Is There a Causal Link Between Acute Myocarditis and COVID-19 Vaccination: An Umbrella Review of Published Systematic Reviews and Meta-Analyses

Clinical Medicine Insights: Cardiology
Volume 18: 1–10
© The Author(s) 2024
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11795468231221406

Amine Bouchlarhem[1,2], Soumia Boulouiz[1,2], Zakaria Bazid[1,2], Nabila ismaili[1,2,3] and Noha El ouafi[1,2,3]

[1]Faculty of Medicine and Pharmacy, Mohammed First University, Oujda, Morocco. [2]Department of Cardiology, Mohammed VI University Hospital, Mohammed First University, Oujda, Morocco. [3]Faculty of Medicine and Pharmacy, Mohammed First University, LAMCESM, Oujda, Morocco.

ABSTRACT

INTRODUCTION: A few months after the beginning of the coronavirus disease of 2019 (COVID-19) vaccination, several reports of myocarditis secondary to the vaccines were published, sometimes with fulminant cases, but until today there is no proven causal link between these 2 events, but with many hypotheses proposed.

METHODS: A systematic review of current evidence regarding myocarditis after COVID-19 vaccination was performed by searching several databases including PubMed/Medline and Web of Science. The quality of Meta-analysis was assessed using the AMSTAR-2 tool as well as other qualitative criteria.

RESULTS: Our umbrella review appraised 4 Meta-analysis of retrospective studies (range: 5-12), The number of vaccine doses included ranged from 12 to 179 million, with the number of myocarditis cases observed ranging from 343 to 1489. All types of vaccines were evaluated, with no exclusions. The overall incidence ranged from 0.89 to 2.36 cases of myocarditis per 100 000 doses of vaccine received. Heterogeny was assessed in 3 of the Meta-analysis, and was highly significant (>75%) in all included studies, and with a significant *P*-value ($P < .05$). Regarding publication bias, 3 of the Meta-analysis conducted the egger and begg regression, with a significant result in only 1. Regarding the assessment of the methodology by the AMSTAR-2 scale indicating that the quality was very critical in 1, low in 2, and moderate in 1 Meta-analysis.

CONCLUSION: The quality of current non-randomized evidence on real causality and incidence of myocarditis after COVID-19 vaccine is still low.

KEYWORDS: Myocarditis, COVID-19 vaccines, causality, umbrella review

RECEIVED: April 5, 2023. **ACCEPTED:** October 25, 2023.

TYPE: Systematic Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Amine Bouchlarhem, Faculty of Medicine and Pharmacy, Mohammed First University, Oujda 60000, Morocco. Email: aminbouchlarhem63@gmail.com

Introduction

Coronavirus 2019 (COVID-19) has put the world on an unusual health alert, with serious socio-economic implications. The so-called COVID-19 disease is secondary to infection with the newly emerging strain of the coronavirus family, which will eventually give rise to coronavirus-2 severe acute respiratory syndrome (SARS-CoV-2).[1] Although initially considered a purely respiratory condition, COVID-19 is now considered a general disease with several possible conditions, mainly thrombo-embolic,[2] and cardiovascular disease, which represents a prognostic impairment of the disease.[3] Among the cardiovascular disorders described, it was indeed myocarditis,[4] this can be fatal, due to its mainly rhythmic and hemodynamic complications and worsens the prognosis in the short and medium term.[5] Given the severity of COVID-19, the world needed to have such an effective vaccine as soon as possible. Since the beginning of 2021, several vaccines have been urgently approved for use after passing the necessary clinical trials.[6] After the start of the vaccination in the majority of the countries of the world, and of course the close monitoring of the effectiveness of the vaccine on the one hand which proved by the decrease of severe cases, as well as the decrease of the rate of hospital admission for a COVID-19 disease and the safety by reporting any adverse event. A few months after the start of 2021, several reports of myocarditis secondary to COVID-19 vaccination are published, in some cases with fulminant cases, but to date there is no established causal link between these events, but several hypotheses are proposed. Among these hypotheses we cite the immune hypothesis, with dysregulation of the immune response, with the synthesis of autoantibodies against cardiac myocytes, adding to this, molecular mimicry between autoantigens and the virus' spike protein, which will subsequently lead to an aggressive immune response with inappropriate cytokine secretion, and subsequent aggression of cardiac myocytes.[7] We conducted an umbrella review of all systematic reviews with meta-analyses published in this

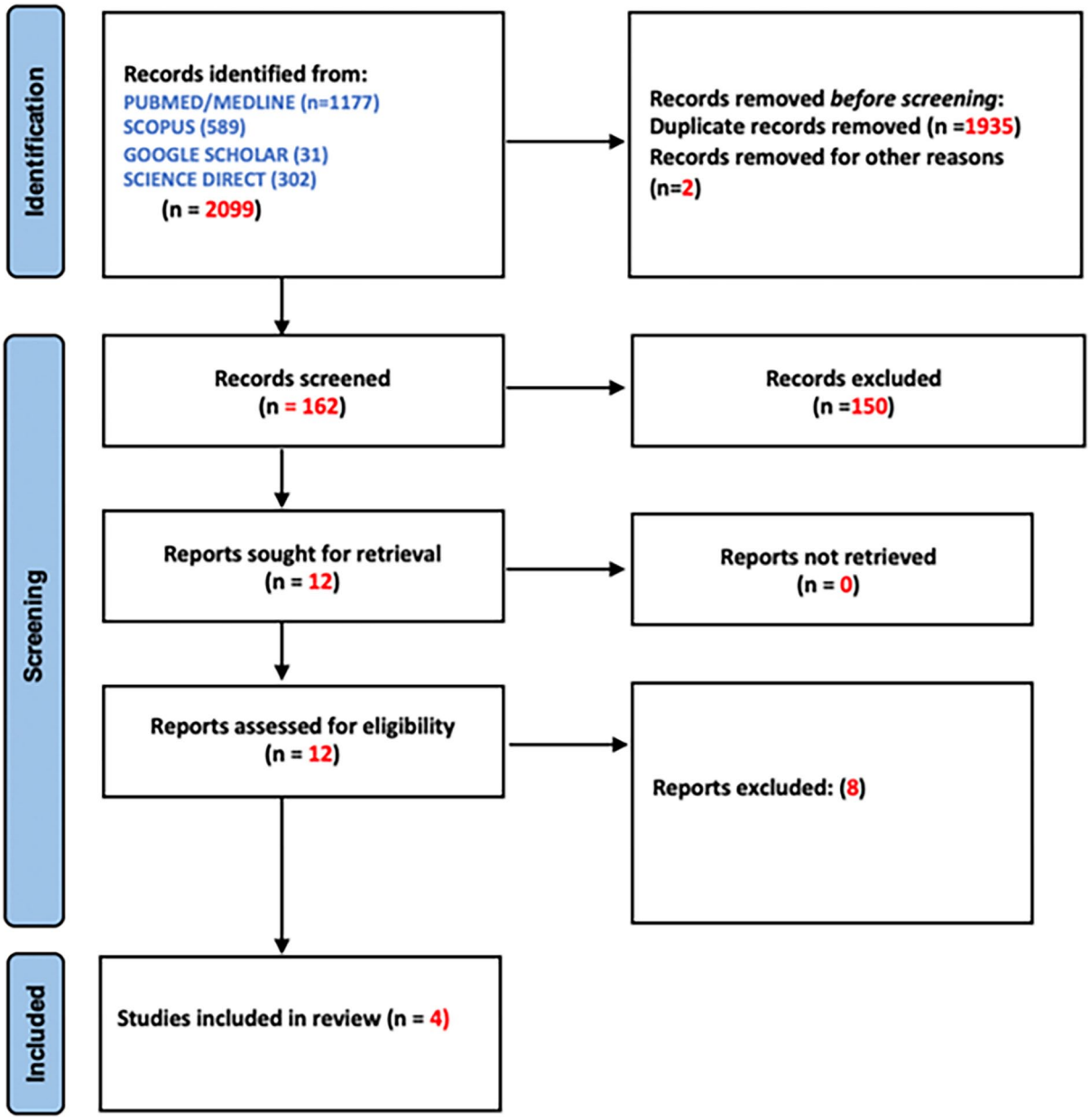

Figure 1. Flow diagram of article selection.

sense, in order to carry out a critical review to be able to draw relevant conclusions for our practice.

Methods

Search strategy

Before proceeding with our systematic review, and based on international guidelines for the proper conduct of a systematic review, we first registered our systematic review in the PROSPERO International Prospective Register of Systematic Reviews (registration number : CRD42021297893), this is an international database from the University of York (UK), whose main objective is to prospectively register systematic reviews as well as meta-analyses for the purpose of limiting duplication and improving transparency of work.[8] After this registration stage, a search was conducted for systematic reviews and meta-analyses published in the literature that report or study the occurrence of myocarditis after vaccination against COVID-19, from December 2021 to October 2022. First, the search is done in the PUBMED/MEDLINE database, where the majority of medical journals are indexed, using the following keywords:

[(coronavirus vaccine) *OR* COVID-19 vaccine *OR* SARS-COV-2 vaccine] AND (Myocarditis *OR* Myocardial inflammation *OR* Myopericarditis) AND (Systematic review *OR* meta-analysis), additional searches are performed in the Scopus, google Scholar databases. To limit the language bias, we performed a search onscience direct and Em-consulte for articles published in French, and CNKI (China Nationale Knowledge Infrastructure) for Chinese. Eligible articles are carefully examined in full text and reviewed (Figure 1).

Eligibility criteria

Before being selected for inclusion in our umbrella review, all articles selected for inclusion in the review fulfilled our inclusion criteria which are: (a) a systematic review and/or meta-analysis and (b) the study population is patients with confirmed myocarditis either by cardiac magnetic resonance imaging (MRI) or endo-myocardial biopsy in the immediate aftermath of vaccination. Narrative, editorial, commentary and hypothesis articles are excluded from our review.

Study selection and assessment of methodological quality

The quality of our review method was assessed using the AMSTAR-2 checklist. This tool is highly recommended for assessing the quality of meta-analyses of human observational and interventional studies and systematic reviews. It is based on a grid of 16 questions in total, 7 of which are core questions (Q2, Q4, Q7, Q9, Q11, Q13, and Q15), and is not intended to calculate an overall score. Based on these questions, the quality of systematic reviews and meta-analyses is classified as high, moderate, low, or very low. The assessment based on AMSTAR-2 was first performed by AB and reviewed independently by SB, with disagreements sorted by consensus.

Data extraction

For all included reviews, both authors (AB and SB) collected data manually. Firstly, we started with the collection of the parameters on which we performed the general description of the reports and this on the following parameters: author and country, type of vaccine evaluated, journal of publication, number of included studies as well as the type of studies, and then the number of events described in relation to the number of included patients. Then for the meta-analysis, the main event described, the risk ratios with 95% confidence intervals, the heterogeneity with its *P*-value, and the risk of bias analysis by determining the *P*-value of the Egger and Begg test for each meta-analysis were described. Finally, to assess the quality of each MA, we determined the following parameters: registration or not in the PROSPERO database, use or not of the Newcastle Ottawa Scale (NOT); subgroup analysis, grey literature search and finally funding. Forest plotting of overall effects based on RRs and their confidence intervals was performed using data extracted from each meta-analysis.

Grading the evidence

The evidence was graded into 4 classes, according to the type of studies included (prospective or retrospective), *P*-value of the overall effect, level of heterogenicity, sample size, or inclusion or not of the null value in the 95% confidence interval.

The 4 classes of evidence are as follows[9]:

- Class I (convincing): when number of cases>1000, $P<10^{-6}$, $I^2<50\%$, 95% prediction interval excluding the null, no small-study effects, and no excess significance bias.
- Class II (highly suggestive): number of cases>1000, $P<10^{-6}$, largest study with a statistically significant effect and class I criteria not met.
- Class III (suggestive): number of cases>1000, $P<10^{-3}$ and classes I and II criteria not met
- Class IV (weak): $P<.05$ and classes I and III criteria not met
- Non-significant when $P>.05$

Results

General characteristics of included systematic reviews and meta-analyses

General characteristics. We included 4 systematic reviews (SRs) with meta-analyses (MAs) in our umbrella review (Table 1). All of these reviews are published in 2022, with the number of included studies ranging from 5 to 12 studies. All studies included in these SRs were retrospective observational. The number of vaccine doses ranged from 12 to 179 million, with the number of myocarditis cases observed ranging from 343 to 1489. All types of vaccines were evaluated, with no exclusions.

Meta-analysis of the total incidence of myocarditis after COVID-19 vaccination. All Mas evaluated the incidence of myocarditis regardless of the type of vaccine or number of doses (Table 2). The overall incidence ranged from 0.89 to 2.36 cases of myocarditis per 100 000 doses of vaccine received (Figure 2). Heterogeny was assessed in 3 of the MAs, and was highly significant (>75%) in all included studies, and with a significant *P*-value ($P<.05$). Three of the included MAs conducted sensitivity analysis with a meta-regression to search for the source of heterogeny. In 2 Mas,[10,11] the incidence did not change significantly, but in only 1 MA,[12] age, gender, and ethnicity were detected as sources of heterogeneity, although the incidence did not change in the subgroup analysis. Regarding publication bias, 3 of the MAs conducted the Egger and Begg regression, with a significant result in only 1.[11]

Critical appraisal of included systematic reviews and meta-snalyses

General review. Of the 4 MAs included, only 1 was not registered in the PROSPERO database (Table 3). Writing guidelines and reporting, including Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), were used in all included MAs. Three of the MAs used the NOS scale to

Table 1. General characteristics of included systematic reviews and meta-analyses.

AUTHORS	VACCINES STUDIED	JOURNAL	COUNTRY	NOMBRE OF INCLUDED STUDIES	TYPES OF INCLUDED STUDIES	EVENTS	PATIENT ENROLLMENT
Ling et al.[10]	All types	*Lancet Respiratory Medicine*	England	5	Retrospective observational cohort	1489	179 664 350
Voleti et al.[11]	All types	*Frontiers in Cardiovascular Medicine*	United States	12	Retrospective observational Cohort	709	55 500 000
Gao et al.[12]	All types	*American Journal of Preventive Medicine*	China	11	Retrospective observational cohort	5473	58 630 611
Chou et al.[13]	All types	*Clinical Research in Cardiology*	China	12	Retrospective observational cohort	343	12 602 625

Table 2. Outcomes, heterogeneity, and publication bias in included meta-analyses.

AUTHORS	END POINT	POOLED RATE PER 100 000 DOSES [95% CI]; *P*-VALUE	HETEROGENEITY (I^2); *P*-VALUE	SOURCE OF HETEROGENEITY EVALUATED?	RESULTS OF THE SENSITIVITY ANALYSIS	*P*-VALUE OF PUBLICATION BIAS TESTS
Ling et al.[10]	Incidence of myocarditis	0.89 (0.67; 1.18) Not rapported	96% ($P = .001$)	Yes (sensitivity analysis and meta-regression)	The pooled incidence of myocarditis for COVID-19 vaccines did not change significantly.	Egger's tets ($P = .12$)
Voleti et al.[11]	Incidence of myocarditis	1.95 (1.44; 2.65) Not rapported	73% ($P = .0005$)	Yes (sensitivity analysis and meta-regression)	The pooled incidence of myocarditis for COVID-19 vaccines did not change significantly.	Egger's test ($P = .01$) Begg's test ($P = .14$)
Juan et al.[12]	Incidence of myocarditis	2.36 (1.55; 3.58) $<.001$	91.4% ($P < .001$)	Yes (sensitivity analysis and meta-regression)	Meta-regression analysis indicated that the heterogeneity was influenced by age ($P = .014$), sex ($P = .033$), and location ($P = .012$), but the pooled incidence of myocarditis for COVID-19 vaccines did not change significantly.	Begg's and Egger's tests suggested that there was no publication bias across the studies ($P > .05$)
Chou et al.[13]	Incidence of myocarditis	2.234 (0.846; 5.899) Not rapported	95.79%	No	—	—

assess the quality of the non-randomised studies included in each, while only 1 MA used the JBI scale. Regarding subgroup analysis, it was used in all MAs. Funding was reported in only 1 MA, and the limitations of each MA were discussed in the discussion.

Critical appraisal and evidence grading of included meta-analyses based on AMSTAR-2. Regarding the assessment of the methodology by the AMSTAR-2 scale indicating that the quality was very critical in 1, low in 2 MAs, and moderate in 1 MA (Tables 4 and 5). For the critical questions of this scale (Q2,

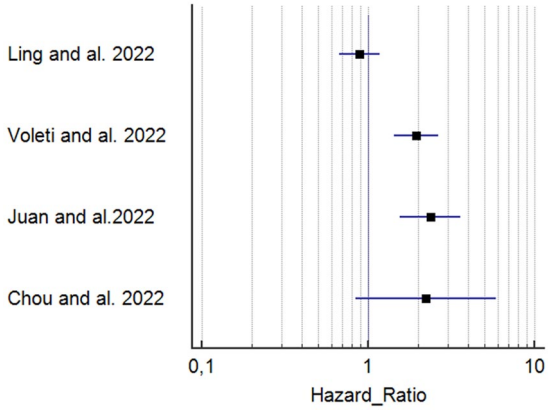

Figure 2. Forest plots of pooled hazard ratio's for myocarditis per 100 000 persons.

Q4, Q7, Q9, Q11, Q13, and Q15) we find: for question Q2 that all the MAs have already registered their protocols in the PROSPERO database with a description of the rationale, the research strategy, the inclusion and exclusion criteria and finally the assessment of the risk of bias. For question Q4, a comprehensive review was only partially conducted in 3 MAs, and fully conducted in 1 MA. For the excluded studies (Q7), none of the MAs presented the reasons for exclusion. For the risk bias assessment (Q9), only 1 MA did not conduct this critical assessment tool. The methods for combining results (Q11) were appropriate in only 1 MA, partially in 2 others, and unclear in 1. For the impact of individual studies (Q13) and publication bias (Q15), only 1 MA met the necessary requirements, 2 MAs partially met them, and finally, only 1 MA did not conduct the meta-analysis. All MAs were classified as level IV evidence except 1, which was classified as level III, and this was due to the retrospective nature of the included studies and the failure to report the *P*-value of the overall effect.

Discussion

In this umbrella review, we conducted a critical analysis of the different published meta-analyses regarding the link between post-vaccination myocarditis and COVID-19.

While the methodology of writing a meta-analysis was respected in the majority of the included studies, with regard to the registration of the meta-analysis protocol, the respect of the PRISMA diagram to detail the studies included in the meta-analysis, the quality assessment of each study by the newcastle ottawa scale (NOS), but the heterogeneity was very important even after sensitivity analysis or subgroup analysis for the majority of the MAs. This can only be explained by the moderate quality of the initial studies included in each of the meta-analyses, and although the incidence is in the range of 0.89 to 2.36 cases of myocarditis per 100 000 doses of vaccine, there is still a need for more methodologically rigorous cohorts in order to be able to perform high quality, outcome-relevant meta-analyses of the true incidence of myocarditis in post-vaccination COVID-19.

Vaccination against COVID-19

The main target of the different COVID-19 vaccines is the binding domain of the spike protein receptor characteristic of COVID-19, which represents the main binding point to the angiotensin-converting enzyme-2 receptor on the host cell.[14] Schematically, vaccines can be divided into 4 types: the inactivated vaccine, the mRNA vaccine, the viral vector vaccine, and the peptide nanoparticle vaccine.[15] Table 6 Summarizes the different vaccines available and their characteristics.

Effectiveness of COVID-19 vaccination

The efficacy of the various COVID-19 vaccines has been well established, especially after the second dose, and on the different variants. This efficacy has been observed in the reduction in the rate of admission to intensive care units for severe forms of the disease, and in the reduction in the severity of symptoms.

The various meta-analyses which analyzed the total effectiveness of the different vaccines concluded with similar results, with total effectiveness after the first dose of the vaccine at 71% (95% CI 0.65, 0.78), and at 91% (95% CI 0.88, 0.94) after the second dose. This effectiveness was confirmed even for the different variants.[27]

Pathophysiology of COVID-19 post-vaccination myocarditis

Mechanisms are likely to be involved in the generation of myocarditis after the introduction of a COVID-19 vaccine (Figure 3). Firstly, for RNA vaccines, the mRNA may act as an antigen, so that it is recognized by the immune system and activates functions of the adaptive immune system. Some of these functions are capable of activating cardiotropic clones of T and B cells which will result in cardiac inflammation.[28] Molecular autoimmune mimicry between the Spike glycoprotein and troponin C1 may account for the cardiac insult after vaccine introduction and this may be due to an autoimmune cross-reaction between IgM antibodies to the SARS-CoV-2 Spike glycoprotein and cardiac autoantigens,[20] and potentially induce myocardial inflammation.[29] The role of sex hormones is thus incriminated in myocardial inflammation, given the frequency of the latter especially in young people. This pathophysiological hypothesis is based on the fact that testosterone activates specific helper T-cell responses, whereas estrogen inhibits pro-inflammatory T-cell responses. Finally, the genetic profile and the genes coding for the human Leukocyte Antigen (HLA) system predispose to post-vaccine cardiac inflammatory reactions.[30]

From clinical suspicion to diagnosis

Early detection of suspected cases of myocarditis after vaccination is an essential step in management,[32] with the aim of

Table 3. Qualitative assessment of appraised systematic reviews and meta-analyses.

AUTHORS	REGISTERED ON PROSPERO?	THE REPORTING GUIDELINE USED?	ASSESSING THE QUALITY	SUBGROUP ANALYSIS PROVIDED?	GRAY LITERATURE SEARCHED?	FUNDING ACKNOWLEDGED?	META-ANALYSIS LIMITATIONS STATED?
Ling et al.[10]	Yes (CRD42021275477)	Yes (PRISMA)	Yes (JBI scale)	Yes	Yes, but excluded	No funding received	Yes
Voleti et al.[11]	No	Yes (PRISMA)	Yes (NOT)	Yes	Yes, but excluded	Yes	Yes
Juan et al.[12]	Yes (CRD42022308108)	Yes (PRISMA)	Yes (NOT)	Yes	Yes, but excluded	No funding received	Yes
Chou et al.[13]	Yes (CRD42022315126)	Yes (PRISMA)	Yes (NOT)	Yes	Yes, but excluded	No funding received	Yes

Table 4. Critical appraisal of included meta-analyses based on AMSTAR-2 and evidence grading.

AUTHORS	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	AMSTAR-2 OVERALL QUALITY
Ling et al.[10]	Yes	Yes	Yes	PY	Yes	Yes	No	PY	Yes	No	PY	Yes	Yes	Yes	PY	Yes	Low quality review
Voleti et al.[11]	Yes	Yes	No	PY	Yes	Yes	No	Yes	Yes	Yes	PY	Yes	Yes	Yes	PY	Yes	Low-quality review
Juan et al.[12]	Yes	Yes	Yes	Yes	Yes	Yes	No	PY	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate-quality review
Chou et al.[13]	Yes	Yes	Yes	PY	Yes	Yes	No	Yes	No	No	No	No	No	No	No	Yes	Critical-low-quality review

Table 5. Evidence grading of appraised meta-analyses.

AUTHORS	ENDPOINT	NUMBER OF CASES >1000	*P*-VALUE OF OVERALL EFFECT	HETEROGENEITY (I^2) <50%	95% PREDICTION INTERVAL EXCLUDING THE NULL	DESIGN OF INCLUDED STUDIES	EVIDENCE GRADING
Ling et al.[10]	Incidence of myocarditis	Yes	Data not available	No	No	Retrospective studies	Classe IV
Voleti et al.[11]	Incidence of myocarditis	Yes	Data not available	No	Yes	Retrospective studies	Classe IV
Juan et al.[12]	Incidence of myocarditis	Yes	.001	No	Yes	Retrospective studies	Classe III
Chou et al.[13]	Incidence of myocarditis	Yes	Data not available	No	No	Retrospective studies	Classe IV

establishing a very rapid therapeutic strategy to avoid fatal scenarios such as fulminant myocarditis and rhythmic organ failure that can lead to sudden cardiac death.[33]

Symptomatology usually develops 2 to 3 days after vaccine administration and especially after the second dose.[34] These are mostly young patients with no previous history. Clinically, the patient is generally altered, with a fever between 38° and 39° without other infectious signs. An influenza-like syndrome is possible with myalgias and arthralgias. The most frequent symptom is chest pain. Dyspnea is less common but several reports have cited it as the main symptom. In some situations, patients have had palpitations or fainting and these are cases that have developed the fulminant form. ECG may show ST segment abnormalities between over- and under-elevation. PQ segment depression is common especially in the inferior leads, and finally supraventricular, ventricular arrhythmias or conductance disorders are quite rare.

Echocardiography may be normal, in which case it may show pericardial effusion, segmental or global impairment of systolic function. Biological investigation shows the

Table 6. Summarizes the different vaccines available and their characteristics.

TYPES	NAME	LABORATORY	THE TARGET	EFFICACY	ADVANTAGES
Inactivated[16-19]	BBIBP-CorV; Strain : HB02	Sinopharm	Whole virus	79%-86%	Induction of a humoral immune response
	CoronaVac; Strain: CN2	Sinovac life sciences Co.	Whole virus	83.5%	The low rate of incidence of side effects; Seroconversion rate above 90%, safety of administration even in the elderly people
	BBV152; Strain: NIV-2020–770	Bharat Biotech	Whole virus	63.6%-77.8% for asymptomatic infection and 93.4% against severe infection	The vaccine allows both cellular and humoral and humoral response, as well as a long-lasting memory
	Inactivated whole virus COVID-19 vaccine; strain: WIV04	Sinopharm	Whole virus	NR	Immunogenic with a low rate of side effects
mRNA[20-22]	mRNA-1273	Moderna	Spike glycoprotein (S-2P antigen)	94.1%	Immunogenicity is fast and powerful, antigen-specific T-follicular helper cells are induced by prolonged protein expression
	BNT162b1	BioNTech and Pfizer	RBD of the spike protein	93.8%	Immunostimulators elicit both humoral and cell-mediated antiviral immunity
	BNT162b2	BioNTech and Pfizer	Full-length spike	95%-100% depending on age	Systematic reaction is mild in older subjects, with good tolerance and efficacy in younger subjects
Recombinant[23-25]	ChAdOx1 nCoV-19 OR AZD1222	AstraZeneca	Whole spike protein	Overall efficacy—70.4%	Single-dose of ChAdOx1 nCoV-19 elicits Increased spike-specific antibody and elicit both humoral and cellular responses
	Sputnik V, (GamCOVID-Vac)	Developed by The Gamaleya National Center of Epidemiology and Microbiology	Spike protein vector	91.6% after 2 doses	Induced strong humoral and cellular immune responses in 100% of healthy participants
Nanoparticles[25,26]	NVX-CoV2373	Novavax	Trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1, a saponin-based adjuvant Vector type-Baculovirus	89.7%	Stimulates both high neutralizing Antibody responses and T Cells restraining new variants

inflammatory state by the increase of the C-reactive protein. The increase in troponin above the upper normal range is a specific and sensitive biological sign of myocardial injury.[28] As with other presentations of viral, hypereosinophilic, or autoimmune myocarditis, cardiac MRI is relevant in post-vaccine myocarditis, and the diagnosis is based on the modified Lake Louise criteria.[35] According to a position paper of the European Society of Cardiology on the management of myocarditis, indicates the presence of either of the following signs: Late gadolinium enhancement (LGE) and/or CMR oedema in symptomatic patients mainly with thrombotic pain, fever, troponin elevations and electrical changes, in which situation MRI retains high specificity.[36] In contrast, in asymptomatic patients, the presence of the 2 signs mentioned above is essential for the diagnosis. At the time of writing, there is little data available on the imaging characteristics of post-vaccine

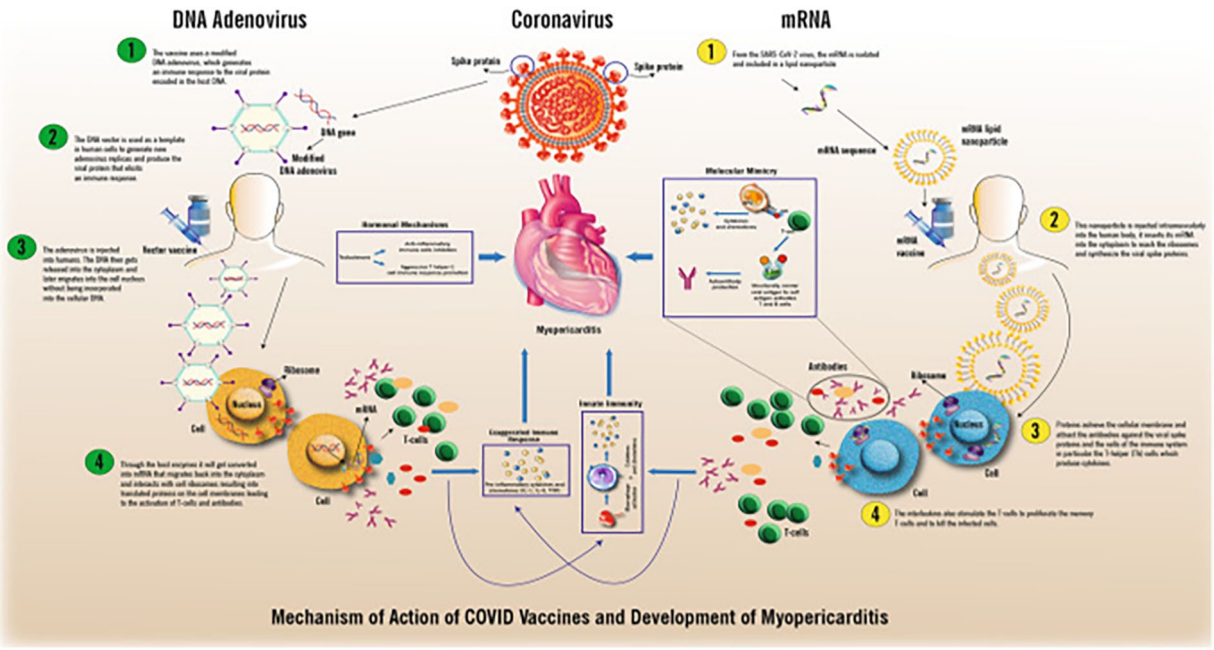

Figure 3. Summarizes the myocarditis hypothesis following COVID-19 vaccination (by Furgan et al.[31])

myocarditis, either due to lack of data in published reports or failure to perform cardiac MRI in these patients, and in addition, there are few cases in published reports that meet both imaging and histological criteria on endomyocardial biopsy (EMB).

Endomyocardial biopsy is rarely performed in the setting of simple post-vaccine myocarditis. According to the European Society of Cardiology (ESC) guildines and the scientific statements of the American heart association (AHA), the indications for an endo-myocardial biopsy are limited to the following situations :

(a) Acute myocarditis with acute heart failure or cardiogenic shock
(b) Acute myocarditis with ventricular arrhythmias or high-degree atrioventricular block
(c) Acute myocarditis or dilated cardiomyopathy suspected as chronic inflammatory cardiomyopathy with continuous/recurrent release of inflammatory and cardiac markers
(d) When diagnosis has an impact on further therapy

The analysis should include the morpho-molecular characteristics of the myocardial inflammatory lesions which may suggest the pathophysiological mechanism involved. Among the signs mentioned: the presence of eosinophils among the inflammatory infiltrates of the myocardium, which may suggest the possibility of a hypersensitivity reaction similar to that described by the smallpox vaccine, and other drugs.

Therapeutic management

There is no real consensus on the therapeutic management of this condition, but the management will be based on that of myocarditis as indicated in the American Heart Association guidelines.[37]

Firstly, treatment of heart failure with the currently recommended treatments: angiotensin-converting enzyme inhibitors or angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors.[38] In the case of rhythm disorders, the patient's stability and thromboembolic risk should be assessed before deciding on a therapeutic strategy. If the patient has a conduction disorder, definitive pacing may be discussed if the disorder is not reversible.

In the case of fulminant myocarditis, the management consists in setting up a circulatory assistance such as ExtraCorporelle Membrane Oxygenation (ECMO) arterial-venous or Impella while waiting to re-establish an acceptable ventricular function.[39]

With regard to anti-inflammatory treatment such as corticosteroids or immunomodulators such as immunoglobulins, there is no evidence to date of the efficacy of these treatments after post-vaccination myocarditis, despite diagnostic hypotheses that suggest the involvement of cellular immunity in this condition. A few case reports have discussed the benefit of glucocorticoids in patients with fulminant myocarditis, but without scientific evidence.

Future direction and perspectives

COVID-19 post-vaccination myocarditis is still poorly understood, and despite all the work done to date, much progress is still needed, especially with regard to the following questions:

Pathophysiological mechanism. It is necessary to know the mechanism of myocardial damage after COVID-19 vaccination, the type of vaccines most likely to induce this damage, after which doses the risk is high. The systems involved in the

genesis of this damage. All these questions are still a matter of debate, the answer to which requires stricter cohorts in terms of methodology, and thus the examinations carried out, mainly endo myocardial biopsy. Although the latter is not always indicated, its performance will lead to a deeper understanding of the histopathological mechanism.

Risk factors. Knowing the risk factors for developing myocarditis may help clinicians to identify the phenotypes most likely to be complicated by myocarditis. To date, young age, second dose, and mRNA-type vaccines[40] are the main risk factors, but it is clear that other risk factors may be overlooked, such as HLA genetics and the role of sex hormones. Larger analytical cohorts are needed in this respect.[41]

Therapeutic management. Several reports suggest that the use of glucocorticoids or immunoglobulins may limit myocardial damage, but there is no scientific evidence to date, and their use remains an expert opinion. Clinical trials in animal models remain an avenue to be discussed in the near future in order to confirm or deny this hypothesis.

Conclusion

In this umbrella review, we can conclude firstly that the incidence of myocarditis after COVID-19 vaccination does not differ from the incidence of other etiologies of myocarditis, as systematic reviews published in this sense, and analyzed in our study show a high degree of heterogeneity, not allowing us to conclude the true causal link between the COVID-19 vaccine and myocarditis. For these reasons, we strongly recommend adherence to the COVID-19 vaccination campaign, since the incidence of myocarditis does not differ from that described in the general population prior to vaccination.

Acknowledgements

None

Author Contributions

AB developed the project idea; conceptualization writing—original draft preparation and literature research, and writing—review and editing. AB and SB contributed to writing and revising the proofs; they also provided reciprocal feedback and appraised the selected MAs. NI, NE, and ZB supervised the project and final editing. All authors contributed to the article and approved the submitted version.

Ethical Approval

Not required.

Consent to Publication

Not required.

Systematic Reviews Registration

PROSPERO CRD42021297893.

ORCID iD

Amine Bouchlarhem https://orcid.org/0000-0001-5750-6932

REFERENCES

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC, Joost Wiersinga W. A review. *JAMA*. 2020;324:782-793.
2. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:2950-2973.
3. Clerkin KJ, Fried JA, Jayant R, et al. COVID-19 and cardiovascular disease. *Circulation*. 2020;141:1648-1655.
4. Siripanthong B, Nazarian S, Muser D, et al. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17:1463-1471.
5. Izquierdo A, Mojón D, Bardají A, et al. Myocardial injury as a prognostic factor in mid- and long-term follow-up of COVID-19 survivors. *J Clin Med*. 2021;10:5900.
6. Dooling K, McClung N, Chamberland M, et al. The advisory committee on immunization practices' interim recommendation for use of pfizer-biontech COVID-19 vaccine-United States, 2020. *Morb Mortal Wkly Rep*. 2020;69:1857-1859.
7. Ceasovschih A, Sorodoc V, Shor A, et al. Distinct features of vascular diseases in COVID-19. *J Inflamm Res*. 2023;16:2783-2800.
8. Schiavo JH. PROSPERO: an international register of systematic review protocols. *Med Ref Serv Q*. 2019;38:171-180.
9. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evid Based Ment Health*. 2018;21:95-100.
10. Ling RR, Ramanathan K, Tan FL, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. *Lancet Respir Med*. 2022;10:679-688.
11. Voleti N, Reddy SP, Ssentongo P. Myocarditis in SARS-CoV-2 infection vs. COVID-19 vaccination: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:951314.
12. Gao J, Feng L, Li Y, et al. A systematic review and meta-analysis of the association between SARS-CoV-2 vaccination and myocarditis or pericarditis. *Am J Prev Med*. 2022;64:275-284.
13. Chou OHI, Mui J, Chung CT, et al. COVID-19 vaccination and carditis in children and adolescents: a systematic review and meta-analysis. *Clin Res Cardiol*. 2022;111:1161-1173.
14. Hajra A, Gupta M, Ghosh B, et al. Proposed pathogenesis, characteristics, and management of COVID-19 mRNA vaccine-related myopericarditis. *Am J Cardiovasc Drugs*. 2022;22:9-26.
15. Khandker SS, Godman B, Jawad I, et al. A systematic review on covid-19 vaccine strategies, their effectiveness, and issues. *Vaccines (Basel)*. 2021;9:1-37.
16. Xia S, Duan K, Zhang Y, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. *JAMA* 2020;324:951-960.
17. Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis*. 2021;21:39-51.
18. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398:213-222.
19. Ella R, Reddy S, Blackwelder W, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet*. 2021;398:2173-2184.
20. Tsilingiris D, Vallianou NG, Karampela I, Liu J, Dalamaga M. Potential implications of lipid nanoparticles in the pathogenesis of myocarditis associated with the use of mRNA vaccines against SARS-CoV-2. *Metabol Open*. 2022;13:100159.
21. Li J, Hui A, Zhang X, et al. Safety and immunogenicity of the SARS-CoV-2 BNT162b1 mRNA vaccine in younger and older Chinese adults: a randomized, placebo-controlled, double-blind phase 1 study. *Nat Med*. 2021;27:1062-1070.
22. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.
23. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. *Nat Med*. 2021;27:270–278.
24. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet*. 2021;396:1979-1993.
25. Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med*. 2021;385:1172-1183.

26. Keech C, Albert G, Cho I, et al. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med*. 2020;383:2320-2332.
27. Marzieh S, Khateri S, Moradpour F, et al. The efficacy and effectiveness of COVID-19 vaccines around the world: a mini-review and meta-analysis. *Ann Clin Microbiol Antimicrob*. 2023;22:42.
28. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol*. 2022;19:75-77.
29. Caso F, Costa L, Ruscitti P, et al. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? *Autoimmun Rev*. 2020;19:102524.
30. Weiner J, Suwalski P, Holtgrewe M, et al. Increased risk of severe clinical course of COVID-19 in carriers of HLA-C*04:01. *EClinicalMedicine*. 2021;40:101099.
31. Furqan M, Chawla S, Majid M, et al. COVID-19 vaccine–related myocardial and pericardial inflammation. *Curr Cardiol Rep*. 2022;24:2031-2041.
32. Farahmand R, Trottier CA, Kannam JP, Ho KKL. Incidence of myopericarditis and myocardial injury in coronavirus disease 2019 vaccinated subjects. *Am J Cardiol*. 2022;164:123-130.
33. Shiyovich A, Witberg G, Aviv Y, et al. Myocarditis following COVID-19 vaccination: magnetic resonance imaging study. *Eur Heart J Cardiovasc Imaging*. 2022;23:1075-1082.
34. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med*. 2021;385:2140-2149.
35. Malik MB, Amer SA, Merrell E, et al. Effect of low dose acetylsalicylic acid and anticoagulant on clinical outcomes in COVID-19, analytical cross-sectional study. *Health Sci Rep*. 2022;5:e699.
36. Meyer-Szary J, Bazgier M, Lubocka P, Dorniak K, Sabiniewicz R. Cardiac magnetic resonance characteristics of acute myocarditis occurring after mRNA-based COVID-19 vaccines immunization. *Cardiol J*. 2022;29:160-162.
37. Law YM, Lal AK, Chen S, et al. Diagnosis and management of myocarditis in children: a scientific statement from the American heart association. *Circulation*. 2021;144:e123-e135.
38. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.
39. Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: this document was endorsed by the american college of cardiology (ACC), the American heart association (AHA), the society of critical care medicine (SCCM), and the society of thoracic surgeons (STS) in April 2019. *Catheter Cardiovasc Interv*. 2019;94:29-37.
40. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18:169-193.
41. Caforio ALP. Receipt of mRNA vaccine against Covid-19 and myocarditis. *N Engl J Med*. 2021;385:2189-2190.