cases of Takotsubo cardiomyopathy, myocardial infarction, myocardial infarction with non-obstructive coronary arteries, and isolated tachycardia were also reported following immunisation with mRNA COVID-19 vaccines. We acknowledge that only reviewing case reports and case series studies is one potential limitation of our study. We found that myocarditis was the most commonly reported adverse cardiac event associated with mRNA COVID-19 vaccines, which presented as chest pain with a rise in cardiac biomarkers. Further large-scale observational studies are recommended.

KEYWORDS
cardiac complications, COVID-19, myocardial infarction, myocarditis, pericarditis, SARS-CoV-2, systematic review

1 | INTRODUCTION

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic in late 2019, different therapeutic approaches have been developed, such as nucleoside analogues, interleukin (IL)-6 inhibitors, herbal medicine and immunotherapy.[1,2] In addition, scientists have also examined different platforms for vaccine development, including viral-based and protein-based vaccines, in order to prevent infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or to reduce the severity of the disease, with an ultimate aim to reduce mortality and morbidity.[3] As of 22 October 2021, 128 vaccines were in clinical development and 194 were in the pre-clinical phase.[4]

COVID-19 mRNA vaccines, like mRNA-1273 (i.e., Moderna vaccine) and BNT1626b2 (i.e., Pfizer-BioNTech vaccine), trigger innate immunity, cytotoxic and helper T cells, and in particular B-cell responses.[5] Most of the reported adverse events were non-serious local or systemic reactions, such as injection site pain, erythema, swelling, fever, headache and myalgia.[6] However, a wide range of adverse events and complications have been reported for mRNA-based COVID-19 vaccines, which can affect the nervous and cardiovascular systems and may even be life-threatening, such as acute myocardial infarction, pulmonary embolism, stroke and venous thromboembolism.[7–9]

The adverse cardiac events associated with mRNA COVID-19 vaccines range from inflammations (e.g., pericarditis or myocarditis) to thrombosis and ischaemia.[9] Although some studies have reported the frequency of cardiac complications following COVID-19 mRNA vaccines,[10] to our knowledge there is no large-scale observational study or systematic review to specifically focus on mRNA vaccines. However, as the adverse cardiac events associated with mRNA COVID-19 vaccines are rare, most of the papers are case reports and case series. Therefore, we aimed to conduct a systematic review of case reports and case series to summarise the cardiac complications associated with COVID-19 mRNA vaccines.

2 | METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including the PRISMA 2020 update for Abstracts.[11]

2.1 | Literature search

PubMed, Scopus, Web of Science and the medRxiv databases were searched up to 25 September 2021, to identify publications reporting the incidence of cardiac complications following vaccination with an mRNA COVID-19 vaccine. The first 100 pages of the Google Scholar search engine were manually screened to identify any further eligible studies. No restrictions were applied to any search fields, such as language or study type. The search strategy included a combination of the following words: (COVID-19 OR SARS-CoV-2) AND (BNT162b2 OR mRNA-1273) AND (myocarditis OR pericarditis OR 'myocardial infarction' OR 'cardiac complication'). A description of the stages of the search for each database are summarised in Table S1.

2.2 | Study selection

All studies identified through the electronic and manual searches were exported to EndNote 20 (Clarivate Analytics), and any duplicate were removed. Two of the review authors (A.F. and M.Z.) independently screened the title and abstract of the papers and excluded those that were irrelevant. After the initial screening, the same two authors reviewed the full-text of the remaining articles, according to the inclusion and exclusion criteria. All steps of the screening process were conducted using EndNote 20 software (Clarivate Analytics). The other reviewers were consulted to resolve any discrepancies.

Studies were included if (1) they were case reports or case series; (2) reported cases of cardiac complications after receiving at least one dose of an mRNA COVID-19 vaccine; (3) enrolled patients who tested negative for SARS-CoV-2 at time of symptom onset; and (4) comprehensively reported the clinical manifestations of the cases. We excluded articles using the following criteria (1) if they were designed as cross-sectional, case-control, cohorts or clinical trials; (2) review articles, in vitro/laboratory studies and those conducted on animals; (3) analysed data extracted from databases gathering vaccine-related adverse event reports; and (4) presented cases receiving vaccines other than mRNA vaccines.

2.3 | Data extraction

Data extraction was conducted using predefined forms in Microsoft Office Excel. Two researchers (A.F. and M.Z.) extracted the following information from each study: (1) the basic information about the studies, including title, digital object identifier (DOI), first authors' name, publication date and study design; (2) the characteristics of the presented cases, including number of reported cases, age, sex, past medical history (PMH), name of vaccine received, the dose of the vaccine that subsequently manifested symptoms, time from vaccination to symptom onset, duration of hospitalisation and occurrence of death; (3) accompanying symptoms, including chest pain, fever, headache, fatigue, myalgia, chills, dyspnoea, shortness of breath, palpitation, diaphoresis and nausea/vomiting; (4) laboratory tests including troponin, creatinine kinase-myocardial band (CK-MB) and N-terminal-prohormone brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); (5) cardiac testing, including electrocardiogram (ECG), trans-thoracic echocardiography (TTE) and cardiac magnetic resonance imaging (C-MRI) findings; and (6) treatments, including anti-inflammatory medications, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics and any other medications. All extracted data were double-checked by other authors.

2.4 | Critical appraisal

We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case reports[12] and case series[13] for appraising the quality of the included articles. The JBI checklist for case reports consists of an 8-item scale which includes the patient's demographic characteristics, medical history, current clinical condition, description of diagnostic tests, treatment, post-intervention clinical condition, adverse events and the provision of takeaway lessons.[12] The JBI checklist for case series is a 10-item scale which evaluates the inclusion criteria, method of condition measurement, validity of the diagnostic methods, whether there was consecutive inclusion of participants, completeness of participants' inclusion, reporting of the demographic characteristics, clinical information, outcomes, presenting clinic demographic information and the appropriateness of the statistical analysis.[13]

3 | RESULTS

3.1 | Study selection

The systematic search identified 591 records, of which 512 remained after the removal of 79 duplicates. In total, 419 records were excluded after screening the title/abstracts. After assessing the 93 articles for eligibility, 2 studies evaluated complications for non-mRNA vaccines,[14,15] 7 discussed non-cardiac complications,[16–22] 14 studies were not case report/case series,[8,23–35] one study did not provide sufficient data[36] and these were therefore excluded. Finally, 69 articles met the eligibility criteria and were included in the present systematic review (Figure 1).

3.2 | Study characteristics

Of the 69 included studies, 43 were case reports and 26 were case series. All were peer-reviewed and were published in 2021. Thirty eight studies were conducted in the United States, 7 in Italy,[37–43] 6 in Israel,[44–49] 5 in Germany,[50–54] and 13 in other countries.[55–67] Overall, 227 patients were diagnosed as cases of myocarditis/myopericarditis from 61 studies, along with 7 patients with pericarditis.[45,62,68,69] The details on each case are presented in the supplementary material. Meanwhile, other rare cardiac manifestations were reported as four patients with Takotsubo cardiomyopathy,[56,61,69,70] three with myocardial infarction (MI),[61,66,71] one with myocardial infarction with non-obstructive coronary arteries (MINOCA),[61] and one with isolated tachycardia.[72]

3.3 | Myocarditis/myopericarditis

The median age of the 227 myocarditis/myopericarditis patients was 21 years (ranging from 12- to 70-year-old), with most being male (92.1%). The majority of the reported cases were from the United States (72.8%), followed by Israel (14.1%) and Italy (6.2%).

3.3.1 | Clinical presentations

More than half (55.8%) of the patients had no PMH, while hypertension (6.5%) and asthma (5.2%) were among the most common comorbidities. Six patients (4.0%) were reported to have a previous history of myocarditis[41,46,49,73–75] and a small number (10.6%) had a previous history of SARS-CoV-2 infection.[37,42,43,53,75–80] In addition, none of the cases tested positive for COVID-19 at the time of presentation and only 5.6% presented with evidence of any other type of viral infection at the time of symptom onset.[38,53,75,77,78]

The majority (74.4%) of the cases developed myocarditis/myopericarditis after receiving the BNT162b2 vaccine and the rest (25.6%) after receiving the mRNA-1273 vaccine. Most of the cases (87.7%) were recorded after the second immunisation dose.

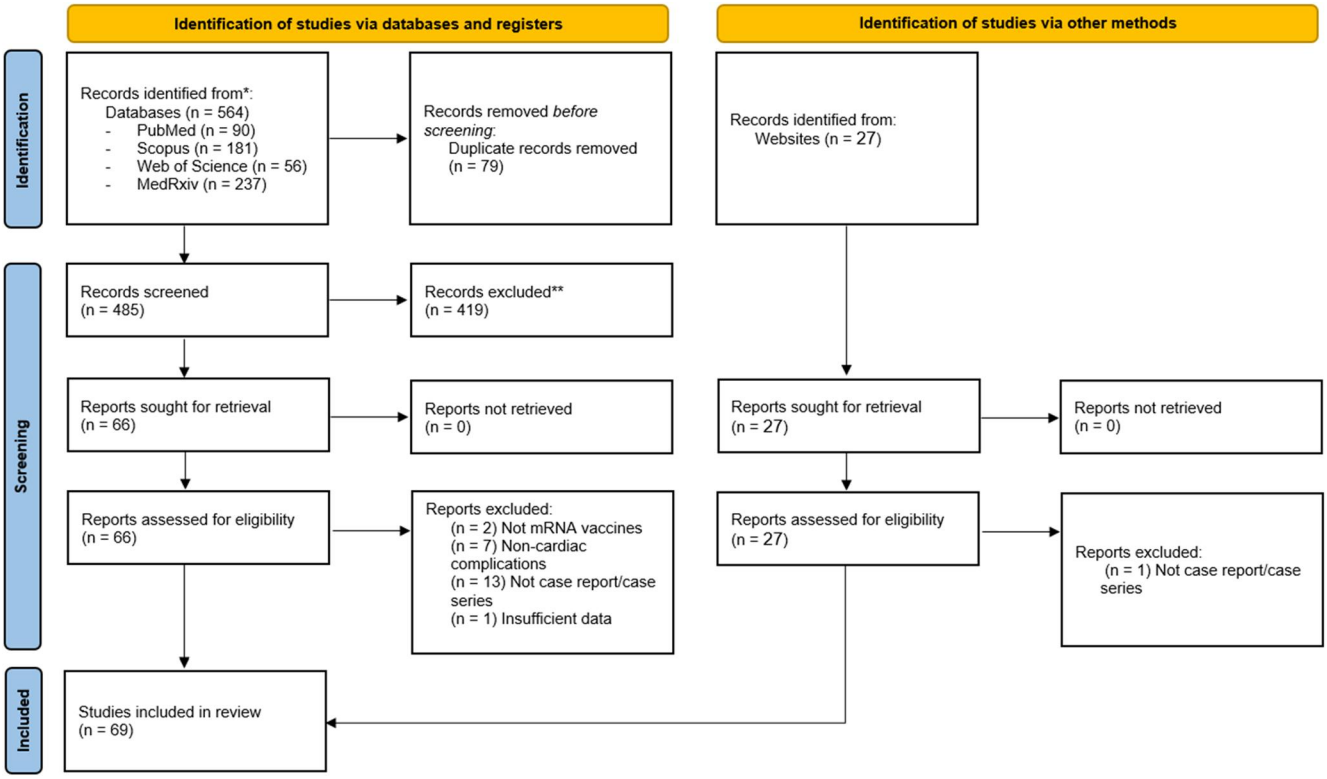

FIGURE 1 Flow chart of the study selection process

Furthermore, the median time from vaccination to symptom onset was 3 days (ranging from 1.5 h to 3 months) and the median length of hospitalisation was 3 days (ranging from 1.5 h to 73 days).

The most commonly reported symptom on presentation was chest pain (96.1%), followed by fever (38.2%), headache (18.8%), myalgia (18.8%), fatigue (15.5%), chills (12.6%) and shortness of breath (10.1%). There were two cases of death, the first of whom was as a result of recurrent cardiac arrest and refractory shock, secondary to multiorgan failure, 21 h after receiving the BNT162b2 vaccination.[81] The second death was due to cardiogenic shock 3 days after receiving the mRNA-1273 vaccine[82] (Table 1, Tables S4 and S5).

3.3.2 | Laboratory findings

Troponin levels were elevated in 99.5% of subjects. Moreover, other cardiac biomarkers, such as CK-MB and NT-proBNP, were also elevated in 100% and 78.3% of patients, respectively. Furthermore, an increased level of inflammatory markers, including CRP and ESR, were reported in 90.1% and 60.5% of cases, respectively (Tables 2 and S6).

3.3.3 | Cardiac testing

The ECG was normal in 21.8% of the patients. The most commonly observed abnormal ECG findings were diffuse ST elevations (43.8%), inferolateral ST elevations (7.5%), lateral ST elevations (6.5%), PR depression (9.5%), T-wave abnormality (9.0%) and sinus tachycardia (5.0%).

In terms of TTE testing, 44.5% of patients exhibited normal findings. Decreased left ventricular ejection fraction (LVEF) values of lower than 50% were found in 18.2% of the patients, LV hypokinesis in 11.5%, pericardial effusion in 4.8% and wall motion abnormality in 1.4%.

None of the cases showed normal C-MRI. Non-ischaemic late gadolinium enhancement (LGE) pattern was recorded in 94.1% of the patients and T2-weighted images, indicating myocardial oedema, were found in 68.0% of the cases (Tables 3 and S7).

3.3.4 | Histopathological findings

An endomyocardial biopsy (EMB) was conducted in seven patients.[51,53,60,81,82] Diffuse infiltration of the immune cells, including CD68-positive macrophages and CD3-positive T lymphocytes, were observed in five samples,[51,53,81,82] while two others found no evidence of inflammatory cell infiltration.[60] Myocyte necrosis, minimal interstitial fibrosis and foci of cytoplasmic vacuolisation in the myocytes were other EBM findings. In one patient, viral genome analysis, by polymerase chain reaction (PCR), was negative for SARS-CoV-2, echovirus and coxsackievirus[53] (Table 4).

3.3.5 | Management

There are several medications that are normally used to reduce inflammation and to treat heart failure associated with myocarditis.

TABLE 1 Demographic features and clinical characteristics of myocarditis/myopericarditis and pericarditis patients

	Myocarditis/myopericarditis		Pericarditis	
	N		*N*	
Patient characteristics				
Median age	158	21 (12–70)	7	37 (21–80)
Male/female	227	209 (92.1%)/18 (7.9%)	7	5 (71.4%)/2 (28.6%)
Country	227		7	
USA		165 (72.8%)		3 (42.8%)
Israel		32 (14.1%)		2 (28.6%)
Italy		14 (6.2%)		0
Germany		6 (2.6%)		0
Other		10 (4.3%)		2 (28.6%)
PMH	154		6	
Healthy		86 (55.8%)		0
HTN		10 (6.5%)		2 (33.4%)
Asthma		8 (5.2%)		0
DM		4 (2.6%)		1 (16.6%)
Hyperlipidaemia		4 (2.6%)		0
Previous history of myocarditis		6 (4.0%)		0
Previous history of pericarditis		0		3 (50%)
Prior history of COVID-19	141		3	
Positive		15 (10.6%)		0
Negative		126 (89.4%)		3 (100%)
Other viral test at presentation	107		3	
Positive		6 (5.6%)		0
Negative		101 (94.4%)		3 (100%)
Name of vaccine	227		7	
BNT1621B2		169 (74.4%)		7 (100%)
mRNA-1273		58 (25.6%)		0
Vaccine dose	277		7	
Second		199 (87.7%)		3 (42.8%)
First		27 (11.9%)		3 (42.8%)
First and second		1 (0.4%)		1 (14.4%)
Median time from vaccination to symptom onset	158	3 days (1.5 h to 3 months)	7	4 days (1–11 days)
Median time of hospitalisation	119	3 days (1.5 h to 73 days)	0	–
Symptoms	207		7	
Chest pain		199 (96.1%)		6 (85.7%)
Fever		79 (38.2%)		1 (14.3%)
Headache		39 (18.8%)		0
Myalgia		39 (18.8%)		0
Fatigue		32 (15.5%)		0
Chills		26 (12.6%)		0

(Continues)

TABLE 1 (Continued)

	Myocarditis/myopericarditis		Pericarditis	
	N		*N*	
Shortness of breath		21 (10.1%)		1 (14.3%)
Nausea/vomiting		19 (9.2%)		0
Dyspnoea		16 (7.7%)		1 (14.3%)
Palpitation		7 (3.4%)		1 (14.3%)
Diaphoresis		6 (2.9%)		1 (14.3%)
Death	227	2 (0.9%)		0

Abbreviations: COVID-19, Coronavirus disease 2019; DM, diabetes mellitus; HTN, hypertension; PMH, past medical history; USA, United States of America.

TABLE 2 Laboratory findings of myocarditis/myopericarditis and pericarditis patients

	Myocarditis/myopericarditis		Pericarditis	
	N		*N*	
Troponin	222		5	
Elevated		221 (99.5%)		0
Normal		1 (0.5%)		5 (100%)
CK-MB	22		0	
Elevated		22 (100%)		0
Normal		0 (0%)		0
NT-proBNP	23		1	
Elevated		18 (78.3%)		0
Normal		5 (21.7%)		1 (100%)
CRP	111		5	
Elevated		100 (90.1%)		4 (80%)
Normal		11 (9.9%)		1 (10%)
ESR	43		3	
Elevated		26 (60.5%)		2 (66.6%)
Normal		17 (39.5%)		1 (33.4%)

Abbreviations: CK-MB, creatinine kinase-myocardial band; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; NT-proBNP, N-terminal-prohormone brain natriuretic peptide.

Among anti-inflammatory pharmacological options, non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for 48% of the patients (mainly ibuprofen and aspirin), followed by colchicine (22.5%), steroids (14.1%) and intravenous immunoglobulin (IVIg) (11.5%). Furthermore, 10.1% of the patients needed beta-blockers, 5.9% of them needed ACE inhibitors, and 2.2% needed diuretics for managing possible heart failure (Tables 5 and S8).

3.4 | Pericarditis

The median age of the seven patients[45,62,68,69] who were diagnosed as isolated cases of pericarditis was 21 years (ranging from 21- to 80-year-old patients), with 71.4% being male. Almost half (42.8%) were from the United States, 28.6% from Israel and 28.6% from other countries. The most common comorbidities included hypertension (33.4%) and diabetes (16.6%). In addition, a previous history of pericarditis was found in three patients.[45,62,68]

There were no confirmed COVID-19 infections prior to vaccination, with no patients testing positive for SARS-CoV-2 or any other viral infection. All episodes of pericarditis were found after immunisation with BNT162b2. The pericarditis symptoms appeared after the second vaccine dose in three patients,[62,69] three after the first dose,[45,69] and one patient after both doses.[68] The median time from vaccination to onset of the first symptoms was 4 days (ranging from one to 11 days) (Tables 1 and S9).

TABLE 3 Cardiac testing of myocarditis/myopericarditis and pericarditis patients

	Myocarditis/myopericarditis		Pericarditis	
	N		*N*	
ECG				
Normal	36		2	
Abnormal	165		5	
Diffuse ST elevations		88 (43.8%)		1 (14.3%)
Inferolateral ST elevations		15 (7.5%)		1 (14.3%)
Lateral ST elevations		13 (6.5%)		0
Anterior ST elevations		8 (4.0%)		0
Anterolateral ST elevations		7 (3.5%)		0
Inferior ST elevations		5 (2.5%)		0
T-wave abnormality		18 (9.0%)		1 (14.3%)
Sinus tachycardia		10 (5.0%)		1 (14.3%)
PR depression		19 (9.5%)		0
RBBB		4 (2.0%)		0
TTE				
Normal	93		1	
Abnormal	116		6	
LVEF<50%		38 (18.2%)		0
LV hypokinesis		24 (11.5%)		0
Pericardial effusion		10 (4.8%)		6 (85.7%)
Wall motion abnormality		3 (1.4%)		0
C-MRI				
Normal	0		0	
Abnormal	153		0	
Non-ischaemic LGE pattern		144 (94.1%)		0
Evidence of oedema on T2 imaging		104 (68.0%)		0

Abbreviations: C-MRI, cardiac magnetic resonance imaging; ECG, electrocardiogram; LGE, late galodinium enhancement; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; TTE, Trans-thoracic echocardiography.

The most frequent symptom was chest pain, which occurred in 85.7% of the patients. Other symptoms included fever, shortness of breath, nausea/vomiting, dyspnoea, and palpitations. Regarding laboratory testing, although the troponin level was normal in all patients, the levels of inflammatory markers, such as CRP and ESR, were elevated in 80% and 66.6% of cases, respectively (Table 2). Furthermore, the ECG was normal in two patients,[45,69] with the irregularities including diffuse ST elevations, inferolateral ST elevations, T-wave abnormality, and sinus tachycardia. TTE findings revealed no abnormality in one patient[62] and pericardial effusion in all other cases (85.7%) (Tables 3 and S9).

Anti-inflammatory medications constitute the main approach for treating pericarditis. Accordingly, colchicine was prescribed for all subjects, and then NSAIDs (71.4%) and steroids (14.3%) (Tables 5 and S9).

3.5 | Other cardiac complications

Apart from inflammatory conditions (i.e. myocarditis and pericarditis) some rare cases of Takotsubo cardiomyopathy (stress-induced cardiomyopathy),[56,61,69,70] MI,[61,66,71] MINOCA,[61] and isolated tachycardia[72] were also reported following immunisation with mRNA COVID-19 vaccines. The median age of the four cases of Takotsubo cardiomyopathy were 61.5 years old, three of which were female. Two patients presented with symptoms after receiving BNT162b2 and the two other after mRNA-1273. Similarly, half of the cases showed symptoms after the second vaccine dose and the other half after the first dose. In addition, the time from immunisation to symptom onset ranged from 15 min to 4 days. Chest pain and elevated troponin levels were evident in all patients. The ECG findings showed inferolateral ST changes and T-wave inversion to be

TABLE 4 Endomyocardial biopsy findings

First author name	Findings
Ehrlich et al.[51]	Endomyocardial biopsy reveals areas of inflammation and myocyte necrosis. The majority of immune cells represent CD68-positive macrophages but also numerous CD3-positive T cells are present in the interstitium
Nguyen et al.[53]	Endomyocardial biopsy revealed no cardiomyocyte hypertrophy, no giant cells, and minimal interstitial fibrosis without proliferating myofibroblast. There were also no signs for haemochromatosis or amyloidosis. Instead, the haematoxylin and eosin stains displayed myocardial oedema and profound mononuclear infiltration in the absence of myocardial necrosis Immunohistochemistry identified substantial numbers of CD68-positive macrophages and CD3-positive T lymphocytes. Importantly, viral genome analysis of two independent myocardial biopsy samples by quantitative PCR was negative for SARS-CoV-2, echovirus, and coxsackievirus
Abbate et al.[81]	Endomyocardial biopsy showed cardiomyocytes with minute foci of cytoplasmic vacuolisation and rare interstitial lymphocytic infiltrate, which is consistent with healing myocarditis
Koizumi et al.[60]	Endomyocardial biopsy showed no inflammatory cell infiltration
Koizumi et al.[60]	Endomyocardial biopsy showed no inflammatory cell infiltration
Verma et al.[82]	Endomyocardial biopsy showed an inflammatory infiltrate predominantly composed of T-cells and macrophages, admixed with eosinophils, B cells and plasma
Verma et al.[82]	Endomyocardial biopsy showed an inflammatory infiltrate admixed with macrophages, T-cells, eosinophils and B cells

TABLE 5 Medications used for the treatment of myocarditis/myopericarditis and pericarditis patients

	Myocarditis/myopericarditis	Pericarditis
Anti-inflammatory medications		
NSAIDs	109 (48.0%)	5 (71.4%)
Colchicine	51 (22.5%)	7 (100%)
Steroids	32 (14.1%)	1 (14.3%)
IVIg	26 (11.5%)	0
Beta-blocker	23 (10.1%)	0
ACE inhibitor	12 (5.9%)	0
Diuretics	5 (2.2%)	0

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; IVIg, intravenous immunoglobulin; NSAID, non-steroidal anti-inflammatory drugs.

more common among the cases. The main characteristic of Takotsubo cardiomyopathy, known as apical akinesis or dyskinesis (apical ballooning), was observed in the TTE findings of all subjects. The C-MRI indicated no manifestation of LGE, while in one patient the T2-imaging was positive for oedema.[56] All patients were cured and no deaths occurred. Conservative therapy was initiated for one patient[61] and two were treated with beta-blockers, diuretics and ACE inhibitors.[69,70]

Three cases of MI, with a median age of 86 years old, were recorded 30 min to 6 h after the administration of the first dose of either the BNT162b2 (two patients) or mRNA-1273 (one patient) vaccines. Two patients presented with chest pain and increased troponin levels,[61,71] while the other died due to cardiogenic shock and recurrent brady-arrhythmias.[66] The ECG findings showed ST changes for all of the patients and more than 50% occlusion of the coronary arteries were seen in the angiography. A primary percutaneous coronary intervention (PCI) of the occluded arteries was performed in two patients,[61,66] while the other patient underwent a heparin drip.[71] The latter case was a 73-year-old woman diagnosed with MINOCA 2 h after vaccination with the first dose of the BNT162b2 vaccine. She presented with shortness of breath and palpitations, along with elevated troponin levels. The ECG and TTE were normal, while coronary angiography revealed a haemodynamically non-significant moderate LAD artery lesion.

The last case of cardiac complication, following mRNA vaccination, was a 29-year-old woman who presented with palpitations recorded 6–8 h after the second dose of the BNT162b2 vaccine. She had no other symptoms, except tachycardia (heart rate: 130/min) and all laboratory tests were within normal limits. The tachycardia was refractory to conservative therapy and after administration of one dose of metoprolol the tachycardia was resolved within one day. Detailed information on each case is summarised in Table 6.

3.6 | Quality assessment

Among case reports, three studies[59,83,84] received a perfect score (8/8 score) and three studies[37,52,56] had the lowest score (4/8), with an overall mean score of 6.37. The highest scoring criteria were reporting the current clinical condition of patients on presentation and clear reporting of the diagnostic tests or assessment methods

TABLE 6 Demographic features, clinical characteristics, laboratory and cardiac findings, and treatment of patients with cardiac complications, other than myocarditis and pericarditis

First author name		Lee et al.[61]	Boscolo Berto et al.[56]	Fearon et al.[70]	Vidula et al.[69]	Lee et al.[61]	Boivin et al.[71]	Tajstra et al.[66]	Lee et al.[61]	Tate et al.[72]
Demographic features, clinical characteristics	Country	Singapore	Switzerland	USA	USA	Singapore	USA	Poland	Singapore	USA
	Age	44	63	73	60	70	96	86	73	29
	Sex	Female	Female	Male	Female	Female	Female	Male	Female	Female
	Diagnosis	Takotsubo cardiomyopathy	Takotsubo cardiomyopathy	Takotsubo cardiomyopathy	Takotsubo cardiomyopathy	MI	MI	MI of the inferior wall with triple coronary artery thrombosis	MINOCA	Isolated tachycardia
	PMH	Mitral valve prolapse Mild MR	N/A	HTN CKD RA Asthma Viral pericarditis in 2018 MINOCA	Stent placed in the LAD three years ago	Type 2 diabetes HTN Hyperlipidaemia Previous stroke	HTN	Prostate cancer in 2006; Paroxysmal atrial fibrillation	HTN	N/A
	Name of vaccine received	BNT162b2	mRNA-1273	mRNA-1273	BNT162b2	BNT162b2	mRNA-1273	BNT162b2	BNT162b2	BNT162b2
	mRNA vaccine dose	1st	1st	2nd	2nd	1st	1st	1st	1st	2nd
	Prior history of SARS-COV-2 infection	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	N/A
	Other viral test positive at presentation	N/A	N/A	No	No	N/A	N/A	N/A	N/A	N/A
	Time from vaccination to symptom onset	15 min	1 day	17 h	4 days	6 h	1 h	30 min	2 h	6–8 h
	Duration of hospitalisation	N/A	N/A	8 days	N/A	N/A	3 days	3 days	N/A	N/A
	Death	No	No	No	No	No	No	Yes	No	No
	Symptoms	Chest pain Palpitation	Fever Dyspnoea	Fatigue Dyspnoea Chest pain Shortness of breath Orthopnoea	Chest pain	Chest pain Diaphoresis Nausea	Chest pain	Unconsciousness; Cardiogenic shock and recurrent bradyarrhythmias	Shortness of breath; Palpitation	Palpitation; Tachycardia (HR: 130/s)

(Continues)

TABLE 6 (Continued)

First author name		Lee et al.[61]	Boscolo Berto et al.[56]	Fearon et al.[70]	Vidula et al.[69]	Lee et al.[61]	Boivin et al.[71]	Tajstra et al.[66]	Lee et al.[61]	Tate et al.[72]
Laboratory findings	Elevated cardiac troponin	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	No
	Elevated CK-MB	N/A	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Elevated NT-proBNP	N/A	Yes	Yes	N/A	N/A	N/A	N/A	N/A	N/A
	Elevated CRP	N/A	Yes	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Elevated ESR	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cardiac testing	ECG	ST elevations in the inferolateral leads	Negative T waves over the inferior/ anterior leads	ST changes in inferolateral leads; Poor anterior R wave progression	Inferolateral T wave inversions	Diffuse ST depressions over the precordial and limb leads; ST elevation in aVR	ST elevation in the anterior leads of V2, V3, and avL	Acute ST elevation myocardial infarction of the inferior wall	Normal	Sinus tachycardia
	TTE	Mildly decreased LVEF of 50% with apical ballooning	Apical ballooning	Grade I diastolic dysfunction TR Mild MR LVEF: 20% Mid-ventricular ballooning of the LV	Apical akinesis LVEF: 44%	Normal	Anterior and apical wall motion abnormality LVEF: 35%	N/A	Normal	Normal
	C-MRI	N/A	Extensive oedema in the mid-ventricular/ apical segments Extracellular volume fraction was elevated at 35% No evidence of LGE	No evidence of oedema or LGE	N/A	N/A	N/A	N/A	N/A	N/A

TABLE 6 (Continued)

First author name		Lee et al.[61]	Boscolo Berto et al.[56]	Fearon et al.[70]	Vidula et al.[69]	Lee et al.[61]	Boivin et al.[71]	Tajstra et al.[66]	Lee et al.[61]	Tate et al.[72]
	Angiography	Normal	Normal	Normal	Normal	100% occlusion of the left proximal circumflex artery; Diffuse 75% stenosis in the proximal-mid left anterior descending artery; 50% stenosis in the right coronary artery	N/A	Occlusions/distal embolisation in the distal part of the left anterior descending coronary artery, in the first diagonal branch, and in the distal part of the dominant right coronary artery, with large thrombus	Single-vessel coronary artery disease; Haemodynamically non-significant moderate left anterior descending artery lesion	Normal
Treatment		Conservative treating	N/A	FurosemideIV diuresis; BB (metoprolol); Losartan	BB (metoprolol); Lisinopril	PCI of the occluded circumflex artery	Heparin	PCI of the right coronary artery with manual aspiration thrombectomy; Coronary balloon angioplasty; Glycoprotein IIb/IIIa receptor inhibitor (eptifibatide)	N/A	Lactated ringers; Lorazepam; Tylenol; BB (metoprolol)

Abbreviations: C-MRI, cardiac magnetic resonance imaging; CK-MB, creatinine kinase-myocardial band; CKD, chronic kidney disease; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; HTN, hypertension; LAD, Left anterior descending; LGE, Late gadolinium enhancement; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; MR, mitral regurgitation; N/A, not available; NT-proBNP, N-terminal-prohormone brain natriuretic peptide; PMH, past medical history; RA, rheumatoid arthritis; TTE, transthoracic echocardiography; USA, United States of America.

(43/43, 100%) and description of the adverse events (harms) or unanticipated events (42/43, 97.67%). The lowest scores were for the existence of takeaway lessons (4/43%, 9.3%) and clear reporting of intervention(s) or treatment procedure(s) (34/43, 79.07%) (Table S2).

Among the case series, three received a 10/10 score[74,85,86] and the lowest score was received by one study (3/10),[47] with an overall mean score of 7.73. Having complete inclusion of participants were the highest scoring criteria (26/26%, 100%), while the least reported criteria was appropriate statistical analysis (10/26%, 38.5%) (Table S3).

4 | DISCUSSION

In this systematic review of case reports and case series, we found that myocarditis/myopericarditis was the most reported cardiac complication of mRNA COVID-19 vaccines, particularly among young adult men, while MINOCA and isolated tachycardia were the least common. Moreover, individuals who received the BNT162b2 vaccine, especially the second dose, were more susceptible to myocarditis/myopericarditis than those receiving the mRNA-1273 vaccine were. CK-MB and troponin levels were suitable predictors of myocardial complications, as they increased in almost all patients, while the ECG was normal in one out of five subjects. This finding is clinically relevant to decide the management of patients who present with cardiac symptoms post COVID-19 mRNA vaccination. Patients with evidence of cardiac inflammation together with normal cardiac biomarkers and a relatively normal TTE study possibly have pericarditis and can be managed on an outpatient basis. On the other hand, a suggestive diagnosis of myocarditis would mean longer hospital monitoring for the patient and more definitive investigations such as C- MRI, known to be the gold standard test for diagnosing inflammation of the myocardium.

Although no cases of cardiac complications were reported in phase 3 trials of the mRNA vaccines,[6,87] there have been several reports of complications, particularly myocarditis, after COVID-19 vaccination. A previous report[88] evaluated the safety of BNT162b2 in a nationwide setting of more than 800,000 vaccinated participants who had no prior history of confirmed vaccine-related adverse events. They reported the risk ratio of developing myocarditis after vaccination to be 3.2 (1.6–12.4), followed by pericarditis (1.3 (0.7–2.3)) and myocardial infarction (1.1 (0.7–1.6)).[88] Another study[89] investigating myocarditis events after BNT162b2 immunisation in Israel reported the occurrence of 136 probable or definitive cases of myocardial inflammation up to 30 days post second dose vaccination, with mild presentations in 95% of the cases and only one fatality. The risk of this adverse event was 3.83 cases per 100,000 after the second dose and 0.64 case per 100,000 after the first dose. Compared with the historical data, the standardised incidence ratio was 5.3 (4.5–6.4) and the highest ratio was after the second vaccination in male recipients aged 16–19 years old (13.6 (9.3–19.2)).[89] Also, analysing the data of 2.5 million vaccinated health care workers revealed an incidence rate of 2.13 myocarditis cases per 100,000 persons who had received at least one dose of BNT162b2.[90]

A study by Kaur and colleagues on the cardiovascular adverse events associated with COVID-19 vaccines, which included 30,523 participants and went up to January 2021, found that tachycardia, which occurred in 16.4% of subjects, was the most common presentation.[10] However, most of the case reports and case series included in our systematic review reported myocarditis/myoepicarditis as the most common presentation. This finding is likely to be related to reporting bias, where a more severe form of illness, such as myocarditis, is more likely to be diagnosed, reported, and published compared to tachycardia, which is considered a less significant issue.

Interestingly, a multinational network cohort study, which evaluated the overall background rate of 15 adverse events associated with COVID-19 vaccines, and included more than 126 million participants, showed that myocarditis or pericarditis were more common among men and that the highest occurrence was found in the 75–84 age group (54 and 39 per 100,000 person-year incidence rate in males and females, respectively).[91] Consequently, the sex pattern of myocarditis or pericarditis events related to vaccination with mRNA COVID-19 vaccines is in accordance with the background observations, although we found that myocarditis and pericarditis were more common in the third and fourth decades of age. This discrepancy might be due to the fact that vaccine immune response is more potent and the reactogenicity is more common in younger adults that shift the maximum background incidence of inflammatory cardiac conditions in older ages to younger ages post-vaccination. In another study, performed with the aim of pooling data on myocarditis related to COVID-19 vaccines, PubMed was searched up to 27 June 2021 and they found two case series and six case reports.[92] Similar to our results, they found that 93% of myocarditis occurred in males with a mean age of 28 years old and that the BNT162b2 vaccine was associated more strongly with myocarditis than the mRNA-1273 vaccine, especially after the second dose (60% vs. 33%).[92] Nevertheless, no serious complications were reported by the previous study,[92] whereas we reported two deaths. Another research letter assessed vaccine-associated myocarditis by searching the international pharmacovigilance database VigiBase up to 7 May 2021 and noted that 17.1% of all myocarditis was COVID-19 vaccine related and that the mRNA COVID-19 vaccines had a more significant association with myocarditis.[93] Furthermore, they found that people with myocarditis had a mean age of 35 years and that it was more common in males.[93] Concurrent pericarditis was also found in 47 out of the 214 cases and they also reported five mortalities.[93]

In the current study, we found that chest pain was the most frequent sign of cardiac complications post mRNA COVID-19 vaccine, which occurred in 96% of the subjects and usually appeared within 3 days of vaccination. In line with our finding, Shay et al. suggested that chest pain 3–5 days after vaccination was a typical feature of immune-related myocarditis.[94]

A systematic review on the ECG findings of COVID-19 patients revealed that ST-T abnormalities, especially ST elevation, was the most common ECG feature.[95] Also, ST elevation (25%), ST depression (25%) and T inversion (25%) were common in those with COVID-19

associated myocarditis.[96] Similar patterns in ECG features were also found following an mRNA COVID-19 vaccination, as ST-segment or T-wave changes were the most common presentations.[32] In addition to ST-elevation and T-wave abnormality, which occurred in 57.8% and 9% of the subjects, PR-segment depression was another ECG feature following an mRNA vaccination. Previous research showed a mean LVEF of 53.5%,[92] while in our study we found that 18.2% of the patients had an LVEF of less than 50%. Although C-MRI is the gold standard method for the diagnosis of myocarditis,[97] its use at times may be limited because of a lack of availability in all regions and the associated high operating costs. In the absence of C-MRI, a thorough history taking and examination along with a rise in cardiac biomarkers, ECGs and TTE should be enough to diagnose myocarditis reliably.

A systematic review on the histopathological findings of COVID-19 showed that inflammatory cardiomyopathy (18%), myocarditis (14%), interstitial macrophages (9%), and individual myocyte necrosis (8%) were among the most frequent cardiac features in patients with COVID-19.[98] The cardiac pathological features following mRNA COVID-19 vaccination were very similar to SARS-CoV-2 infection and include macrophage and lymphocyte infiltration, myocyte necrosis and minimal interstitial fibrosis.

The management of myocarditis and pericarditis post vaccination was similar to other forms of myocarditis. We noted that many patients of myocarditis/myopericarditis were treated with NSAID's initially, a medication which is primarily used in pericarditis and should be avoided in myocarditis. An article by Sawalha et al.[96] showed that glucocorticoids (58%), immunoglobulin therapy (17%), and colchicine (17%) were the most common medical therapies for COVID-19 related myocarditis. In addition, inotropic and mechanical support, as well as anti-inflammatory drugs (e.g., tocilizumab and interferon), were also commonly used.[96] The management of myocarditis/myopericarditis following an mRNA COVID-19 vaccination is similar, in that NASIDs and colchicine were the most commonly used anti-inflammatory drugs. Nevertheless, beta-blockers, ACE inhibitors, and diuretics were also used in a small number of cases. However, it should be noted that the spontaneous resolution of cardiac presentations, following COVID-19 vaccination, is common and therefore therapies should be individual-based and be based upon the severity of the disease.[99]

We acknowledge that our study has some limitations. Firstly, despite the thorough approach we took in screening the databases, the probability of missing some related articles cannot be completely ruled out. Secondly, we only included case reports and case series, due to the limited numbers of original studies published on the cardiac complications of mRNA COVID-19 vaccines, until the preparation of the present review. Therefore, there is a potential risk of bias, since case report/series are not indicative and so the results should be interpreted with some caution. Thirdly, most of studies did not provide all the required information, particularly about the results of laboratory and cardiac testing. Moreover, it should be noted that the testing methods used for the detection of cardiac biomarkers were not the same every case (e.g., TnI, TnT and hsTn). Fourthly, we also included those studies with a previous history of COVID-19, which may affect the results, since COVID-19 can also cause cardiac complications. In response to this issue, we reported the prior history of COVID-19 in all studies included.

5 | CONCLUSIONS

Although cardiac complications that are associated with mRNA COVID-19 vaccines are rare, they can be life-threatening. Chest pain should be considered an alarming symptom, especially in those who had received a second dose of the BNT162b2 vaccine in the last 3 days. For diagnosis, CK-MB and troponin are better biomarkers to confirm myocarditis than CRP, ESR, and NT-proBNP. Furthermore, large-scale observational studies and systematic reviews on those studies are highly recommended. Moreover, subgroup analysis needs to be conducted, based on behavioural risk factors (e.g., alcohol consumption and smoking), comorbidities, and prior history of SARS-CoV-2 infection.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

AUTHOR CONTRIBUTIONS

Asra Fazlollahi, Mahdi Zahmatyar and Saeid Safiri designed the study. Asra Fazlollahi, Mahdi Zahmatyar, Maryam Noori and Seyed Aria Nejadghaderi wrote the first draft of the manuscript; Mark J. M. Sullman, Reza Shekarriz-Foumani, Ali-Asghar Kolahi, Kuljit Singh and Saeid Safiri critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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