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Myocarditis following mRNA Covid-19 vaccination: A pooled analysis

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ABSTRACT

Background: Post-marketing surveillance studies have raised concerns of increased myocarditis rates following coronavirus disease-19 (Covid-19) mRNA vaccines. The present study aims to accumulate the published mRNA Covid-19 vaccine-associated myocarditis cases, describe their clinical characteristics and determine the factors predisposing to critical illness.

Methods: Medline, Scopus, Web of Science, CENTRAL and Google Scholar were systematically searched from inception. Studies reporting adult myocarditis cases following BNT162b2 or mRNA-1273 vaccination were included. Individual participant data coming from case reports/series were pooled. Proportional random-effects *meta*-analysis was conducted by combining the pooled cohort and observational studies with aggregated data.

Results: Overall, 39 studies were included with a total of 129 patients. Most cases occurred in young males after the second vaccine dose. Myocarditis after the first dose was significantly associated with prior Covid-19 (*p-value*: 0.025). The most common electrocardiographic finding was ST-segment elevation, while late gadolinium enhancement was invariably observed in cardiac magnetic reasoning. Logistic regression analysis demonstrated that signs of heart failure were predictive of subsequent critical illness (Odds ratio: 19.22, 95% confidence intervals-CI: 5.57–275.84). Proportion *meta*-analysis indicated that complete resolution of symptoms is achieved in 80.5% of patients (95% CI: 59.3–92.1), while the proportion of participants necessitating intensive care unit admission is 7.0% (95% CI: 3.8–12.9).

Conclusions: Myocarditis following mRNA Covid-19 vaccination is typically mild, following an uncomplicated clinical course with rapid improvement of symptoms. Future research is needed to define its exact incidence, clarify its pathophysiology and determine the optimal management plan depending on its severity.

Protocol registration: dx.https://doi.org/10.17504/protocols.io.bxwtppen.

1. Introduction

Coronavirus disease 19 (Covid-19), caused by the betacoronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has been declared as a pandemic by the World Health Organization in March 11, 2020[1]. Following the emergency use authorization of Covid-19 vaccines, mass vaccination efforts have resulted in the administration of at least one dose in more than 40% of the global population through August 2021 [2]. Vaccines using mRNA (messenger ribonucleic acid) technology have played a central role in vaccination programs, allowing the *in vivo* delivery of viral mRNA with the use of lipid nanoparticles [3]. Randomized phase 3 clinical trials evaluating the BNT162b2 and mRNA-1273 vaccines have demonstrated high efficacy with a beneficial safety profile [4,5]. Subsequent real-world studies have confirmed that mRNA vaccines present high effectiveness against the alpha variant, as well as adequate protection against severe disease by the delta variant, especially after the administration of two doses [6]. Recently, the heavily mutated Omicron variant has emerged, characterized by increased transmissibility and immune evasion [7]. As a result, in the absence of readily available Omicron-specific vaccines, there is an increasing need of administering booster doses of existing mRNA vaccines in order to broaden the immunologic response and achieve cross-reactive neutralization of Omicron [8].

Concerns about potential adverse effects fuel vaccine hesitancy and constitute the main barrier to the wide immunization of the general population [9]. Phase 3 trials have not identified signals of serious systemic adverse reactions, although the short follow-up and the selected population of healthy volunteers may limit

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the ability of randomized controlled trials to fully elucidate possible safety concerns with these vaccines. As a result, both active and passive post-marketing surveillance systems are of great importance in detecting potential safety concerns with vaccines [10]. To this end, analysis of Israeli integrated data repositories revealed that receipt of the BNT162b2 vaccine is associated with increased rates of myocarditis, lymphadenopathy, appendicitis and herpes zoster infection. Specifically, the excess of myocarditis cases is estimated at 3 cases per 100,000 persons, although it should be stated that SARS-CoV-2 infection itself is linked to an 18-fold higher risk of myocarditis [11].

The present study aims to accumulate current literature and evaluate the clinical course of the reported myocarditis cases following the receipt of mRNA Covid-19 vaccines. To achieve this, the demographic, clinical and imaging characteristics of adult patients presenting with myocarditis are described and the potential factors associated with critical illness are explored.

2. Materials and methods

2.1. Study design

The present systematic review was designed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12]. The protocol of the study was prospectively registered (dx.https://doi.org/10.17504/protocols.io.bxwtppen). After institutional review board consultation, no ethical approval was required, as already published data were used and no patients were directly involved in the present study.

2.2. Eligibility criteria

The population of the study consists of adult patients diagnosed with myocarditis following vaccination with mRNA Covid-19 vaccines (BNT162b2 or mRNA-1273). Myocarditis could be diagnosed with clinical criteria, based on clinical signs, electrocardiogram, echocardiography and serum troponin values. Alternatively, in case of cardiac magnetic resonance imaging (cMRI) availability, the Lake Louise criteria were used for case definition [13]. A definitive diagnosis of acute myocarditis was ascertained in cases with histopathologic confirmation. Outcomes of interest include electrocardiographic changes, development of heart failure, cardiac magnetic resonance findings, admission to the intensive care unit and death. Case reports and case series reporting individual participant data were included. Observational cohort studies were also included, requesting individual patient data from the authors of original articles. Patients vaccinated with non-mRNA vaccines, those with age < 18 years or patients with pericarditis without myocardial involvement were excluded.

2.3. Data sources

Literature search was conducted by systematically searching Medline, Scopus, Web of Science and CENTRAL (Cochrane Central Register of Controlled Trials). Google Scholar was also searched to provide coverage of the grey literature. The reference lists of the included studies were screened aiming to identify potentially eligible articles, using the snowball method [14]. Search was performed from inception to September 9, 2021. No date or language restrictions were applied. The search strategy included the use of both Medical Subject Headings (MeSH) terms and key-words. The main search algorithm was the following: "("Vaccines"[Mesh] OR vaccin* OR BNT162b2 OR mRNA-1273) AND ("COVID-19"[Mesh] OR "Coronavirus"[Mesh] OR covid OR sars) AND ("Myocarditis"[Mesh] OR myocarditis OR myopericarditis OR heart OR cardiac)".

2.4. Study selection

The studies of the present review were selected following three stages. At first, the titles and abstracts of electronical records were screened to assess for potential eligibility. Subsequently, all articles that were considered to be possibly eligible were retrieved in full-text form. Finally, any study that did not satisfy the pre-defined inclusion and exclusion criteria was excluded from the analysis. This process was performed by two researchers independently, resolving any conflicts through the consensus of all authors.

2.5. Data extraction

The following data were extracted from the included studies: number of cases, sex, age, vaccine type, days from vaccination, vaccine dose, cardiovascular comorbidities, history of Covid-19, clinical presentation with chest pain, anti-spike SARS-CoV-2 antibodies, electrocardiographic findings, presence of heart failure, ejection fraction, magnetic resonance findings, treatment, symptom resolution, length of hospital stay, admission to intensive care unit (ICU) and death. Data were collected in pre-piloted forms by two reviewers independently; any discrepancy was resolved through consensus.

2.6. Quality assessment

Evaluation of risk of bias was performed by taking into account the domains of selection, ascertainment, causality and reporting [15]. Specifically, the selection domain referred to whether the presented cases represent the whole experience of the researchers. Ascertainment of diagnosis was assessed based on confirmation of myocarditis with cMRI or biopsy. The domain of causality was judged by considering whether alternative causes of myocarditis were excluded while the reporting domain referred to the adequacy of description of the cases clinical course. Risk of bias assessment was conducted by two researchers independently, resolving any disagreement with discussion.

2.7. Data analysis

Individual participant data coming from case reports and case series were combined, forming the pooled cohort. Statistical significance was defined by a two-sided *p-value* threshold of 0.05. The normality of distributions was assessed with the Shapiro-Wilk test [16]. Normally distributed data were compared using the Student's *t-test*; otherwise, the Mann-Whitney *U* test was applied. Categorical variables were compared with the chi-square or the Fisher's exact test, as appropriate. Logistic regression analysis was implemented to evaluate potential factors associated with admission to ICU. Both univariable and multivariable models were fitted to test the effects of age, sex, vaccine type (BNT162b2 or mRNA-1273), vaccine dose, presence of cardiovascular comorbidities, prior Covid-19, pericardial involvement, ST-segment elevation in the electrocardiogram and signs of heart failure.

Proportional *meta*-analysis was conducted by combining the pooled cohort and observational studies with aggregated data. Meta-analysis estimates were derived using the random intercept logistic regression method [17]. Inter-study heterogeneity was quantified with the inconsistency index (I^2) values, with I^2 greater than 50% indicating significant heterogeneity [18]. Statistical analysis was performed in R-4.0.5 (package "*meta*" [19]).

3. Results

3.1. Study selection

Overall, 1,897 records were identified by literature search. Following deduplication and article screening, a total of 49 studies were retrieved as full-texts. Subsequently, 10 studies were excluded for the following reasons: inclusion of pediatric cases (n = 7) [20–26], diagnosis of multisystem inflammatory syndrome (n = 1) [27], analysis of incidence data of a pharmacovigilance database (n = 1) [28] and opinion paper (n = 1) [29]. Therefore, 39 studies were included; 37 of them [30–66] provided individual data of 86 participants, forming the pooled cohort. On the other hand, 2 observational studies [67,68] reported aggregated data of 43 patients. The study selection process is illustrated in the PRISMA flowchart (Fig. 1).

3.2. Quality assessment

The outcomes of quality assessment of the included studies are presented in Fig. 2. Overall, 20 studies were judged to be at low risk of bias and the remaining 19 studies at moderate risk of bias. Specifically, concerns of selection bias were raised in 3 studies presenting only severe myocarditis cases. Some concerns of bias were assigned to the domain of ascertainment in 7 studies since no magnetic resonance imaging or cardiac biopsy was performed. In addition, in 40% of studies the causality could not be safely established, as no specific testing was implemented to exclude potential alternative causes. The reporting of cases was evaluated as adequate in the majority (89.7%) of studies. No study was assessed to be at high risk of bias.

3.3. Pooled cohort

The data extracted from the included studies are exhibited in Suppl. Table 1. The clinical characteristics, presentation and outcomes of the participants included in the pooled cohort are presented in Table 1. Among 86 patients, 64 received the BNT162b2 vaccine and 22 patients the mRNA-1273 vaccine. The mean age of participants was 24 years (range: 18 to 70), while the majority of them (90.7%) were males. Most myocarditis cases (87.2%) occurred following the second vaccine dose, after a median time interval of 3 days. A prior diagnosis of Covid-19 was present in the medical history of 6 patients and was significantly associated with the development of myocarditis after the 1st dose (Fisher's exact test *p-value*: 0.025). Anti-spike SARS-CoV-2 antibodies were measured in 18 patients and were positive in 16 of them.

The most common electrocardiographic finding was ST-segment elevation, followed by sinus tachycardia. Episodes of ventricular tachycardia were rare (7.0%). Echocardiography revealed regional wall abnormalities in 27.9% and a low left ventricular ejection fraction in 23.3% of patients. Pericardial involvement was present in 34.9% of cases. All patients presented increased values of serum troponin. The diagnosis was ascertained with cardiac magnetic reasoning in 74 patients, with late gadolinium enhancement being consistently detected. Colchicine and non-steroidal anti-

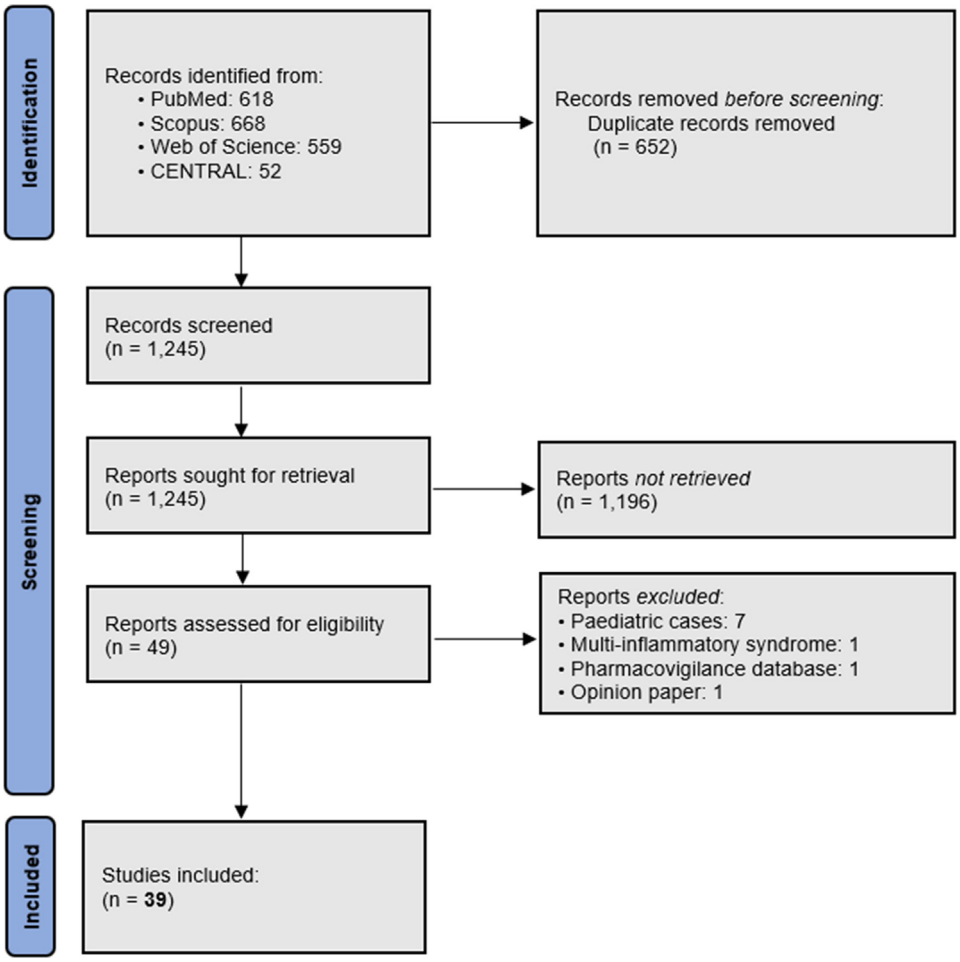

Fig. 1. PRISMA flowchart of literature search.

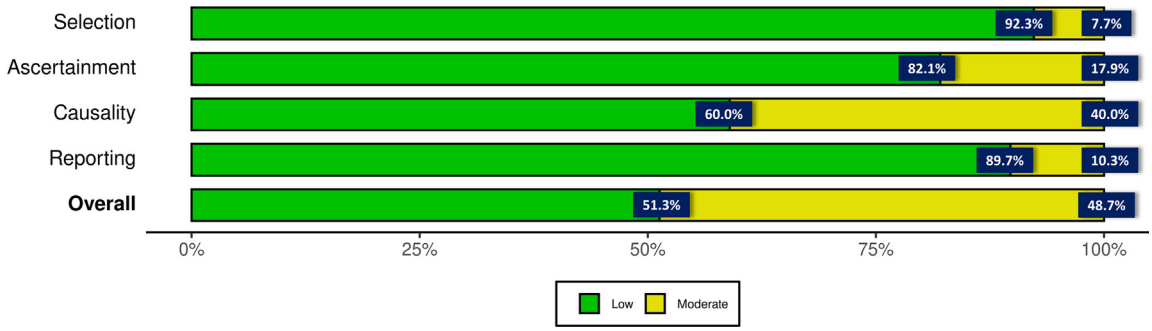

Fig. 2. Outcomes of the quality assessment.

Table 1
Clinical characteristics and outcomes in myocarditis cases stratified by vaccine type.

Variable	Overall (n = 86)	BNT162b2 vaccine (n = 64)	mRNA-1273 vaccine (n = 22)	*p-value*
Clinical characteristics				
Age (years)	24 [21–33.5]	24 [20.8–32]	27 [22–37.5]	0.226
Male sex	78 (90.7%)	61 (95.3%)	17 (77.3%)	**0.024**
Second vaccine dose	75 (87.2%)	55 (85.9%)	20 (90.9%)	0.721
Days from vaccination	3 [2–4]	3 [2–4]	3 [2–4]	0.979
Prior Covid-19	6 (7.0%)	3 (4.7%)	3 (13.6%)	0.172
Cardiac comorbidity	8 (9.3%)	4 (6.3%)	4 (18.2%)	0.195
Clinical presentation				
Chest pain	78 (90.7%)	59 (92.2%)	19 (86.4%)	0.416
Sinus tachycardia	21 (24.4%)	16 (25.0%)	5 (22.7%)	1
ST-segment elevation	59 (68.6%)	46 (71.9%)	13 (59.1%)	0.396
Ventricular tachycardia	6 (7.0%)	5 (5.8%)	1 (4.5%)	1
Any ECG change	76 (88.4%)	58 (90.6%)	18 (81.8%)	0.270
Left ventricle ejection fraction < 50%	20 (23.3%)	15 (23.4%)	5 (22.7%)	1
Regional wall motion abnormality	24 (27.9%)	13 (20.3%)	9 (40.9%)	**0.033**
Pericardial involvement	30 (34.9%)	23 (35.9%)	7 (31.8%)	0.929
MRI performed	74 (86.0%)	57 (89.1%)	17 (77.3%)	0.282
Cardiac edema	58 (78.4%)	46 (82.5%)	12 (70.6%)	0.502
Late gadolinium enhancement	73 (98.6%)	56 (98.2%)	17 (100%)	1
Management				
Treated for heart failure	12 (14.0%)	8 (12.5%)	4 (18.2%)	0.494
Colchicine	30 (34.9%)	25 (39.1%)	5 (22.7%)	0.260
Aspirin/NSAIDs	34 (39.5%)	29 (45.3%)	5 (22.7%)	0.106
Corticosteroids	10 (11.6%)	8 (12.5%)	2 (9.1%)	1
Outcome				
Complete symptom resolution	80 (93.0%)	60 (98.4%)	20 (90.9%)	0.280
Intensive care unit admission	7 (8.1%)	5 (7.8%)	2 (9.1%)	1
Death	2 (2.3%)	1 (1.6%)	1 (4.5%)	0.448

Continuous data are presented as median [interquartile range].Categorical data are presented as number of patients (column percentage). ECG: electrocardiogram; MRI: magnetic resonance imaging; NSAIDs: non-steroidal anti-inflammatory drugs

inflammatory drugs were the most commonly used medications, while 12 patients were treated for heart failure. The median length of hospital stay was 3 days (interquartile range: 2 to 5.75). The majority of cases followed a mild clinical course with complete resolution of symptoms; however, 7 patients were admitted to the intensive care unit and 2 of them eventually died. The outcomes of the logistic regression analysis indicated that the development of heart failure was associated with subsequent intensive care unit admission; no predictive role was suggested for age, sex, vaccine type and dose, prior Covid-19, cardiac comorbidities, ST-segment elevation and pericardial involvement (Table 2).

3.4. Observational studies

Aggregated participant data were available in 2 studies. Specifically, Diaz *et al.*[68] presented 20 mRNA Covid-19 vaccine-associated myocarditis cases, with 11 of them following the mRNA-1273 vaccine. Most patients (75%) were males with a median age of 36 years. The median length of hospital stay was 2 days, while 2 patients developed critical illness necessitating intensive care unit admission but no deaths were observed. Complete resolution of symptoms was achieved 13 patients, while symptom improvement was noted in the remaining 7 patients. Montgomery *et al.*[67] reported the clinical course of 23 myocarditis cases. All were males with a median age of 25 years. The electrocardiogram was abnormal in 19 patients, while 4 cases were complicated with reduced left ventricular ejection fraction. cMRI was performed in 8 participants and all of them met the Lake Louise criteria for myocarditis diagnosis. No patient developed critical illness. Symptoms resolved in 16 (69.6%) patients within the first week, while chest discomfort persisted in 7 patients.

3.5. Meta-analysis

The outcomes of proportional *meta*-analysis are depicted in Fig. 3. The percentage of male sex was 90.9% (95% CI: 74.1 to 97.2). Myocarditis occurred mainly after the second vaccination dose (86.1%, 95% CI: 78.9 to 91.0), while the BNT162b2 vaccine

Table 2
Logistic regression analysis for the prediction of intensive care unit admission.

Variable	Univariable model	*p-value*	Multivariable model	*p-value*
Age	1.02 (0.94–1.08)	0.625	1.02 (0.92–1.11)	0.711
Sex				
Female	Reference	0.092	Reference	0.244
Male	0.21 (0.03–1.64)		0.17 (0.01–4.02)	
Vaccine type				
BNT162b2	Reference	0.850	Reference	0.745
mRNA-1273	1.18 (0.16–5.96)		0.61 (0.02–10.20)	
Vaccine dose				
First	Reference	0.902	Reference	0.749
Second	0.87 (0.13–17.31)		1.65 (0.01–69.41)	
Prior Covid-19				
Yes	Reference	0.442	Reference	0.840
No	2.47 (0.12–19.06)		0.67 (0.01–20.94)	
Cardiac comorbidity				
No	Reference	0.092	Reference	0.829
Yes	4.87 (0.61–28.78)		0.69 (0.01–16.17)	
ST-segment elevation				
No	Reference	0.329	Reference	0.129
Yes	2.94 (0.47–57.12)		12.63 (0.88–900.93)	
Pericardial involvement				
No	Reference	0.053	Reference	0.143
Yes	5.40 (1.08–39.55)		5.58 (0.65–87.69)	
Heart failure				
No	Reference	**0.004**	Reference	**0.010**
Yes	11.83 (2.25–70.05) *		19.22 (5.57–275.84) *	

Asterisks denote statistical significance.

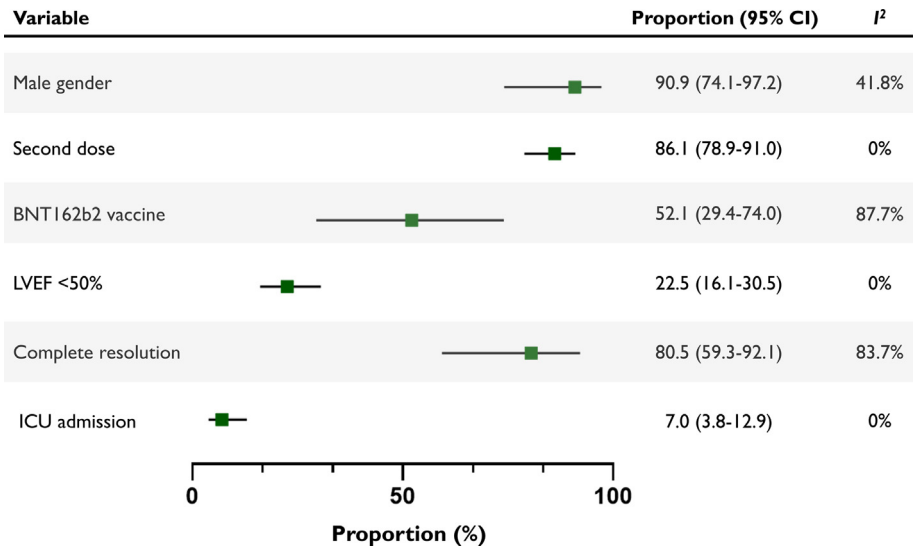

Fig. 3. Outcomes of the proportional *meta*-analysis combining the pooled cohort with observational studies. *LVEF: left ventricular ejection fraction; CI: confidence intervals; I^2: inconsistency index.*

had been administered in 52.1% of cases (95% CI: 29.4 to 74.0). The proportion of patients with reduced left ventricular ejection fraction was estimated at 22.5% (95% CI: 16.1 to 30.5). Complete symptom resolution was achieved in 80.5% of cases (95% CI: 59.3 to 92.1), while the risk of intensive care unit admission was calculated to be 7.0% (95% CI: 3.8 to 12.9), Inter-study heterogeneity was high in the variables of vaccine type and complete symptom resolution, while no heterogeneity was observed concerning vaccine dose, reduced left ventricular ejection fraction and intensive care unit admission (I^2: 0%).

4. Discussion

The present study accumulated current literature cases of myocarditis following mRNA Covid-19 vaccination in adults, evaluating a total of 129 patients. Myocarditis commonly occurred in young males with chest paint being the main symptom at presentation. Admission electrocardiogram was potentially a sensitive tool since the majority of cases presented at least one abnormality, especially ST-segment elevation. Coronary artery imaging is typically normal, while cMRI should represent the main modality for confirming the diagnosis of myocarditis since late gadolinium enhancement with or without edema in T2-weighted imaging is observed in the majority of patients in our case series. Most cases follow an uncomplicated clinical course and complete resolution of symptoms is rapidly achieved. The presence of heart failure signs should raise the suspicion of severe myocarditis, since it was significantly associated with subsequent intensive care unit admission.

The vast majority of cases occurred following the second vaccination dose, while myocarditis after the first dose was significantly

associated with prior Covid-19. This observation suggests the hypothesis that previous infection with SARS-CoV-2 may predispose to myocardial injury. Histological findings from biopsy-confirmed cases indicate that cardiac inflammation is mainly lymphocytic with abundancy of CD3 + lymphocytes and CD68 + macrophages [53,64]. This pattern of inflammatory injury contrasts the findings of myocarditis following small-pox vaccination, which is characterized by eosinophilic predominance [69]. As a result, it may be assumed that the lymphocytic histological pattern may partially explain the mild clinical course of most mRNA Covid-19 vaccination-associated cases since giant cell or eosinophilic myocarditis have been linked with significantly higher mortality rates [70].

Management of myocarditis remains largely supportive and is based on the restoration of hemodynamic stability and the administration of guideline-directed heart failure and arrhythmia treatment [71]. Patients with preserved ventricular function and non-severe features were often treated with colchicine or non-steroidal anti-inflammatory drugs as in acute pericarditis, although potential concerns of toxicity have been raised in animal models of viral myocarditis [72,73]. A minority of patients with moderate to severe disease received corticosteroids due to their potential efficacy in autoimmune forms of myocarditis, although evidence is less clear regarding viral myocarditis [74]. Immunosuppressive therapy should be also considered on an individual basis for cases with non-infectious lymphocytic myocarditis, given that no other contraindications exist [75]. Nonetheless, further research is needed before firm conclusions about the optimal management plan can be drawn.

The present study has several strengths. A comprehensive literature search of 5 databases was conducted, ensuring the inclusion of all published cases of mRNA Covid-19 vaccination-associated myocarditis. Individual participant data were used to form a cohort of 86 patients, allowing logistic regression analyses to be performed. This cohort was also combined with two observational studies, providing pooled outcomes by applying proportional *meta*-analysis. On the other hand, the interpretation of the outcomes may be limited by the sample size since it did not allow the detection of a high number of events (intensive care unit admissions or deaths). The variability of patients across studies should be also taken into account due to the lack of diagnosis confirmation by cMRI in all studies. In addition, it should be stated that case reports and case series present inherent limitations due to their design and are prone to publication bias since the most serious or atypical cases are preferentially reported. Attrition bias is also a concern since follow-up periods may differ among studies.

In conclusion, myocarditis following mRNA Covid-19 vaccination typically affects young males and follows a mild clinical course, resulting in a rapid complete resolution of symptoms. Severe disease and development of critical illness are rare and should be suspected when signs of heart failure are present. Future research should focus on the continuous monitoring of vaccines' safety profile with active post-marketing surveillance aiming to clarify the exact incidence of myocarditis after COVID-19 vaccination. Anti-nucleocapsid SARS-CoV-2 antibodies should be routinely tested in order to evaluate the potential presence of prior exposure to the virus, especially among patients presenting after the first vaccine dose. The optimal treatment plan of severe vaccine-related myocarditis remains to be elucidated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.02.017.

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