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Systematic Review

Cardiopulmonary Complications Following COVID-19 Vaccinations: A Systematic Review

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Abstract

Introduction

Clinical trials of COVID-19 vaccines were insufficient to detect uncommon adverse outcomes that are crucial for risk-benefit analyses and informing clinical practice post-vaccination. As a result, detection of infrequent adverse events has become a global research priority. The current study aims to estimate the rate of cardiopulmonary complications associated with COVID-19 vaccination.

Methods

Two databases and one search engine were explored to identify English language-related studies published up to January 2023.

Results

The literature search turned up a total of 3974 relevant studies. Of them, 37 articles matched the inclusion criteria. Overall, seven studies from the United States. The mean age of patients was 25 years and about 77% of them were male. The most common reported consequence was inflammatory heart disease (myo-peri-cariditis), followed by pulmonary embolism (17%), and myocardial infarction (5%). The majority of complications were reported following mRNA COVID-19 vaccinations, particularly following the administration of the second dose. Pfizer has a slightly higher risk of cardiac complications following vaccination (4.1 per 100000 persons) than Moderna (3.7 per 100,000 persons).

Conclusion

Although cardiopulmonary complications associated with COVID-19 vaccinations are uncommon, they can be life-threatening. Therefore, more large-scale observational studies and review articles of those studies are strongly recommended.

1. Introduction

The coronavirus disease 2019 (COVID-19) initially emerged in December 2019, in Wuhan, China, and quickly spread around the world [1,2]. Vaccination against COVID-19 was the principal strategy for limiting the outbreak [3]. Given the immediate need to prevent the virus's spread, thirteen vaccines were licensed for emergency use in several countries before completing all three phases of clinical trials, encouraging researchers to closely monitor the adverse effects of vaccination [4]. Since they received provisional Food and Drug Administration (FDA) authorization in the United States (US) in December 2020, two types of messenger RNA (mRNA)-based COVID-19 vaccines, BNT162b2 (PfizerBioNTech) and mRNA-1273 (Moderna), have been administered in hundreds of millions of doses [5]. Despite ongoing viral mutations and the detection of weaker strains, the infections have been mild, with many patients exhibiting no symptoms or recovering at home [6]. There has been vaccination anxiety among families with young children who are now eligible to get the COVID-19 vaccine. This hesitation persists despite the Centers for Disease Control and Prevention (CDC) advice that everyone aged five and above should receive the COVID-19 vaccines [7]. As of 23 January 2023, more than 13 billion doses of COVID-19 vaccines had been administered worldwide [8]. Covid-19 vaccines have been studied in randomized trials to determine effectiveness and safety [9]. However, clinical trials of COVID-19 vaccines were insufficient to detect uncommon adverse outcomes that are crucial for risk-benefit analyses and informing clinical practice post-vaccination. As a result, detection of infrequent adverse events has become a global research priority [10]. Several cardiac consequences have occurred as a result of COVID-19 mRNA vaccines, such as myocarditis, pericarditis, perimyocarditis, coronary thrombosis, myocardial infarctions (MI), and stress-induced cardiomyopathy [11]. Since then, an increased number of cases of cardiopulmonary complications have been reported to the CDC, particularly in adolescents and young adults who received mRNA-based vaccines [9,12]. The focus has currently shifted from the hazard of the infection to potential vaccination side effects [6].

The current study aims to estimate the rate of cardiopulmonary complications associated with COVID-19 vaccination in individuals who have received at least one dose of an authorized vaccine.

2. Methods

2.1. Study design

The current study was undertaken according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [13]. As it is a systematic review and meta-analysis of published studies, ethical approval and/or written informed consent by the patients are not required.

2.2. Data sources and search strategy

A comprehensive systematic literature search in the English language alone was conducted on two databases (PubMed, Scopus) and one search engine (Google Scholar) for published studies up to January 1, 2023. The following medical subject headings and keyword terms were used: Covid-19, SARS-COV-2, vaccination(s), complication(s), consequence(s), sequela(e), cardiac adverse event(s), cardiovascular adverse effect(s), myocarditis, pericarditis, myopericarditis, pleuropericarditis, atrial flutter, atrial fibrillation, thoracic complication(s), myocardial infarction, hypertension, blood-pressure, acute coronary syndrome, coronary occlusion, heart failure, cardiomyopathy, respiratory complication(s), cardiopulmonary, pulmonary embolism, pneumonia, pulmonary fibrosis, and interstitial lung disease. In addition, reference lists of the included articles and systematic reviews on similar topics were manually checked to identify any additional eligible studies.

2.3. Eligibility criteria

Eligible studies must have met all the following inclusion criteria: (1) participants must have been vaccinated with one of the approved vaccines; (2) patients with clinically suspected cardiopulmonary complications following COVID-19 vaccination; (3) studies written in the English language (4) patients without COVID-19 infection. Exclusion criteria include all of the following; (1) Complications that developed after 42 days following COVID-19 vaccination; (2) Patient with COVID-19 infection at presentation; (3) Preprint studies; (4) Studies published in predatory journals. Predatory journals were defined according to Kscien's list [14].

2.4. Study selection and data items

Two researchers, both with at least six-year of experience in medicine, independently screened the titles, abstracts, and full texts of the retrieved studies to identify the eligible items. Any disagreement was resolved by the third and fourth researchers specified in the topic.

Three researchers extracted the data from the full texts of the included studies into the "Data Extraction Form" using Microsoft Excel (version 2016). Extracted data were: the first author's name, country, study design, sample size, number of events, age, sex, comorbidities, vaccine type, the dose of vaccine, time from vaccine to symptoms, troponin changes, electrocardiogram (ECG) changes, and echocardiography findings.

2.5. Statistical analysis

All statistical analyses were performed using comprehensive meta-analysis. All outcomes were dichotomous, and the frequency of adverse occurrences was determined using a random-effects model with a 95% confidence interval. The forest plot was used to graphically represent the event rate of the individual studies. We estimated the percentage of heterogeneity and inconsistency between the studies using the I2 statistic, with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. If the heterogeneity was significant and I2 was greater than 50%, the random-effect model was used; otherwise, the fixed-effect model was used.

3. Results

3.1 Search results and study selection

The selection process for the current study is shown in Figure 1. The literature search turned up a total of 3974 relevant studies. About 207 duplicate studies and 43 non-English studies were removed from the record. The titles and abstracts of 3724 publications were screened, with 3279 being excluded due to irrelevant content. Overall, 445 publications were retrieved for full-text evaluation, with 399 being excluded for various reasons. The remaining articles were subjected to reference screening, which revealed an additional 15 related articles. After the application of selection criteria, 24 studies were excluded. Finally, 37 articles matched the inclusion criteria and they were included in the meta-analysis.

3.2 Characteristics of the included studies and patients

All of the included studies were observational. Overall, eleven studies were conducted in the USA, six in Israel, four in Korea, three in Canada, two in China, two in France, two in Denmark, and the reminders from England, Hong Kong, Thailand, Georgia, Greece, Malaysia and Australia. PfizerBioNTech, Moderna, AstraZenica, and Janssen were among the reported vaccines in the included studies. Table 1 shows the baseline characteristics of the studies included in the meta-analysis. The mean age of patients who developed cardiopulmonary complications after receiving the vaccines was 25.6 years, and 77% of them were male. The mean interval from vaccination to the onset of symptoms was four days, ranging from 1 to 41 days.

The most common reported consequence was inflammatory heart disease (myo-peri-cariditis), followed by pulmonary embolism (PE) (17%), and MI (5%). About 91% of complications were reported following m-RNA vaccination (43% Moderna, 30% Pfizer, and 18% undifferentiated) (Table 2).

3.3 Risk of cardiopulmonary complications following COVID-19 vaccination

The pooled analysis of 19 studies found that the incidence of cardiopulmonary complications following COVID-19 vaccinations was 0.000039%, with a 95% confidence interval of (0.000025% to 0.000062%), which means that the incidence rate was 3.9 per 100,000 doses. The I-squared statistic is 99% which tells that some 99% of the variance in observed effects reflects variance in true effects rather than sampling error. We estimated that the prediction interval is 0.000004 to 0.000351. The true effect size in 95% of all comparable populations falls in this interval (Figure 2). The pooled incidence of cardiopulmonary complications after the Moderna COVID-19 vaccination based on the random-effect model of five studies was 0.000037%, with a 95% confidence interval of (0.000016% to 0.000088%). This means that the event rate was 3.7 per 100,000 doses. Based on the random-effect model of 11 studies, the pooled incidence of cardiopulmonary complications following the PfizerBioNTech COVID-19 vaccine was 0.000041%, with a 95% confidence interval of (0.000022% to 0.000079%) (Figure 3), this equals to

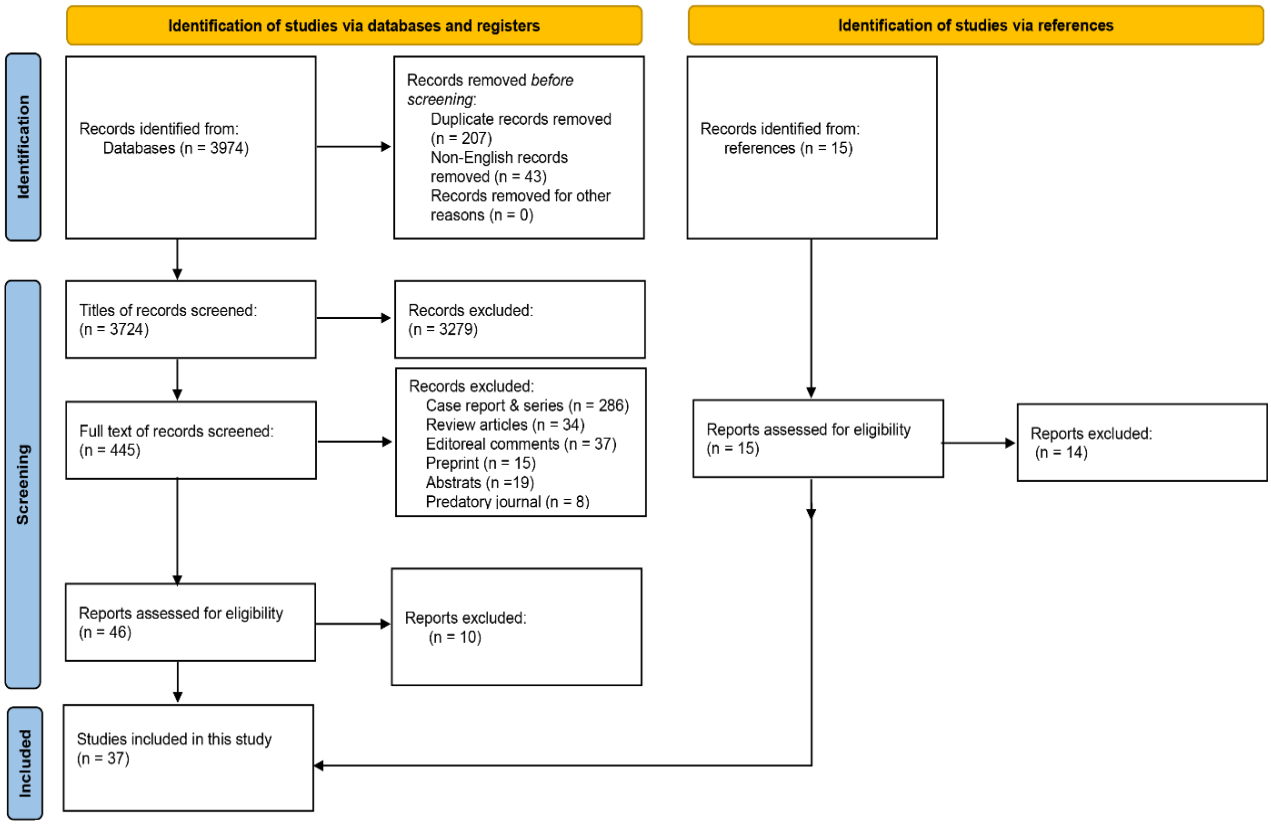

Figure 1: Prisma flow diagram

an incident rate of 4.1 per 100,000 doses. Overall, Pfizer-BioNTech has a slightly higher risk of cardiopulmonary complications following vaccination than Moderna (4.1 and 3.7 per 100,000 doses, respectively).

second dose of vaccination. Individuals who received the BNT162b2 vaccine, especially the second dose, were more susceptible to myocarditis/pericarditis than those receiving the mRNA-1273 vaccine. The mean age of the patients was 25 years (13-67), with more than three-quarters being male.

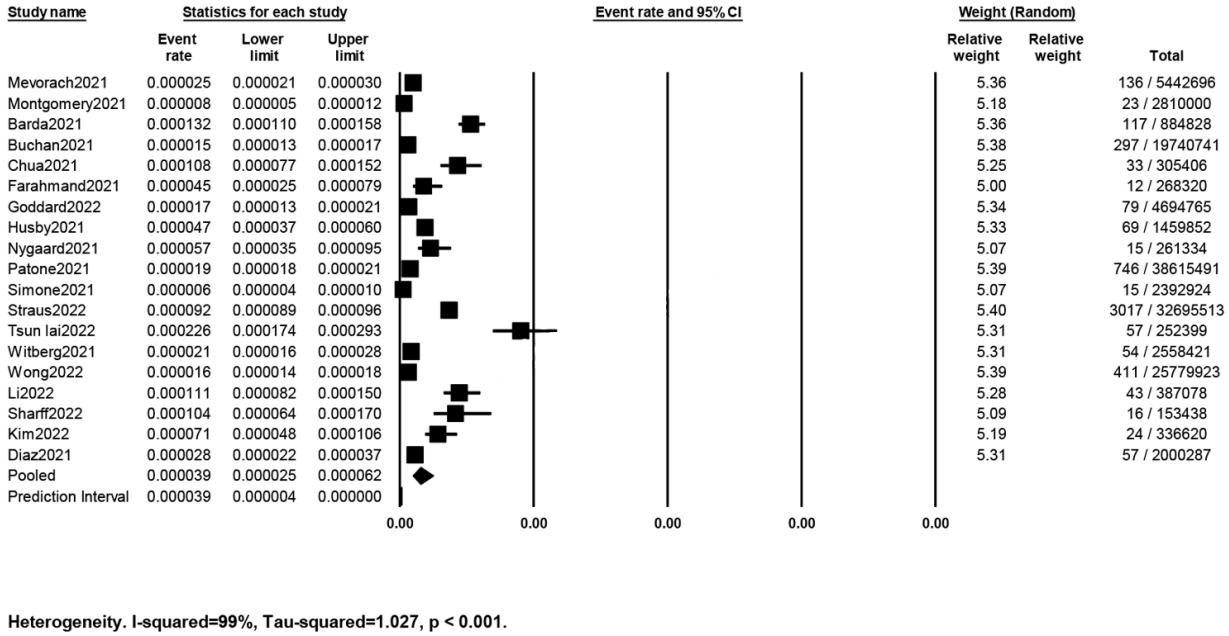

Figure 2: The rate of cardiopulmonary complications following COVID-19 vaccination.

4. Discussion

This systematic review and meta-analysis showed that myocarditis and pericarditis were the most commonly reported cardiopulmonary complications following COVID-19-approved vaccines. The majority of complications have been observed after the administration of the mRNA COVID-19 vaccine. More than two-thirds of the complications occurred following the

The COVID-19 pandemic has evolved as the most critical source of concern for the world's health and political systems. The COVID-19 immunization strategy was deployed in less than a year, representing an important breakthrough in research and development. The initial immunization experience revealed that all approved COVID-19 vaccines are effective and have an

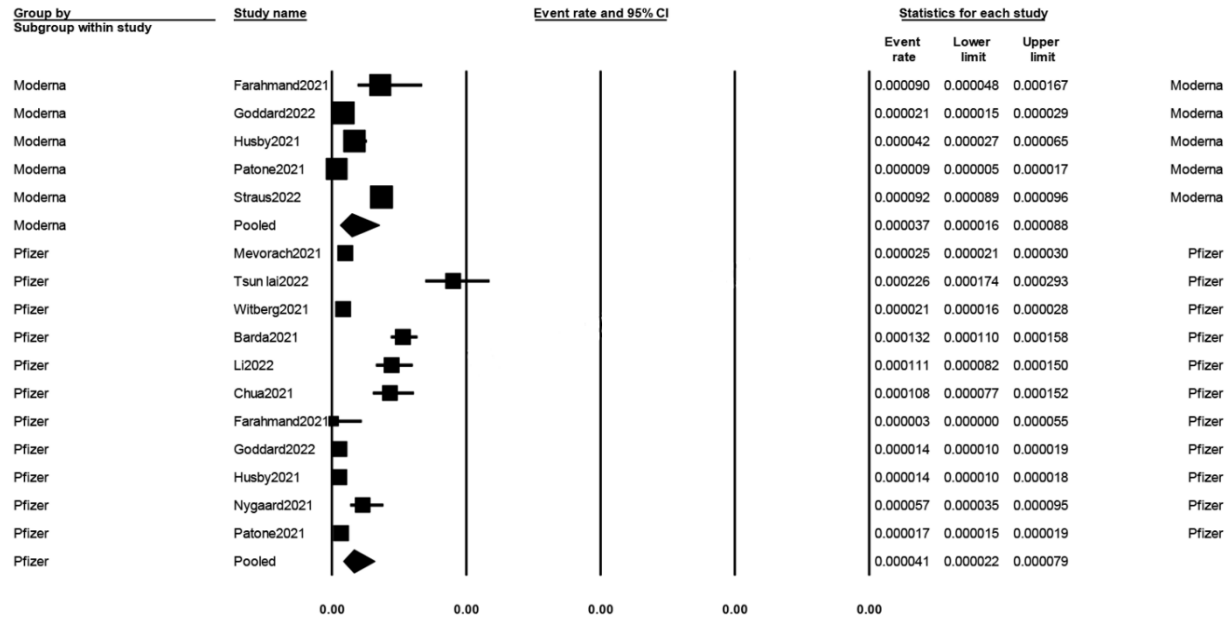

Figure 3: The rate of cardiopulmonary complications following Pfizer and Moderna vaccinations.

Table 1: Baseline characteristics of included studies

Study name	Publishing date	Country	Data Source	No. of Doses	No. of events	Mean age (year)	Sex (male)	Type of vaccination	Dose of vaccination
Abraham2022 [15]	25-May-22	Canada	CAEFISS	19,370,047	372	28	287	Pfizer;143 Moderna: 229	1st dose;82, 2nd dose;290
Barda2021 [16]	25-Aug-21	Israel	Health care organization in Israel	884,828	117	38	N/A	Pfizer;117	N/A
Buchan2022 [17]	24-Jun-22	Canada	Public Health Case and Contact Management Solution	19,740,741	297	24	228	Pfizer;159, Moderna;138	1st dose;90, 2nd dose;207
Chua2021 [18]	28-Nov-21	China	Electronic health records	305,406	33	15	30	Pfizer;33	1st dose;4, 2nd dose;29
Farahmand2021 [19]	4-Oct-21	Israel	Massachusetts Immunization Information System	268,320	12	N/A	6	Moderna;10, Janssen;2	1st dose;5, 2nd dose;7
Foltran2021 [20]	26-Nov-21	France	VigiBase	N/A	242	15.8	205	Moderna and Pfizer; 242	1st dose;37, 2nd dose;68
Fronza2022 [21]	20-Jan-22	Canada	Electronic patient record system	N/A	21	31	17	Pfizer;9, Moderna;12	1st dose;4, 2nd dose;17
Goddard2022 [22]	12-Jul-22	USA	VSD	4,694,765	79	23	68	Pfizer;41, Moderna;38	1st dose;16, 2nd dose;63
Husby2021 [23]	16-Dec-21	Denmark	Danish Vaccination Register	1,459,852	69	N/A	N/A	Pfizer;48, Moderna;21	N/A
Jain2021 [24]	1-Nov-21	USA	CDC's Vaccine Adverse Event Reporting System	N/A	63	16	58	Pfizer;59, Moderna;4	1st dose;1, 2nd dose;62
Kerneis2021 [25]	26-Jun-21	France	VigiBase	N/A	214	35	131	Pfizer;105, Moderna;51 AstrZenica;47	N/A
Kravchenko2022 [26]	10-Mar-22	Germany	Hospital information system	N/A	20	28	12	Pfizer;19, Moderna;1	1st dose;5, 2nd dose;15
Mevorach2021 [27]	6-Oct-21	Israel	Ministry of Health database	5,442,696	136	N/A	N/A	Pfizer;136	N/A
Montgomery2021 [28]	29-Jun-21	USA	Walter Reed National Military Medical Center	2,810,000	23	25	23	Pfizer;7, Moderna;16	1st dose;3, 2nd dose;20
Nygaard2021 [29]	10-Oct-21	Denmark	Danish VAERS	261,334	15	16	13	Pfizer;15	1st dose;8, 2nd dose;7
Oh2022 [30]	2-Mar-22	Korea	COVID-19 IRS	683	21	35	11	Pfizer and Moderna;21	1st dose;9, 2nd dose;11
Patone2021 [10]	14-Dec-21	England	English National Immunisation (NIMS) Database of COVID-19 vaccination	38,615,491	746	50	475	Pfizer;292, Moderna;9, AstrZenica;445	1st dose;406, 2nd dose;340

Table 1. continued...

Sa2022 [31]	17-Feb-22	Korea	VAERS data	N/A	4748	N/A	N/A	Pfizer;2247, Moderna;1921, Janssen;581	N/A
Simone2021 [32]	4-Oct-21	USA	N/A	2,392,924	15	25	15	Pfizer;8, Moderna;7	1st dose;2, 2nd dose;13
Straus2022 [33]	6-Jun-22	USA	Moderna global safety database	32,695,513	3017	29	2263	Moderna;3017	1st dose;518, 2nd dose;1201
Truong2022 [34]	1-Feb-22	USA	Multicenter study	N/A	139	16	126	Pfizer;131, Moderna;5, Janssen;1	1st dose;11, 2nd dose;128
Oster2021 [35]	25-Jan-22	USA	VAERS	354,100,845	1626	21	1334	Pfizer and Moderna;1626	1st dose;254, 2nd dose;1199
Tsun Lai2022 [36]	21-Mar-22	China	Electronic health records of the Hospital Authority (HA)	252,399	38	N/A	N/A	Pfizer;39	1st dose;8, 2nd dose;31
Varma2022 [37]	13-Jul-22	Australia	Monash Children's Hospital	N/A	33	14.6	27	Pfizer;28, Moderna;5	1st dose;6, 2nd dose;27
Witberg2021 [38]	6-Oct-21	Israel	Clalit Health Services Database	2,558,421	54	27	51	Pfizer;54	1st dose;54
Wong2022 [39]	11-Jun-22	USA	Health plan claims databases	25,779,923	411	N/A	N/A	Moderna and Pfizer;411	N/A
Li2022 [40]	25-Feb-22	Hong Kong	Hong Kong territorywide electronic health record database	387,078	43	15	38	Pfizer;43	1st dose;7, 2nd dose;36
Ch'ng2022 [41]	16-Oct-22	Malaysia	N/A	4906	58	33.6	N/A	Pfizer;58	N/A
Syrigos2022 [42]	10-May-22	Greece	N/A	797	7	N/A	4	Pfizer;7	1st dose;0, 2nd dose;7
Sharff2021 [43]	4-Apr-22	USA	KPNW's electronic health record	153,438	16	N/A	14	Pfizer;14, Moderna;2	1st dose;2, 2nd dose;14
Kim2022 [44]	22-Jul-22	Korea	Korean National Health Insurance Service database	168,310	24	N/A	N/A	Pfizer and moderna;24	2nd dose; 24
Showkathali2022 [45]	2-Feb-22	India	N/A	N/A	37	57	32	AstraZenica;28, Other;9	1st dose;24, 2nd dose;13
Diaz2021 [46]	28-Sep-21	USA	State registries of hospitals	2,000,287	57	48	42	Pfizer;23, Moderna;32, Janssen;2	1st dose;19, 2nd dose;38
Mansanguan2022 [47]	19-Aug-22	Thailand	N/A	301	7	15	7	Pfizer;7	2nd dose;7
Patel2021 [48]	7-Oct-21	Gorgia	N/A	N/A	9	16	9	N/A	1st dose;1, 2nd dose;8
Patel2022 [49]	9-Jun-22	USA	N/A	N/A	14	21	N/A	N/A	N/A
Zornitzki2022 [50]	1-Sep-22	Israel	N/A	N/A	9	20	8	Pfizer;9	2nd dose;9

acceptable safety profile [9,51]. Several trials have found that a two-dose mRNA COVID-19 vaccine program provides significant protection against serious infection, hospitalization, and mortality caused by COVID-19 [7]. The COVID-19 vaccine's early approval and subsequent wide availability have resulted in reports of severe reactions following vaccination. The majority of adverse events reported so far have been linked to risks that are equivalent to baseline risks in the general population and have not generated any concerns. However, for highly rare incidents, background hazards may be impossible to be quantified [52].

Multiple nations' post-market vaccine safety surveillance systems have revealed a possible link between COVID-19 mRNA vaccine administration and cardiac inflammatory disease [17]. Regardless of the fact that no cases of cardiac complications were observed in phase 3 trials of the mRNA vaccines, there have been multiple reports of cardiac complications, mainly myocarditis, following COVID-19 vaccination [53]. Myocarditis is an inflammatory condition of the myocardium caused by a viral infection, systemic immune-mediated disorders, or immunomodulatory therapy [54]. Myocarditis is an uncommon consequence of COVID-19 mRNA vaccination that generally develops 2–3 days after the second vaccine dose. The prevalence was highest in young adult and adolescent males. While myocarditis can be life-threatening, the majority of vaccine-associated myocarditis cases have been mild and self-limiting [30]. The risk of acute cardiac inflammation following COVID-19 vaccines is not restricted to myocarditis in young men. There is a significant risk and population burden of pericarditis following the second dose of the BNT162b2 and mRNA-1273 vaccines, frequently included in a combined event of myopericarditis [55]. Pericarditis as a specific entity has received little attention for its relationship with mRNA vaccines, and much less attention for the mRNA-1273 vaccine [55]. The mechanisms of myocarditis/pericarditis related to COVID-19 vaccinations include, but are not limited to, molecular mimicry, autoantibody production, mRNA immunological reactivity, activation of preexisting dysregulated immune processes, and genetic predisposition [56]. Barda et al. and Lai et al. observed a non-significant risk ratio of pericarditis of 1.27 and an odds ratio of 1.06 for the combined effect of the first and second doses of the BNT162b2 vaccination [16, 57]. Patone et al. also discovered a non-significant relative incidence of pericarditis in the week after both doses of the BNT162b2 vaccination of around 0.6, but the correlation with mRNA-1273 was unable to be assessed [10].

Table 2: Complication rate and type of vaccination

Variable	No (Percentage)
Mean age (year)	25.6 (13-67)
Sex	
Male	5630/7321 (77%)
Female	1689/7321 (23%)
Onset of symtoms from vaccination (day)	4 (0-41)
Cardiac complications	
Myo-peri-carditis	9838/12837 (77%)
Myocardial infarction	659/12837 (5%)
Pulmonary embolism	2138/12837 (17%)
Hypertenstion	74/12837 (0.6%)
Pulmonary complications	109/12837 (0.85%)
Other	19/12837 (0.15)
Vaccine type	
Pfizer	3874/12834 (30%)
Moderna	5512/12834 (43%)
AstraZenica	520/12834 (4%)
Janssen	591/12834 (5%)
Pfizer and Moderna	2324/12834 (18%)
Other	11/12834 (0.1%)
Vaccine dose	
1st dose	1583/5660 (28%)
2nd dose	3902/5660 (69%)
3rd dose	175/5660 (3%)

Using data from four US FDA, the rate of myocarditis or pericarditis within 7 days of a second dose of mRNA-1273 ranged from 72.4 cases per 1,000,000 doses (95% CI, 23.2-228.1 cases per 1,000,000 doses) to 283.7 cases per 1,000,000 doses (95% CI, 145.2-573.5 cases per 1,000,000 doses) [58]. In Ontario, a similar risk of myocarditis or pericarditis was reported at 299.5 cases per 1,000,000 doses following a second dosage of mRNA-1273 in males aged 18 to 24 years [17]. The current metanalysis found that the rate of cardiopulmonary complications after COVID-19 vaccination was 0.000039%, with a 95% confidence interval of (0.000025% to 0.000062%). This indicates that the event rate was 3.9 per 100,000 doses.

According to a study, the incidence of acute myocarditis/pericarditis in adolescents after the BNT162b2 vaccination was 18.52 per 100,000 people vaccinated. The majority of cases were healthy teenage men after receiving the second dosage [18]. Carrao et al found a greater risk of myocarditis after BNT162b2 vaccination but a lower risk after mRNA-1273, the second dose of mRNA-1273 was associated with a higher risk of myocarditis than the first dose, and males were at a higher risk of post-vaccine myocarditis than females [51]. In the present review, based on the random-effect model of five studies, the pooled incidence of cardiopulmonary complications after Moderna COVID-19 vaccinations was 3.7 per 100,000 doses, and based on the random-effect model of 11 studies, the pooled incidence of cardiopulmonary complications following the Pfizer COVID-19 vaccination was 4.1 per 100,000 doses.

A recent meta-analysis of over 22 trials for a total of 405,272,721 vaccine doses found three major findings: COVID-19 vaccinations had a lower incidence of myocarditis/pericarditis than non-COVID-19 vaccines (1.6 vs. 5.6 cases/100 000; P = n.s.). Myocarditis and pericarditis were substantially more common with mRNA vaccinations than with non-mRNA vaccinations (2.26 vs. 0.79 cases/100,000; P = 0.001). With increasing age, the likelihood of myocarditis decreases [59]. A recent study of electronic health record data from 40 US healthcare systems discovered that the frequency of cardiac complications following SARS-CoV-2 infection was roughly seven times greater than after the mRNA COVID-19 vaccine [23]. There are many different explanations for the differences in rates across systems, including the adverse event studied, the time from vaccination to disease onset for cases

included in the analyses, the different case classifications used to classify outcomes, completeness in reporting, and health system context (i.e., access to publicly funded health services). Furthermore, country-specific changes in inter-dose intervals and heterologous vaccination regimens may be related to rate variability among countries [17].

There is insufficient evidence to establish a conclusive causal relationship between COVID-19 vaccines and MI. The vaccinations may contribute to MI by increasing heart pressure, but they are not a direct cause of MI. COVID-19 vaccine-associated MI is not a well-known association [9]. According to single-center data, 42% of patients hospitalized with acute coronary syndrome and confirmed to have coronary thrombosis had recently received COVID-19 vaccines [45]. However, another study found that complete COVID-19 vaccination was associated with a lower incidence of acute MI and ischemic stroke compared to COVID-19 infection. The findings suggest vaccination, particularly for people at high risk of cardiovascular disease [44]. A recently published Israeli study found that the BNT162b2 vaccine did not increase the risk of MI (RR, 1.07 [CI, 0.74 to 1.60]), or PE (RR, 0.56 [CI, 0.21 to 1.15]) 42 days after administration [16].

In a preliminary study conducted in the US that used comprehensive health records from a diverse population to monitor 23 serious outcomes on a weekly basis, the incidence of selected outcomes was not significantly higher 1 to 21 days after receiving an mRNA vaccine compared to 22 to 42 days after vaccination. The RRs for acute MI were 1.02 (CI, 0.89 to 1.18) and 1.01 (CI, 0.86 to 1.19) for PE [60]. A nationwide study was carried out in a population of more than 46 million people aged 18 to 74 years, and those who experienced a serious cardiovascular diseases were included. There was no indication of a correlation between the mRNA-based vaccinations and acute MI, stroke, or PE in the three weeks following the first two doses. The Oxford-AstraZeneca vaccine increased the risk of PE slightly, but the two adenoviral-based vaccinations (Oxford-AstraZeneca and Janssen) increased the risk of acute MI. In the second week following the first dosage of the Oxford-AstraZeneca vaccine, the risk of PE and acute MI increased by around 30% [61]. In the current analysis, MI and PE are reported in 5% and 17% of the patients with cardiopulmonary complications, respectively.

The incidence of PE and acute respiratory distress syndrome was approximately 5-7 times greater after a single viral vector vaccination than after either of the mRNA vaccines. Following the mRNA vaccinations, the incidence was greater after the second dosage than after the first. The median onset of acute respiratory distress syndrome was 42 days following administration; however, it was frequently reported between two and six weeks after vaccines. The odds ratio of acute respiratory distress syndrome for males was double that of females, and the odds ratio of the viral vector vaccine to the mRNA vaccines was 2.951 (CI = 1.706–5.105). There was no significant difference between mRNA-1273 and BNT162b2 [31].

5. Conclusion

Although cardiopulmonary complications associated with COVID-19 vaccinations are uncommon, they can be life-threatening, especially in those receiving the second dose of vaccination. Therefore, more large-scale observational studies and review articles of those studies are highly suggested, and subgroup analysis based on behavioral risk variables is required. Further studies based on a longer period of observation will allow us to investigate the risk associated with vaccine doses as well as monitor the long-term cardiopulmonary consequences of these post-vaccination outcomes.

Declarations

Conflicts of interest: The author(s) have no conflicts of interest to disclose.

Ethical approval: Not applicable, as systematic reviews do not require ethical approval.

Patient consent (participation and publication)**:** Not applicable.

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