

A Systematic Review and Meta-analysis of the Association Between SARS-CoV-2 Vaccination and Myocarditis or Pericarditis

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Introduction: There have been reports of potential negative cardiovascular effects from the COVID-19 vaccine, such as myocarditis or pericarditis. This study sought to ascertain the risk of myocarditis/pericarditis after COVID-19 vaccination by conducting an extensive meta-analysis of published cases.

Methods: A systematic literature search was conducted in 7 online databases by March 31, 2022. Heterogeneity was tested by I^2 index. RR and 95% CI were pooled through either random-effect or fixed-effect models. Sensitivity analysis and publication bias were also conducted.

Results: A total of 11 studies with 58,620,611 subjects were included. COVID-19 vaccination correlated with an increased risk of myocarditis or pericarditis (RR=2.04; 95% CI=1.33, 3.14). In addition, an increased risk of myocarditis or pericarditis in people who received the second dose of COVID-19 vaccine compared with that in those who received only the first dose of COVID-19 vaccine was also found (RR=4.06; 95% CI=2.08, 7.92). An increased incidence of pericarditis or myocarditis was noted predominantly in those who received BNT162b2 and mRNA-1273 vaccines (RR=2.19; 95% CI=1.46, 3.29 and RR=4.15; 95% CI=1.87, 9.22, respectively).

Discussion: Study results indicate that a higher incidence of myocarditis or pericarditis was found after COVID-19 vaccination. In addition, the risk of developing myocarditis or pericarditis was greater after the second dose than after the first dose. Nevertheless, the risks of myocarditis and pericarditis in COVID-19 vaccine recipients are still significantly lower than the health risks observed in patients with COVID-19. Therefore, the benefits and harms must be carefully assessed to determine the best management option for patients who are in the high-risk group of myocarditis or pericarditis.

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INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China.¹ On March 11, 2020, coronavirus disease 2019 (COVID-19) was officially declared a global pandemic event by the WHO.² Although most patients have mild symptoms and a favorable prognosis after infection, some patients experience more severe symptoms such as acute respiratory distress syndrome, multiorgan failure with sepsis, and sometimes death.^{3,4} To date, various mutations of the SARS-CoV-2 have

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been documented, with some increasing the transmissibility of COVID-19, thereby allowing the virus to spread easily across community unless adequate preventive measures are adopted. Currently, vaccination is recognized as the most effective means of infection control.⁵

In response to the COVID-19 pandemic, many countries have made significant efforts to develop vaccines against SARS-CoV-2.^{6,7} The use of vaccination can prevent infection, interrupt transmission, and reduce disease severity and the death rate, which is helpful in controlling outbreaks.^{8,9} To date, >300 vaccines have been developed, 169 of which are in clinical trials.¹⁰ The safety and immunogenicity tests of Phase I/II, Phase II, and Phase II/III clinical trials of various vaccines have been published and all showed positive results.^{11–13} However, clinical evidence on the safety and efficacy of the currently approved COVID-19 vaccines is limited. The majority of the data were obtained from relatively small populations and over relatively short periods. Therefore, the adverse reactions from the vaccine are of concern. It has been reported that the most common local adverse reactions include pain and swelling. Systemic adverse reactions include fatigue, headache, and allergy.^{14,15} Some studies have also reported rare adverse events such as thromboembolism, myocarditis, and pericarditis.^{16–18}

Myocarditis is an inflammation of the cardiac muscle most commonly caused by a viral disease, and the clinical presentation may range from chest pain to fever, life-threatening congestive heart failure, arrhythmias, or even death.¹⁹ Acute pericarditis is the most common manifestation of pericardial disease and usually presents as severe chest pain behind the sternum.²⁰ It is believed that myocarditis and pericarditis are the result of autoinflammation and may be related to the immune response to viral infection.²¹ Thus, the aim of this study was to determine the risk of myocarditis/pericarditis after COVID-19 vaccination through an extensive meta-analysis of published cases.

METHODS

This study was conducted in conformity with PRISMA.²² In addition, the study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (<https://www.crd.york.ac.uk/prospero/>; registration number CRD42022308108). During data processing, it was found that there were not enough consistent data to combine other cardiovascular events. However, the data on myocarditis and pericarditis met analysis requirements, and they were selected as the study endpoints.

All published studies on people who received COVID-19 vaccine through March 31, 2022 were searched in the following databases: (1) MEDLINE, (2) Embase, (3) Cochrane Central Register of Controlled Trials, (4) Web of Science, (5) China National

Knowledge Infrastructure, (6) Wanfang Data Knowledge Service Platform, and (7) China Science and Technology Journal VIP Database. The relevant retrieval strategy was as follows: (*mrna vaccin*OR mrna COVID-19 vaccin* OR rna vaccin* OR *pfizer* OR *moderna* OR *biontech* OR *bnt162* OR *mrna-1273* OR mRNA 1273* OR messenger RNA vaccine* OR mRNA-1273 vaccine OR BNT162 vaccine AND sars-cov-2 OR sars cov 2 OR sars-cov 2 OR 2019 novel coronavirus OR covid-19 OR 2019-ncov OR coronavirus disease 2019 AND myocarditides OR myocarditis OR carditis OR pericarditis OR pleuropericarditis*). A manual search for the reference list of the included literature, relevant reviews, or meta-analysis was also performed to identify eligible studies that might be missed in the database search. The detailed search strategy is described in the [Appendix \(available online\)](#).

Studies were selected if the following inclusion criteria were fulfilled: (1) the type of study was a research article (observational studies/RCTs); (2) the main outcome is myocarditis or pericarditis; and (3) ORs, hazard ratios (HRs), or RRs with the 95% CIs can be directly extracted or recalculated. Articles that met 1 of the following criteria were excluded: (1) preclinical study; (2) meta-analysis, case reports, reviews, and guidelines; (3) duplicate articles; (4) valid ending data unable to be extracted or calculated; and (5) full text of the study is not available.

Two authors (JG and LF) independently carried out the data extraction process. Any disagreement was resolved with a senior supervisor (CS) through discussion and consensus. Extracted contents were listed as follows: (1) basic information of the included articles (title, the first author's name, year of publication, geographic locations, and the quality of the studies); (2) baseline characteristics of the subjects in the eligible literature; (3) detail of interventions or exposure factors; and (4) the outcome indicators and outcome measures of interest (OR, RR, HR with the corresponding 95% CI).

The Newcastle-Ottawa Scale was used to evaluate the methodologic quality of the observational studies. The literature was evaluated as low-quality studies with a score of 0–3, moderate-quality studies with a score of 4–6, and high-quality studies with a score of 7–9.²³ The assessment guideline for case-control studies was used for self-controlled case series and noncase series studies. The methodologic quality of the included cross-sectional studies was assessed using an 11-item checklist recommended by the Agency for Healthcare Research and Quality.²⁴ Article quality was assessed as follows: low quality=0–3, moderate quality=4–7, and high quality=8–11.²⁵

The main statistical software used in this study was Stata 16 software. The included studies were analyzed using the pooled RR values. Because myocarditis and pericarditis are rare adverse reactions with an incidence of <10%, ORs and RRs are considered the same.²⁶ Similarly, HRs and RRs were considered identical based on the study by Escrig-Sos J.²⁷ The heterogeneity of included studies was examined by the I^2 index. If the test showed a high level of heterogeneity ($I^2 > 50%$), a random-effect model was used, otherwise a fixed-effect model ($I^2 < 50%$) was used.²⁸ Sensitivity analysis was also performed to investigate the potential interference to the pooled effect size.²⁹ In addition, to estimate the contribution of study characteristics to the overall heterogeneity, we adopted a meta-regression analysis for age, sex, study location, and COVID-19 vaccine type. The authors used Egger's and Begg's tests to assess publication bias for quantitative judgments.^{30,31} Statistical significance was set at $p < 0.05$.

RESULTS

After comprehensive literature search on 7 online databases, 1,123 studies were identified. After removing duplicates, 564 unique citations remained, of which 80 articles were further assessed by scrutinizing the full text. Eventually, 11 studies met the eligibility criteria and were included. The detailed literature search process is shown in [Figure 1](#).

A total of 58,620,611 participants were enrolled in the included studies. Among the included studies, 8 were cohort studies, 1 was cross-sectional study, 1 was case-non-case study and 1 was self-controlled case series analysis. Eight^{17,32–38} of these studies compared the incidence of

myocarditis or pericarditis before and after COVID-19 vaccination, and 3^{32,39,40} studies analyzed the effect of different doses of vaccination on the incidence of myocarditis or pericarditis. The Newcastle–Ottawa Scale scores of included studies were ≥ 6 , and the score of 11-item checklist recommended by Agency for Healthcare Research and Quality for the included cross-sectional study was 5. The detailed characteristics of the included studies are shown in [Appendix Table 1](#) (available online).

Overall, a statistically significant association was discovered between COVID-19 vaccination and myocarditis or pericarditis. Compared to unvaccinated people, myocarditis or pericarditis in those following

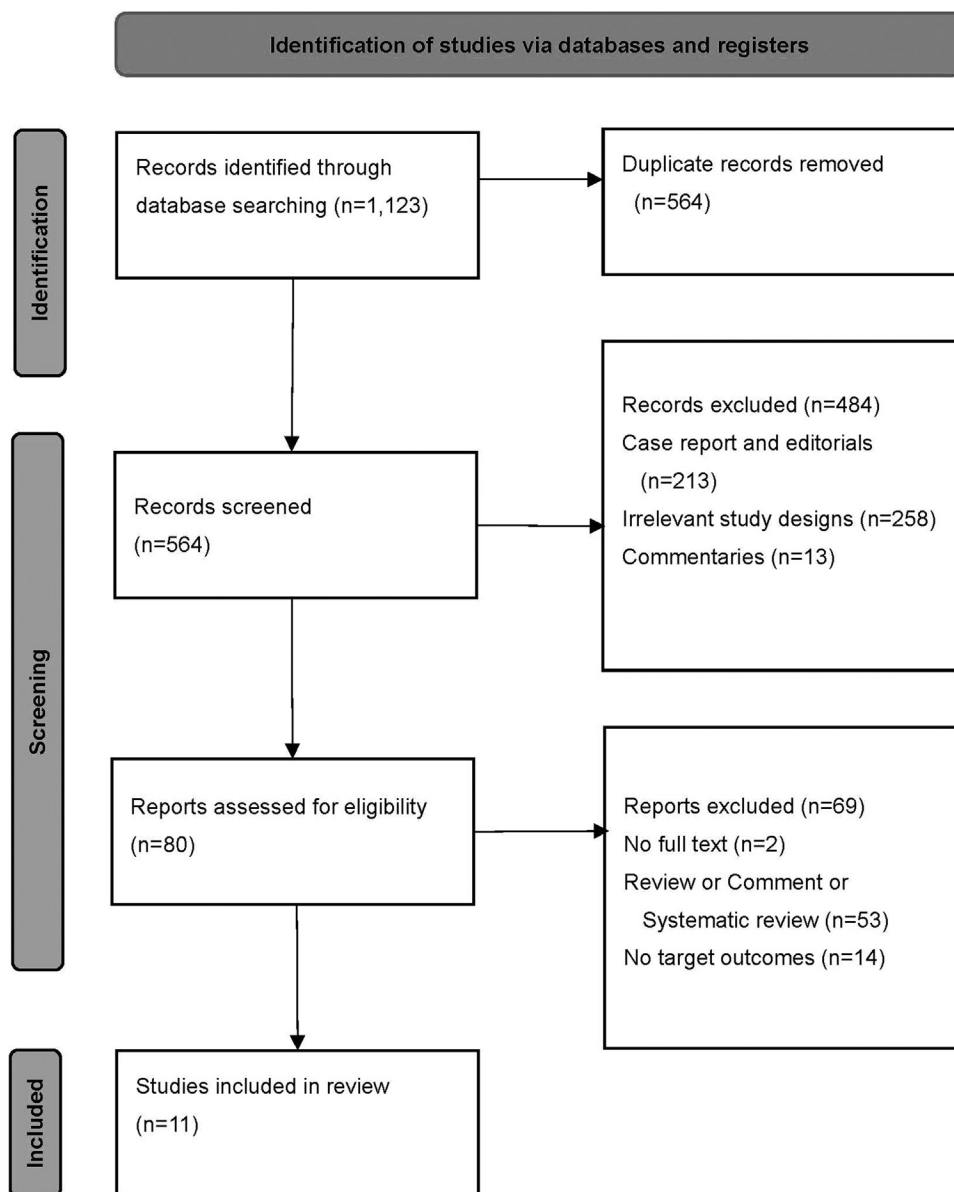


Figure 1. Flow diagram of the study search and selection process.

Table 1. Associated Risks Between COVID-19 Vaccination and the Risk of Myocarditis or Pericarditis

Subgroups	Number of studies	RR (95% CI)	Z	p-value	Heterogeneity	
					I ² (%)	p-value
All studies	8	2.13 (1.55, 2.94)	4.656	<0.001	92.5	<0.001
Outcome						
Myocarditis	5	2.36 (1.55, 3.58)	4.012	<0.001	91.4	<0.001
Pericarditis	2	1.16 (0.74, 1.82)	0.661	0.509	0	0.679
Sex						
Male	5	2.28 (1.60, 3.26)	4.54	<0.001	91.4	<0.001
Female	5	1.50 (1.09, 2.08)	2.479	0.013	83.7	<0.001
Vaccine type						
BNT162b2	7	2.19 (1.46, 3.29)	3.783	<0.001	89.8	<0.001
mRNA-1273	3	4.15 (1.87, 9.22)	3.49	<0.001	91.5	<0.001
Viral vector	3	1.11 (0.81, 1.53)	0.663	0.507	73.2	0.011
Location						
Western countries	4	1.98 (1.37, 2.87)	3.623	<0.001	94.4	<0.001
Asia	4	2.40 (1.17, 4.91)	2.391	0.017	78.1	<0.001
Age, years						
<40	4	4.00 (2.04, 7.83)	4.046	<0.001	89	<0.001
≥40	4	1.44 (1.25, 1.67)	5.009	<0.001	50.5	0.011
Dose						
Second dose versus first dose	3	4.06 (2.08, 7.92)	4.115	<0.001	52.5	0.097
First dose versus unvaccinated	4	1.33 (1.17, 1.51)	4.281	<0.001	0	0.602
Second dose versus unvaccinated	5	2.93 (1.54, 5.58)	3.28	0.001	93.9	<0.001

Note: Boldface indicates statistical significance ($p < 0.05$).

COVID-19 vaccines were 2.13-fold higher (95% CI=1.55, 2.94; $I^2=92.5%$; $p < 0.001$). In addition, a statistically significant association was discovered between COVID-19 vaccination and myocarditis. The pooled RR was 2.02 (95% CI=1.21, 3.37; $I^2=97.8%$; $p < 0.001$). Such association was not found in pericarditis (RR=1.16; 95% CI=0.74, 1.82; $I^2=0$; $p=0.509$). People who received the first dose had an increased risk of myocarditis or pericarditis compared with those who did not receive COVID-19 vaccine, and this risk was more pronounced after receiving the second dose (first dose versus unvaccinated: RR=1.33; 95% CI=1.17, 1.51; $I^2=0$; $p < 0.001$; second dose versus unvaccinated: RR=2.93; 95% CI=1.54, 5.58; $I^2=93.9%$; $p=0.001$). Furthermore, compared with the first dose of a COVID-19 vaccine, the administration of the second dose was associated with an increased risk of reporting pericarditis and/or myocarditis. The pooled RR was 4.06 (95% CI=2.08, 7.92; $I^2=52.5%$; $p < 0.001$). The main results are shown in [Figure 2](#).

The authors also undertook a subgroup analysis stratified by the location where the study was conducted, sex, vaccine types, and age (years). The subgroup analysis indicated that vaccination was statistically significantly associated with myocarditis or pericarditis in both female (RR=1.50; 95% CI=1.09, 2.08; $I^2=83.7%$; $p=0.013$)

and male (RR=2.28; 95% CI=1.60, 3.26; $I^2=83.7%$; $p < 0.001$) ($p_{\text{Heterogeneity between groups}}=0.089$). Further analysis based on different geographic locations of the research revealed a significant association between COVID-19 vaccination and myocarditis or pericarditis in western countries (RR=1.98; 95% CI=1.37, 2.87; $I^2=94.4%$; $p < 0.001$) and East Asia (RR=2.40; 95% CI=1.17, 4.91; $I^2=78.1%$; $p < 0.05$) ($p_{\text{Heterogeneity between groups}}=0.664$). Subgroup analysis based on age groups found an increased risk of myocarditis or pericarditis in people of all ages after COVID-19 vaccination ($p_{\text{Heterogeneity between groups}}=0.014$). Regarding vaccine types, there was a statistically significant association in both the BNT162b2 vaccine and mRNA-1273 vaccinated populations compared with those receiving the viral vector vaccine ($p_{\text{Heterogeneity between groups}}=0.002$). Detailed results of the subgroup analysis are summarized in [Table 1](#) and [Figure 2](#).

This study used a random-effects model as the pooling method because of the high degree of heterogeneity across most studies. The heterogeneity was reduced when subgroup analyses were performed based on sex, age, and study region, suggesting that these factors may be the source of heterogeneity. Meta-regression analysis also indicated that the heterogeneity of the association between COVID-19 vaccination and increased risk of

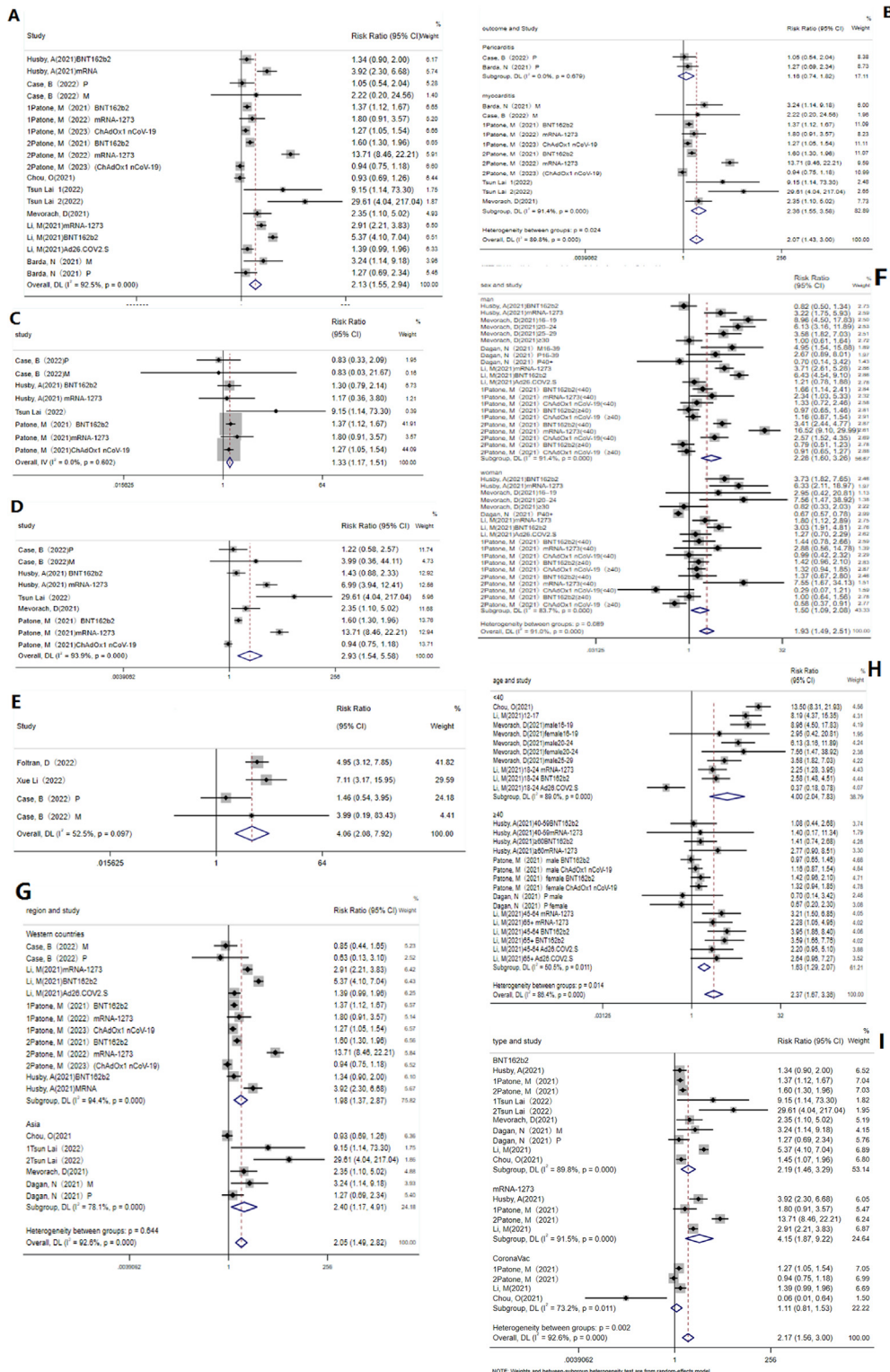


Figure 2. Forest plot of the relative risks with corresponding 95% CIs from studies on: (A) Association between COVID-19 vaccination and risk of myocarditis or pericarditis; (C) Association between the first dose and risk of myocarditis or pericarditis; (D) Association between the second dose and risk of myocarditis or pericarditis; (E) Association between different doses and risk of myocarditis or pericarditis. Note: Forest plots for subgroup analysis on the association between COVID-19 vaccination and risk of myocarditis or pericarditis were analyzed by random-effects model: (B) grouped by study outcome, (F) grouped by sex, (G) grouped by region, (H) grouped by for age, and (I) grouped by vaccine type.

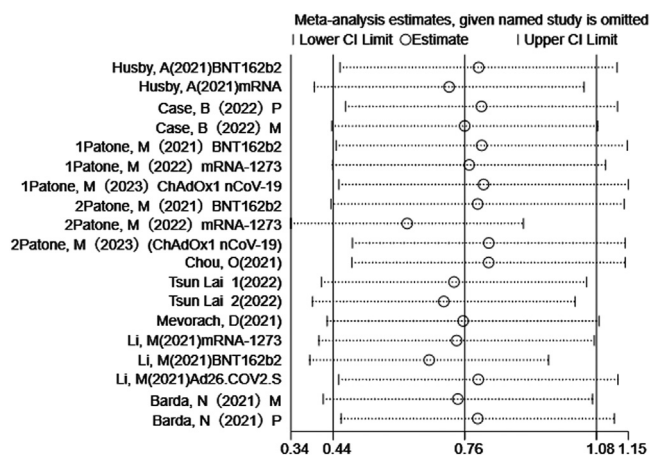


Figure 3. Sensitivity analysis on COVID-19 vaccination and the risk of myocarditis or pericarditis.

myocarditis or pericarditis was influenced by age ($p=0.014$), sex ($p=0.033$), and location ($p=0.012$), but not by COVID-19 vaccine type ($p=0.926$).

Sensitivity analyses were conducted by omitting the included studies one by one, and the changes observed in the pooled risk ratio were nonsignificant, suggesting that the results of the meta-analysis were stable (Figure 3). The results of Begg's and Egger's tests suggested that there was no publication bias across the studies ($p>0.05$). The funnel plot shows a certain symmetry (Appendix Figure 1, available online).

DISCUSSION

Based on the results of this meta-analysis, COVID-19 vaccination is associated with an increased risk of myocarditis/pericarditis. Moreover, an increased risk of myocarditis alone was clearly shown. It is noteworthy that although an increased risk of pericarditis was not found, only 2 studies of pericarditis were included in the analysis, therefore, the result on pericarditis risk needs to be interpreted with caution. Nevertheless, the potential mechanisms of association between COVID-19 vaccination and myocarditis or pericarditis remains uncertain. It has been suggested that this may be related to the active ingredients of the vaccine or to the immune response after vaccination.³⁵ A proposed mechanisms is molecular mimicry, which is the interaction between the components of the vaccine and the susceptibility of the subject. The COVID-19 vaccine produces SARS-CoV-2 viral spike glycoprotein and induces an adaptive immune response that recognizes and destroys the virus expressing the spike protein, namely the SARS-CoV-2 virus. However, because of the similarity between the antibodies directed to SARS-CoV-2 spike glycoproteins

and myocardial α -myosin heavy chain, an immune cross-reaction may occur, leading to autoimmune diseases.^{41,42} Some studies have shown differences in cardiac side effects with different doses of COVID-19 vaccination and this analyses revealed similar results. Compared to those who did not receive COVID-19 vaccine, those who received either the first or second dose had a significantly increased risk of myocarditis or pericarditis. In addition, those who received the second dose of COVID-19 vaccine had a higher risk of myocarditis/pericarditis compared with those who received only the first dose of COVID-19 vaccine.

To further explore the relationship between the COVID-19 vaccine and risk of myocarditis/pericarditis, subgroup analyses were conducted. The results suggested both BNT162b2 vaccine and mRNA-1273 vaccine correlated with an elevated risk of myocarditis/pericarditis, which is consistent with several studies.^{43–45} No increased risks were found in other types of COVID-19 vaccines. Previous studies have shown that the risk of myocarditis is greater after mRNA vaccination than viral vector vaccination.^{46,47} A possible pathogenic mechanism of mRNA vaccine-induced myocarditis may be over-activation of cytokine production.⁴⁸ This is because mRNA vaccines contain an excipient, polyethylene glycol, which is primarily used to increase the water solubility of the drug but has the potential to stimulate a stronger immune response.⁴⁹ Although both BNT162b2 vaccine and mRNA-1273 vaccine are mRNA vaccines, BNT162b2 and mRNA-1273 vaccines were evaluated separately as previous studies have suggested mRNA-1273 was more likely to be linked to myocarditis and pericarditis young people.^{43,50} The results showed a higher risk of myocarditis or pericarditis in those vaccinated with mRNA-1273 than in those vaccinated with BNT162b2. Some previous studies are consistent with this finding.^{36,38}

In the subgroup analysis based on age, those younger than 40 years old had a higher risk of developing myocarditis or pericarditis after COVID-19 vaccination than those who were 40 years old and older. Previous studies have also suggested that myocarditis and pericarditis may be more likely to occur in younger people.^{43,50} In addition, an increased risk of myocarditis or pericarditis in both men and women who had received the COVID-19 vaccine was found in this meta-analysis, and heterogeneity did not differ significantly between male and female subgroups. However, according to previous studies, myocarditis or pericarditis usually occurs in young men.^{43,51,52} Previous clinical and experimental studies have suggested that testosterone acts through a combined mechanism of suppression of anti-inflammatory cells and commitment to a T-helper 1-type immune

response.⁵³ In contrast, estrogen has a suppressive effect on pro-inflammatory T cells, leading to a decrease in cell-mediated immune responses.⁵⁴ Results of subgroup analyses according to region showed a statistically significant association between COVID-19 vaccination and increased risk of myocarditis or pericarditis both in Western countries and East Asia, but the differences between regions were not significant. This may be related to the fact that mRNA vaccination was the predominant type of vaccine in the included studies, and results from different national health system surveillance studies, case series, and cohort studies also showed an association between COVID-19 vaccination and the risk of myocarditis or pericarditis.^{35,55–57}

Meta-regression results suggested that sex, age, and study area all contributed to heterogeneity, whereas vaccine type was not likely the source of heterogeneity. The difference may be because the population characteristics of the included studies varied considerably, encompassing different age groups, as well as different sex ratios. Furthermore, some countries have modified their vaccination policies because of reports of adverse vaccine events, and that the enrolled studies of the meta-analysis might include vaccinated populations based on different vaccination policies, which might also have affected heterogeneity.

Although an increased risk of myocarditis and pericarditis was found among individuals who received COVID-19 vaccine, it is worth noticing that myocarditis or pericarditis was predominantly mild in the vaccinated individuals.⁴¹ In addition, a study noted that the spontaneous resolution of vaccine-associated myocarditis is common.⁵⁸ The clinical trial results of the COVID-19 vaccine showed a very good safety profile, however, the sample size of the trial was not large enough to detect the rare adverse events that may occur. In addition, some studies have shown that the incidence of myocarditis or pericarditis resulting from vaccination is much lower than that in people infected with COVID-19.^{33,59} Despite the meta-analysis results suggesting a higher risk of myocarditis or pericarditis with COVID-19 vaccination, vaccination should still be recommended because benefits of the vaccine likely outweigh its harms. More importantly, adjustment of vaccination strategies to reduce the incidence of adverse events based on monitoring data from the vaccine adverse event system is needed if necessary.

In contrast to the previously published study by Ling et al.,⁶⁰ the control population included in this study comprised people who had not received the COVID-19 vaccine, as opposed to the former, which primarily compared those who had received other non-COVID-19 vaccines as controls; it is not clear whether this will have

an impact on the results. In addition, our findings are in general agreement with the results of the former meta-analysis. Among people who received COVID-19 vaccines, the risk of myocarditis or pericarditis was significantly higher in people younger than 40 years old (versus ≥ 40 years), after receiving mRNA vaccine (versus non-mRNA vaccine), and after the second dose of vaccine (versus first dose). The meta-analysis provides more reliable and practical evidence for vaccine roll out in the general population. Moreover, most of the studies included were cohort studies, which minimized selection and recall bias, and increased the statistical power. Therefore, the risk of publication bias in this study is low, and sensitivity analysis indicated the stability of the findings.

Limitations

Several inherent limitations need to be cited when interpreting the results of this meta-analysis. First, the presence of post-vaccination COVID-19 infection in vaccine recipients was not considered in the included studies, which may have falsely increased the risk of myocarditis or pericarditis with vaccination to some extent. Second, there are some articles for which the full text cannot be retrieved when searching the literature. Third, some articles did not provide information on the dose of vaccination and did not consider the possibility of mixing different types of COVID-19 vaccines in the same individual, which may have an impact on the results. Fourth, the results of the studies ultimately included in analysis showed high heterogeneity, and the conclusion that the COVID-19 vaccine increases the risk of developing myocarditis or pericarditis should be made with caution. Fifth, although the vaccines used in most included studies were at different doses, only one study provided detailed data between the second and first doses, therefore a network meta-analysis to compare the risks of vaccines at different doses was not conducted. Thus, the conclusion that the second dose had a higher risk than the first dose should, again, be interpreted with caution. Finally, the search strategy mainly focused on myocarditis and pericarditis as the main outcome, it might pose a slight risk of missing some patients and studies, which might theoretically underrepresent the risk of myocarditis/pericarditis.

CONCLUSIONS

The current evidence suggests that COVID-19 vaccination is associated with an increased risk of myocarditis or pericarditis. Also, compared with the first dose, people who received the second dose have a higher risk for developing myocarditis or pericarditis. Therefore,

decisions about COVID-19 vaccination should include a risk assessment of the benefits of COVID-19 vaccination in all age and sex groups. However, the findings are limited by the number and quality of included studies, and more well-designed studies are needed to explain the potential mechanisms by which COVID-19 vaccines can increase the risk of myocarditis or pericarditis.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at <https://doi.org/10.1016/j.amepre.2022.09.002>.

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