SYSTEMATIC REVIEW

The global prevalence and association between the risk of myocarditis and mRNA-based COVID-19 vaccination: A network meta-analysis [version 1; peer review: awaiting peer review]

Mohammad Rohman1, Jonny Karunia Fajar2, Gatot Soegiarto3, Laksmi Wulandari4, Muhammad Anshory5, Muhammad Ilmawan6, Dewi Marlysawati7, Yeni Purnamasari8, Andy Pranata Kusuma9, Anisa Asmiragani9, Dimas Adhiatma9, Andi Permana8, Erwin Alexander Pasaribu8, Helnida Anggun Maliga10, Yuri Pamungkas11, Putu Wina Margarani Puteri12, Vebri Anita Sinaga13, Dedy Setiawan14, Effika Nurningtyas Putri15, Eliza Techa Fattima16, Olivia Listiowati Prawoto17, Rina Safitri18, Roma Yuliana19, Kholisotul Hikmah20, Laili Nurzaidah21, Lianto Lianto22, Meiliana Dwi Cahya22, Muhammad Ikhsan23, Ibrahim Ibrahim24, Anggara Dwi Samudra25, Fredo Tamara2, Dessy Aprilia Kartini8, Aditya Indra Mahendra2, Kuldeep Dhama26, Harapan Harapan27-30

1Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
2Brawijaya Internal Medicine Research Center, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
3Division of Allergy & Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
4Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
5Division of Allergy & Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
6Department of Urology, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
7Department of Epidemiology, Faculty of Public Health, Universitas Indonesia, Depok, 16424, Indonesia
8Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
9Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
10Department of Neurology, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, Indonesia
11Department of Electrical Engineering, Institut Teknologi Sepuluh Nopember, Surabaya, 60111, Indonesia
12Department of Pharmacy, Institut Teknologi Bandung, Bandung, 40132, Indonesia
13Department of Obstetric and Gynecology, Faculty of Medicine, Universitas Padjadjaran, Bandung, 45363, Indonesia
14Department of Pediatric, Faculty of Medicine, Universitas Airlangga, Surabaya, 60286, Indonesia
15Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia
16Department of Cardiology and Vascular Medicine, Universitas Padjadjaran, Bandung, 45363, Indonesia
17Department of Obstetrics and Gynecology, Universitas Udayana, Bali, 80361, Indonesia
18Department of Public Health Nutrition, Faculty of Public Health, Universitas Indonesia, Depok, 16424, Indonesia
19Department of Biostatistics and Population Studies, Faculty of Public Health, Universitas Indonesia, Depok, 16424, Indonesia
Abstract

Background: Cases of myocarditis development have been reported after administration of messenger ribonucleic acid (mRNA)-based coronavirus disease (COVID-19) vaccines. However, the reports vary among the studies, and the types of mRNA vaccines with potential to cause myocarditis remain unidentified. The objective was to assess the cumulative prevalence of myocarditis and determine the association between myocarditis and mRNA-based COVID-19 vaccination.

Methods: We performed a network meta-analysis by searching articles in PubMed, Scopus, and Web of Science. Information on the prevalence of myocarditis after the mRNA-based COVID-19 vaccination was collected from each study. Analysis was performed by calculating the pooled prevalence rate, and the association was determined using the Z-test. Data networking was performed using the Bayesian method.

Results: A total of 18 papers was included in our analysis. We found that the cumulative prevalence of myocarditis was 1.7, 1.9, 1.2, and 1.1 per 100,000 population after vaccination with different types of mRNA-based COVID-19 vaccines, namely all mRNA COVID-19 vaccines, BNT162b1, mRNA-1273, and the combination of BNT162b1 and mRNA-1273, respectively. Moreover, the results revealed that BNT162b1 vaccination increased the risk of myocarditis by 1.64- and 1.71-folds compared to mRNA-1273 and the combination of BNT162b2 and mRNA-1273, respectively. Similar risks of developing myocarditis were observed after mRNA-1273 and the combination of BNT162b1 and mRNA-1273 vaccination.

Conclusions: Our findings suggest the cumulative prevalence of myocarditis after mRNA-based COVID-19 vaccination with maximum prevalence was observed after BNT162b2 administration. BNT162b2 was associated with a higher risk of developing myocarditis than the other mRNA-based COVID-19 vaccines.

Keywords

Myocarditis, side effect, vaccination, mRNA, COVID-19
Corresponding authors: Mohammad Rohman (ippoenk@yahoo.com), Jonny Karunia Fajar (gembyok@gmail.com), Gatot Soegiarto (gatot_soegiarto@fk.unair.ac.id)

Author roles: Rohman M: Conceptualization, Data Curation, Methodology, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Fajar JK: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Soegiarto G: Conceptualization, Data Curation, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Wulandari L: Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Anshory M: Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Ilmawan M: Data Curation, Formal Analysis, Methodology, Software; Marlysawati D: Data Curation, Project Administration, Resources; Purnamasari Y: Data Curation, Formal Analysis, Methodology, Resources, Software; Kusuma AP: Data Curation, Formal Analysis, Project Administration, Resources; Asmiragani A: Data Curation, Formal Analysis, Project Administration, Resources; Adhiatma D: Data Curation, Formal Analysis, Resources; Permana A: Data Curation, Formal Analysis, Resources; Pasaribu EA: Data Curation, Formal Analysis, Resources; Maliga HA: Data Curation, Formal Analysis, Resources; Pamungkas Y: Data Curation, Formal Analysis, Resources; Setiawan D: Data Curation, Formal Analysis, Resources; Puteri PWM: Data Curation, Formal Analysis, Resources; Sinaga VA: Data Curation, Formal Analysis, Resources; Yuliana R: Data Curation, Formal Analysis, Resources; Hikmah K: Data Curation, Formal Analysis, Resources; Putri YS: Data Curation, Formal Analysis, Resources; Prawoto OL: Data Curation, Formal Analysis, Resources; Safitri R: Data Curation, Formal Analysis, Resources; Yuliana R: Data Curation, Formal Analysis, Resources; Putri EN: Data Curation, Formal Analysis, Resources; Hikmah K: Data Curation, Formal Analysis, Resources; Putri YS: Data Curation, Formal Analysis, Resources; Nurzaidah L: Data Curation, Formal Analysis, Resources; Lianto L: Data Curation, Formal Analysis, Resources; Cahya MD: Data Curation, Formal Analysis, Resources; Ikhsan M: Data Curation, Formal Analysis, Resources; Ibrahim I: Data Curation, Formal Analysis, Resources; Sukma AD: Data Curation, Formal Analysis, Resources; Tamara F: Data Curation, Formal Analysis, Resources; Kartini DA: Data Curation, Formal Analysis, Resources; Mahendra AI: Data Curation, Formal Analysis, Resources; Dhama K: Supervision, Validation, Writing – Review & Editing; Harapan H: Supervision, Validation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2022 Rohman M et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Rohman M, Fajar JK, Soegiarto G et al. The global prevalence and association between the risk of myocarditis and mRNA-based COVID-19 vaccination: A network meta-analysis [version 1; peer review: awaiting peer review] F1000Research 2022, 11:862 https://doi.org/10.12688/f1000research.122139.1

First published: 29 Jul 2022, 11:862 https://doi.org/10.12688/f1000research.122139.1
Introduction
Since early 2021, the COVID-19 vaccination program has been initiated in many regions. The program involves administration of several types of COVID-19 vaccines such as inactivated, protein subunits, messenger ribonucleic acid (mRNA)-based, and vector vaccines. It is widely known that a vaccine development usually requires 10-15 years before it is ready to use in human subjects. Moreover, it undergoes various steps including antigen identification and production, non-clinical (animal) testing, clinical trials (phase I-III), filing and licensing, and surveillance. However, the vaccine development process for COVID-19 was completed in approximately a year. The fact that the COVID-19 pandemic resulted in very high mortality rates globally, led to an urgent need for the vaccine, which explains the short duration of vaccine development. However, this rapid process probably led to unfolding of various side effects gradually. Of all the available vaccines, mRNA-based COVID-19 vaccines have been associated with maximum side effects.

mRNA vaccines have been investigated for several infectious diseases such as Cytomegalovirus, Zika virus, Human Metapneumovirus, Respiratory Syncytial Virus, Influenza, Chikungunya, and Rabies. Of these viruses, some serious side effects like toxic epidermal necrolysis were reported in the case of mRNA Rabies vaccine. Similarly, the mRNA-based COVID-19 vaccine also showed some minor side effects such as pain or redness at the site of injection, fatigue, fever, headache, nausea or vomiting, chest pain, and shortness of breath. Additionally, some fatal side effects such as acute kidney injury, anemia, and myocarditis have been reported. Of these, myocarditis is the most life-threatening condition due to associated high mortality rates (25%-56%). Various observational studies and case reports and series have shown the occurrence of myocarditis after mRNA-based COVID-19 vaccine administration; however, the findings vary across the studies. In the current scenario, global prevalence rate of myocarditis post mRNA-based COVID-19 vaccination should be established precisely, and the types of vaccines associated with this condition should be identified. Therefore, the present study aimed to assess the global prevalence and association between the risk of myocarditis and mRNA-based COVID-19 vaccination, using a networking meta-analysis approach.

Methods
Study design
A meta-analysis following the protocols of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was conducted. The PRISMA checklist in our present study was provided in the supplementary files. To analyze our study objectives, a systematic search was conducted in PubMed, Scopus, and Web of Science and the required data were retrieved to calculate the cumulative prevalence and effect estimates.

Eligibility criteria
Eligibility criteria were defined prior to the systematic search. The inclusion criteria for study sources were as follows: (1) Assessed the prevalence of myocarditis after mRNA-based COVID-19 vaccination and (2) provided the required information to calculate the prevalence and effect estimates. Reviews, commentaries, letters to the editor, and double publications were excluded from the study sources.

Search strategy and data extraction
A systematic search was conducted in PubMed, Scopus, and Web of Science between January and February 2022; as of 3 February 2022 3rd, data collection was finished. Before searching for the primary outcomes, we searched for the type of mRNA-based COVID-19 vaccines involved in our study. The keywords adapted from medical subject headings used were as follows: [“mRNA COVID-19 vaccine” or “BNT162b1” or “Pfizer” or “mRNA-1273” or “Moderna”], [“Myocarditis” or “side effect”], and [“COVID-19” or “Coronavirus disease-19”]. The systematic search was limited to English language and original articles. In case of double publications, only studies with larger sample sizes were included. Moreover, a systematic search of the reference list of relevant systematic reviews was conducted to collect additional articles. Subsequently, the data of interest from the selected articles were extracted and included: (1) first author name, (2) publication year, (3) study design, (4) type of mRNA-based COVID-19 vaccines, (5) trade name of the vaccines, and (6) the incidence of myocarditis after mRNA-based COVID-19 vaccination. Two independent investigators (JKF and MI) performed the systematic search and extracted the data. Prior to performing the systematic search and data extraction, the assessments and ratings given by independent investigators were analyzed using the kappa agreement. Agreement was established if the coefficient of kappa agreement was greater than the p-value.

Assessment of the methodological quality
Before their inclusion in our analysis, the articles were assessed for quality using the Newcastle-Ottawa scale (NOS) with score ranging from 0 to 9. A score of 7-9, 4-6, and 0-3 indicated that the papers were of high, moderate, and low quality, respectively. Low-quality articles were excluded from the analysis. Using a pilot form, quality assessment was performed by two independent authors (JKF and MI) and any discrepancies were resolved through discussion.
Outcome measures
The primary outcomes were cumulative prevalence and risk of myocarditis after mRNA-based COVID-19 vaccination. To identify the potential mRNA-based COVID-19 vaccines, an initial evaluation of the available data in PubMed, Scopus, and Web of Science was performed. We found that BNT162b1 (Pfizer) and mRNA-1273 (Moderna) were suitable for our analysis. Myocarditis cases data were retrieved according to the International Classification of Diseases, Tenth Revision (ICD-10) as follows: I40.0 (infectious myocarditis), I40.1 (isolated myocarditis), I40.8 (other acute myocarditis), I40.9 (acute myocarditis), I41 (myocarditis in diseases classified elsewhere), I51.4 (myocarditis unspecified), or B33.22 (viral myocarditis).

Statistical analysis
Before analyzing the data, potential publication bias and heterogeneity across the studies were assessed. Publication bias was determined using an Egger test, with a p-value < 0.05 indicating a trend towards publication bias. Heterogeneity
among studies was evaluated using the Q test with a p-value < 0.10 suggesting heterogeneity and that a random effect model should be applied for data analysis; otherwise, fixed-effects model were be used. The cumulative prevalence of myocarditis after mRNA-based COVID-19 vaccination was determined using a single-arm meta-analysis with the dichotomous covariate method by calculating the event per sample size from each study. The effect estimate was presented as (logit) event rate. The analysis was performed using R software (RStudio version 4.1.1, MA, US). Confidence in Network Meta-Analysis (CINEMA 1.9.1, Bern, Switzerland) software was used to outline the network diagram of the comparison of the risk of myocarditis among patients administered with different types of mRNA-based COVID-19 vaccines. The effect estimate was presented in a forest plot as the pooled odd ratio and 95% confidence interval (OR 95% CI).

Results

Studies selection
We collected 997 potential papers from the database and 16 papers from the reference list of related systematic reviews. Of these, 22 papers were excluded owing to the duplication of data and 942 papers owing to irrelevant topics. Subsequently, we included 49 full-text review papers. From these, 12 reviews, 16 case reports, and three papers were excluded owing to insufficient data. Finally, a total of 18 papers were analyzed to determine the cumulative prevalence and risk of myocarditis after mRNA-based COVID-19 vaccination.10,16–29 The process of article selection is shown in Figure 1 and the characteristics of the included papers are summarized in Table 1.

| Author and year          | Study location | Study design | Sample size | Type of vaccine | Trade name | NOS |
|--------------------------|----------------|--------------|-------------|-----------------|------------|-----|
| Barda et al., 2021       | Israel         | Retrospective| 938,812     | BNT162b1        | Pfizer     | 7   |
| Choe et al., 2022        | Korea          | Retrospectivecohort | 444,313 | BNT162b1        | Pfizer     | 7   |
| Diaz et al., 2021        | US             | Retrospective | 2,000,287  | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 6   |
| Farahmand et al., 2022   | Israel         | Retrospectivecohort | 268,320 | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 6   |
| Gurdasani et al., 2021   | UK             | Retrospective | 3,918,373  | BNT162b1        | Pfizer     | 7   |
| Hause et al., 2021       | US             | Retrospective | 8,900,000  | BNT162b1        | Pfizer     | 6   |
| Husby et al., 2021       | Germany        | Retrospective | 509,590    | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 7   |
| Kim et al., 2021         | US             | Retrospective | 556,146    | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 7   |
| Mevorach et al., 2021    | Israel         | Retrospective | 2,668,894  | BNT162b1        | Pfizer     | 7   |
| Montgomery et al., 2021  | US             | Retrospective | 2,810,000  | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 6   |
| Nygaard et al., 2022     | Germany        | Prospectivecohort | 261,334   | BNT162b1        | Pfizer     | 6   |
| Perez et al., 2021       | US             | Retrospective | 175,472    | BNT162b1        | Pfizer     | 6   |
| Simone et al., 2021      | US             | Retrospective | 2,392,924  | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 6   |
| Singh et al., 2022       | US             | Retrospective | 12,713,000 | BNT162b1 & mRNA-1273 | Pfizer & Moderna | 7   |
| Witberg et al., 2021     | Israel         | Retrospective | 2,558,421  | BNT162b1        | Pfizer     | 8   |

NOS: New Castle-Ottawa scale.
CI: (12.62, 7.64) (Figure 2C) after mRNA-1273 (Moderna) vaccination, and 90 cases in a population of 8,027,677 (logit event rate: -11.23; 95% CI: -12.44, -10.02) (Figure 2D) after combined vaccination with BNT162b1 and mRNA-1273.

A summary of the cumulative prevalence of myocarditis after the mRNA-based COVID-19 vaccination is outlined in Table 2.

The indirect comparison of the myocarditis risk among mRNA-based COVID-19 vaccination

The indirect comparison (Figure 3A) revealed that the use of BNT162b1 vaccination increased the risk of myocarditis by 1.63-folds compared to mRNA-1273 vaccination (OR: 1.63; 95% CI: 1.35, 1.97; p < 0.0001). Moreover, BNT162b1 was associated with an increased risk of myocarditis compared to the combination of BNT162b1 and mRNA-1273 vaccines (OR: 1.71; 95% CI: 1.37, 2.13; p < 0.0001). mRNA-1273 and the combination of BNT162b1 and mRNA-1273 showed a similar risk of developing myocarditis (OR: 1.05; 95% CI: 0.80, 1.38; p = 0.7270). A summary of the indirect comparison

Figure 2. The prevalence of myocarditis in patients after mRNA-based COVID-19 vaccination. A). All type of mRNA COVID-19 vaccines. B). Pfizer mRNA COVID-19 vaccines. C). Moderna mRNA COVID-19 vaccines. D). The combination of Pfizer and Moderna.

Table 2. Cumulative prevalence of myocarditis after mRNA-based COVID-19 vaccination.

| mRNA vaccines        | Event | Sample size | Logit event rate | 95% CI | pHet | pEg   | p     |
|----------------------|-------|-------------|-----------------|--------|------|-------|-------|
| All mRNA vaccines    | 859   | 51826799    | -10.70          | (-11.24)–(-10.16) | <.0001 | 1.1370 | <.0001 |
| BNT162b1             | 634   | 33088209    | -10.61          | (-11.29)–(-9.93)  | <.0001 | 1.0710 | <.0001 |
| mRNA-1273            | 126   | 10710913    | -10.13          | (-12.62)–(-7.64)  | <.0001 | 2.1770 | <.0001 |
| BNT162b1 & mRNA-1273 | 90    | 8027677     | -11.23          | (-12.44)–(-10.02) | <.0001 | 1.3460 | <.0001 |

CI: confidence interval; pHet: p heterogeneity; pEg: p Egger.
of the risk of myocarditis associated with different mRNA-based COVID-19 vaccines is presented in Table 3 and the network is illustrated in Figure 3B.

Table 3. The indirect comparison on the risk of myocarditis among different mRNA-based COVID-19 vaccines.

| Indirect comparison       | Sample size       | NS  | OR   | 95% CI       | p      |
|---------------------------|-------------------|-----|------|--------------|--------|
| mRNA-1273 vs. Mixed       | 10,710,913 vs. 8,027,677 | 3 vs. 5 | 1.05 | 0.80 – 1.38  | 0.7270 |
| BNT162b1 vs. Mixed        | 33,088,209 vs. 8,027,677 | 10 vs. 5 | 1.71 | 1.37 – 2.13  | <0.0001|
| BNT162b1 vs. mRNA-1273    | 33,088,209 vs. 10,710,913 | 10 vs. 3 | 1.63 | 1.35 – 1.97  | <0.0001|

NS: number of study; OR: odds ratio.

Source of heterogeneity and potential publication bias

Heterogeneity was observed in all the models of analysis. Therefore, we used a random-effects model. Egger’s test was used to assess the potency of bias among the studies. Our pooled analyses revealed no publication bias (Table 2).

Discussion

Our findings revealed that the pooled prevalence rate of myocarditis after mRNA-based vaccination was 1.7 cases per 100,000 population. Specifically, it was 1.9, 1.2, and 1.1 cases per 100,000 population after BNT162b1, mRNA-1273, and combination of BNT162b1 and mRNA-1273 vaccination, respectively. Our study is the first meta-analysis to report the prevalence of myocarditis after administration of different types of mRNA-based COVID-19 vaccines. Previously, a total of four meta-analyses in this context were conducted. However, these reports are limited to the crude prevalence rate and did not investigate different types of mRNA-based COVID-19 vaccinations. According to these reports the cumulative prevalence rate of myocarditis after mRNA-based COVID-19 vaccination was 1.2-11.9 per 100,000 population, which is consistent with our findings. In our study, we included a larger sample size; therefore, the present study might provide a better insight into the precise prevalence rate.

We also reported that BNT162b1 vaccination was associated with 1.6 and 1.7-folds higher risk of developing myocarditis compared to mRNA-1273 and the combination of BNT162b1 and mRNA-1273 vaccines, respectively. On the other hand, mRNA-1273 and the combination of BNT162b2 and mRNA-1273 shared similar risks of developing myocarditis. The underlying mechanism by which BNT162b1 vaccination leads to a higher risk of developing myocarditis remains debatable. Briefly, the principle of mRNA-based COVID-19 vaccination is to produce viral-mRNAs that can encode the perfusion stabilized full-length spike protein, a protein involved in the interaction with ACE2 receptors to infect the target cells. The production of antibodies with high affinity to spike protein may inhibit the interaction between spike protein and ACE2 receptors and therefore may provide protection against COVID-19 infection. Spike proteins of SARS-COV-2 have a molecular weight of 180-200 kDa. On the other hand, myocardial cells consist of actin and myosin proteins. These proteins have a molecular weight of 100-250 kDa. In the theory of cross-immunity, it is known that two different proteins with similar molecular weights, defined as molecular mimicry, may trigger cross-immunity. Therefore, due to the similar molecular weights of spike protein of SARS-COV-2 and actin-myosin, the antibodies may attack latter proteins in myocardial cells as well, resulting in development of myocarditis eventually. Moreover, studies also revealed
that BNT162b1 consisted of highly purified ss-5-capped mRNA, and mRNA-1273 consisted of synthesis of ss-5-capped mRNA. The capability of spike protein production was reported higher in BNT162b1 than mRNA-1273.44,45 Furthermore, previous studies have also reported myocarditis in patients with COVID-19; however, the evidence of whether the myocarditis was caused by the direct infection or the systematic inflammation is not clear.46 On the other hand, a study found that COVID-19 patients with myocarditis showed no signs of injury in electrocardiography and echocardiography, indicating that myocardial damage was a result of systemic inflammation and not direct infection.47 This possible mechanism might explain the findings of our study, which indicate that the immunization with BNT162b1 had higher risk of developing myocarditis compared to other mRNA-based COVID-19 vaccines.

Our study is the first networking meta-analysis to report the prevalence rate and risk of myocarditis after mRNA-based COVID-19 vaccination. We revealed that immunization with BNT162b1 had the highest prevalence rate and risk of developing myocarditis compared to other mRNA-based COVID-19 vaccinations. Our findings may contribute to the development of a COVID-19 immunization policy. If an mRNA-based COVID-19 vaccine needs to be selected, we recommended the use of mRNA-1273 or the combination of mRNA-1273 and BNT162b1 over the use of BNT162b1 alone. Further investigations are required to assess the specific mechanism underlying association of BNT162b1 vaccine with high-risk of myocarditis compared to other mRNA-based COVID-19 vaccines. On the other hand, the knowledge of patients on the side effect of mRNA COVID-19 vaccination should be investigated to assess the willingness for COVID-19 vaccination.48–51

Our study had several important limitations. First, the potential confounding factors that might contribute to the development of myocarditis (e.g., infection due to common causative agents such as Coxsackie virus, group A streptococci, chlamydia, or Trypanosoma cruzi) were not included in the analysis.52 Second, the small prevalence of myocarditis after mRNA-based COVID-19 vaccination impeded the calculation of the precise prevalence and risk association. Third, the design of the included papers in our study was dominated by a retrospective study; therefore, further investigations with better study designs are required. Fourth, the proportion of myocarditis cases in each study was unequal. Fifth, the majority of papers in our analysis assessed BNT163b1 and the number of papers assessing mRNA-1273 was insufficient. Therefore, there is a possibility that calculation bias would have existed.

Conclusions
Our study revealed that the prevalence of myocarditis after mRNA-based COVID-19 vaccination was 1.7 cases per 100,000 population, and BNT162b1 was associated with the highest prevalence rate compared to other mRNA-based COVID-19 vaccines. BNT162B1 vaccination is also associated with a higher risk of myocarditis than other mRNA-based COVID-19 vaccines. Based on these results, we recommend the use of mRNA-1273 vaccine over the BNT162B1 vaccine.

Data availability
Underlying data
Figshare: Supplementary files: The global prevalence and association between the risk of myocarditis and mRNA-based COVID-19 vaccination: A network meta-analysis, https://doi.org/10.6084/m9.figshare.19768498.v2.31

Reporting guidelines
Figshare: PRISMA checklist for “The global prevalence and association between the risk of myocarditis and mRNA-based COVID-19 vaccination: A network meta-analysis”, https://doi.org/10.6084/m9.figshare.19768498.v2.31

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Author contribution
Idea/concept: MSR, JKF. Design: MSR, GS, JKF, LW. Control/supervision: MSR, GS, LW, MA, KD, HH. Data collection/processing: MI, DM, YP, APK, AA, DA, AP, EAP, HAM, YP, DA, PWMP, VAS, DS, ENP, ETF, OLP, RS, KY, YSP, LN, LL, MDC, MI, II, ADS, FT, DAK, AIM. Extraction/Analysis/interpretation: JKF, MI. Literature review: MSR, JKF, MI. Writing the article: MSR, JKF, MI. Critical review: MSR, GS, LW, MA, KD, HH. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgements
We thank Lembaga Pengelola Dana Pendidikan (LPDP) Republic of Indonesia for supporting this project.
References

1. Bagnoli S: The world’s largest COVID-19 vaccination campaign. Lancet Infect. Dis. 2021; 21: 323. PubMed Abstract | Publisher Full Text
2. Kaur SP, Gupta V: COVID-19 Vaccine: A comprehensive status report. Virus Res. 2020; 288: 198. PubMed Abstract | Publisher Full Text
3. Baud D, Qi X, Nielsen-Saines K, et al.: Real estimates of mortality following COVID-19 infection. Lancet Infect. Dis. 2020; 20: 773. PubMed Abstract | Publisher Full Text
4. Singh JA, Upshur REG: The granting of emergency use designation to COVD-19 candidate vaccines: implications for COVID-19 vaccine trials. Lancet Infect. Dis. 2021; 21: e103–e109. PubMed Abstract | Publisher Full Text
5. Menni C, Klaser K, May A, et al.: Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID-19 Symptom Study app in the UK: a prospective observational study. Lancet Infect. Dis. 2021; 21: 939–949. PubMed Abstract | Publisher Full Text
6. Ad A, Hockova B, Kantorova L, et al.: Safety and effectiveness of BNT162b2 mRNA vaccine in a Nationwide Setting. N. Engl. J. Med. 2021; 385: 1076–1090. PubMed Abstract | Publisher Full Text
7. Chaudhry N, Weissman D, Whitehead KA: mRNA vaccines for infectious diseases: principles, delivery and clinical translation. Nat. Rev. Drug Discov. 2021; 20: 817–838. PubMed Abstract | Publisher Full Text
8. Alberer M, Gnadt-Vogt U, Hong HS, et al.: Safety and immunogenicity of a mRNA vaccines in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet. 2017; 390: 1511–1520. PubMed Abstract | Publisher Full Text
9. Alamr E, Alhamzri A, Qasir NA, et al.: Side Effects of COVID-19 Vaccine: Nationwide Phase IV Study among COVID-19 Vaccinated Subjects. J. Prim. Care Community Health. 2021; 12: n71. PubMed Abstract | Publisher Full Text
10. Barda N, Dagan N, Ben-Shlomo Y, et al.: Safety of the BNT162b2 mRNA Vaccine in Children Aged 12-18 Years in Saudi Arabia. Vaccines (Basel). 2021; 9. PubMed Abstract | Publisher Full Text
11. Kuhl U, Schultheiss HP: Myocarditis: early biopsy allows for tailored regenerative treatment. Dtsch. Arztebl. Int. 2012; 109: 361–368. PubMed Abstract | Publisher Full Text
12. Abu Mouch S, Roguin A, Hellou E, et al.: Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021; 39: 3790–3793. PubMed Abstract | Publisher Full Text
13. Habib MB, Hamamhy T, Elias A, et al.: Acute myocarditis following administration of BNT162b2 vaccine. JIDCases. 2021; 25: e91937. PubMed Abstract | Publisher Full Text
14. Deb A, Abdelmalek J, Iwui K, et al.: Acute Myocardial Injury Following COVID-19 Vaccination: A Case Report and Review of Current Evidence from Vaccine Adverse Events Reporting System Database. J. Prim. Care Community Health. 2021; 12: 21501327211029230. PubMed Abstract | Publisher Full Text
15. Rosner CM, Genovesi L, Tehrani BH, et al.: Myocarditis Temporarily Associated With COVID-19 Vaccination. Circulation. 2021; 144: 502–505. PubMed Abstract | Publisher Full Text
16. Choie Y, Yi S, Hwang J, et al.: Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents. Vaccine. 2021. PubMed Abstract | Publisher Full Text
17. Diaz GA, Parsons GT, Gering SK, et al.: Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA. 2021; 326: 1210–1212. PubMed Abstract | Publisher Full Text
18. Ramahand R, Trottier CA, Kannapu R, et al.: Incidence of Myopericarditis and Myocardial Injury in Coronavirus Disease 2019 Vaccinated Subjects. Am. J. Cardiol. 2022; 164: 123–130. PubMed Abstract | Publisher Full Text
19. Gandhi D, Bhatt S, Costello A, et al.: Vaccinating adolescents against SARS-CoV-2 in England: a risk-benefit analysis. J. R. Soc. Med. 2021; 114: 513–524. PubMed Abstract | Publisher Full Text
20. HAUSE AM, GEE J, BAGGS J, et al.: COVID-19 Vaccine Safety in Adolescents Aged 12-17 Years - United States, December 14, 2020–July 16, 2021. MMWR. Morb. Mortal. Wkly Rep. 2021; 70: 1053–1058. PubMed Abstract | Publisher Full Text
21. Husby A, Hansen JV, Fosbol E, et al.: SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. BMJ. 2021; 375: e068665. PubMed Full Text
22. Kim HW, Jenista ER, Wendell DC, et al.: Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol. 2021; 6: 1196–1201. PubMed Abstract | Publisher Full Text
23. Mervorch D, Anis E, Cedar N, et al.: Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N. Engl. J. Med. 2021; 385: 2140–2145. PubMed Abstract | Publisher Full Text
24. Montgomery J, Ryan M, Engler R, et al.: Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021; 6: 1202–1206. PubMed Abstract | Publisher Full Text
25. Ngaard U, Holm M, Bohnstedt C, et al.: Population-based Incidence of Myopericarditis After COVID-19 Vaccination in Danish Adolescents. Pediatr. Infect. Dis. J. 2022; 41: e25–e28. PubMed Abstract | Publisher Full Text
26. Perez Y, Levy ER, Joshi AV, et al.: Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination. Clin. Infect. Dis. 2021. PubMed Full Text
27. Simone A, Harel R, Chen A, et al.: Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older. JAMA Intern. Med. 2021; 181: 1668–1670. PubMed Abstract | Publisher Full Text
28. Singh A, Khilnin R, Mishra Y, et al.: The safety profile of COVID-19 vaccinations in the United States. Am. J. Infect. Control. 2022; 50: 15–19. PubMed Abstract | Publisher Full Text
29. Witberg G, Barda N, Hoss S, et al.: Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N. Engl. J. Med. 2021; 385: 2132–2139. PubMed Abstract | Publisher Full Text
30. Page MJ, McKenzie JE, Bossert PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71. PubMed Full Text
31. Fajjar S: Supplementary files: The global prevalence and association between the risk of myocarditis and mRNA-based COVID-19 vaccination: A network meta-analysis. F1000Research. 2022; 11: 36. PubMed Full Text
32. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur. J. Epidemiol. 2010; 25: 603–605. PubMed Abstract | Publisher Full Text
33. Fazlollahi A, Zahrmaty M, Noorn M, et al.: Cardiac complications following mRNA COVID-19 vaccines: A systematic review of case reports and case series. Rev. Med. Virol. 2021; e2318. PubMed Abstract | Publisher Full Text
34. Matta A, Kundhrajur R, Osman M, et al.: Clinical Presentation and Outcomes of Myocarditis Post mRNA Vaccination: A Meta-Analysis and Systematic Review. Cureus. 2021; 13: e19240. PubMed Full Text
35. Wang M, Wen W, Zhou M, et al.: Meta-Analysis of Risk of Myocarditis After Messenger RNA COVID-19 Vaccine. Am. J. Cardiol. 2022; 167: 155–157. PubMed Full Text
36. Cordera A, Cazorla D, Escobardo D, et al.: Myocarditis after RNA-based vaccines for coronavirus. Int. J. Cardiol. 2022; 353: 131–134. PubMed Abstract | Publisher Full Text
37. Anand P, Stahel VP: Review the safety of Covid-19 mRNA vaccines: a review. Patient Saf. Surg. 2021; 15: 20. PubMed Abstract | Publisher Full Text
38. Huang Y, Yang C, Xu XF, et al.: Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. Acta Pharmacol. Sin. 2020; 41: 1141-1149. PubMed Abstract | Publisher Full Text
39. Govindan S, Sarkey J, Ji X, et al.: Pathogenic properties of the N-terminal region of cardiac myosin binding protein-C in vitro. J. Muscle Res. Cell Motil. 2012; 33: 17-30. PubMed Abstract | Publisher Full Text
40. Cusick MF, Libbey JE, Fujinami RS: Molecular mimicry as a mechanism of autoimmune disease. Clin. Rev. Allergy Immunol. 2012; 42: 102–111. PubMed Abstract | Publisher Full Text
41. Mahendra AI, Fajar JK, Harapan H, et al.: *Porphyromonas gingivalis* vesicles reduce MDA-LDL levels and aortic wall thickness in high fat diet induced atherosclerosis rats. *Artery Res.* 2018; 23: 20–27. Publisher Full Text

42. Wardhani SO, Fajar JK, Nurarifah N, et al.: The predictors of high titer of anti-SARS-CoV-2 antibody of convalescent plasma donors. *Clin. Epidemiol. Glob. Health.* 2021; 11: 100763. PubMed Abstract | Publisher Full Text

43. Wardhani SO, Fajar JK, Wulandari L, et al.: Association between convalescent plasma and the risk of mortality among patients with COVID-19: a meta-analysis. *F1000Res.* 2021; 10: 64. PubMed Abstract | Publisher Full Text

44. Fang E, Liu X, Li M, et al.: Advances in COVID-19 mRNA vaccine development. *Signal Transduct. Target. Ther.* 2022; 7: 94. PubMed Abstract | Publisher Full Text

45. Park JW, Lagintron PNP, Liu Y, et al.: mRNA vaccines for COVID-19: what, why and how. *Int. J. Biol. Sci.* 2021; 17: 1446–1460. PubMed Abstract | Publisher Full Text

46. Li B, Yang J, Zhao F, et al.: Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin. Res. Cardiol.* 2020; 109: 531–538. PubMed Abstract | Publisher Full Text

47. Deng Q, Hu B, Zhang Y, et al.: Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. *Int. J. Cardiol.* 2020; 311: 116–121. PubMed Abstract | Publisher Full Text

48. Harapan H, Anwar S, Bustaman A, et al.: Community Willingness to Participate in a Dengue Study in Aceh Province, Indonesia. *PLoS One.* 2016; 11: e0159139. PubMed Abstract | Publisher Full Text

49. Mudatsir M, Anwar S, Fajar JK, et al.: Willingness-to-pay for a hypothetical Ebola vaccine in Indonesia: A cross-sectional study in Aceh. *F1000Res.* 2019; 8: 1441. Publisher Full Text

50. Fajar JK, Harapan H: Socioeconomic and attitudinal variables associated with acceptance and willingness to pay towards dengue vaccine: a systematic review. *Arch. Clin. Infect. Dis.* 2017; 12. Publisher Full Text

51. Prihatiningisih S, Fajar JK, Tamara F, et al.: Risk factors of tuberculosis infection among health care workers: A meta-analysis. *Indian J. Tuberc.* 2020; 67: 121–129. PubMed Abstract | Publisher Full Text

52. Cooper LT Jr: *Myocarditis.* *N. Engl. J. Med.* 2009; 360: 1526–1538. PubMed Abstract | Publisher Full Text
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com