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SYSTEMATIC REVIEWS

Link between COVID-19 vaccines and myocardial infarction

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Abstract

BACKGROUND
Vaccines for coronavirus disease 2019 (COVID-19) include ChAdOx1-SARS-COV-2 (AstraZeneca), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna), BNT162b2 (Pfizer), BBIBP-CorV (Sinopharm), CoronaVac (Sinovac), and Bharat Biotech BBV152 (Covaxin).

AIM
To find the association between COVID-19 vaccines and myocardial infarction (MI).

METHODS
This is a systematic review that involved searching databases such as MEDLINE, EMBASE, and PakMediNet after making a search strategy using MeSH and Emtree terms. Eligibility criteria were set, and studies having no mention of MI as a complication of COVID-19 vaccination, protocols, genetic studies, and animal studies were excluded. Data was extracted using a predesigned extraction table, and 29 studies were selected after screening and applying the eligibility criteria.

RESULTS
The majority of studies mentioned AstraZeneca (18 studies) followed by Pfizer (14 studies) and Moderna (9 studies) in subjects reporting MI after vaccination. Out of all the studies, 69% reported MI cases after the first COVID-19 vaccination dose and 14% after the second, 44% reported ST-segment elevation MI, and 26% reported non-ST-segment elevation MI. The mortality rate was 29% after MI.

CONCLUSION
In conclusion, many studies linked MI to COVID-19 vaccinations, but no definitive association could be found.

Core Tip: Mechanisms like vaccine-induced thrombotic thrombocytopenia and myocarditis complication have been identified in the literature linking myocardial infarction with coronavirus disease 2019 (COVID-19) vaccination. The majority of myocardial infarction cases reported were after vaccination with the vaccine from AstraZeneca, were ST-segment elevation, and were reported after first dose of vaccine. Although there are reports of myocardial infarction after COVID-19 vaccination, no definitive link was found in the previous literature linking the two.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2. The first case of COVID-19 was reported in Wuhan, China and rapidly spread to the rest of the world[1]. The COVID-19 outbreak was declared a pandemic on March 11, 2020[2]. Although severe acute respiratory syndrome coronavirus 2 primarily affects the respiratory tract, it frequently causes cardiac, gastrointestinal, hepatic, nephrological, and central nervous system distress [3]. It mainly causes nonspecific symptoms like fever, cough, and myalgia; however, in severe cases, it can lead to respiratory failure, septic shock, multiorgan dysfunction, and even death[4].

COVID-19 treatment is most often general supportive care and nutritional support in addition to respiratory care. However, due to the lack of clinically approved interventions for COVID-19 treatment, attempts have been made for vaccine development to prevent the disease[3]. As a result, the safety and efficacy of several vaccines have been approved by the World Health Organization. Among these are AstraZeneca/Oxford, Johnson and Johnson/Janssen, Moderna, Pfizer/BioNTech, Sinopharm, Sinovac, and the Bharat Biotech BBV152 Covaxin vaccine[5]. Vaccines for severe acute respiratory syndrome coronavirus 2 have several different mechanisms of action, including: (1) RNA and DNA vaccines that are genetically engineered to produce a protein that warrants an immune response; (2) Vector vaccines that introduce a type of virus that cannot produce disease but can effectively generate an immune response; (3) Vaccines that use genetically modified viruses to become weaker or inactivated in order not to cause virulence but retain their antigenicity; and (4) Harmless fragments of proteins or protein shells with similar antigenicity to the COVID-19 virus that are used in protein-based vaccines to produce immunity[5].

It is not uncommon to experience side effects following a COVID-19 vaccine. Fatigue, headache, muscle pain, joint pain, chills, fever, generalized body pain, and local reaction at the injection site are some of the side effects that have been reported after COVID-19 vaccination[6]. Several cardiovascular adverse effects have also been reported after COVID-19 vaccination, including myocarditis, pericarditis, and thrombotic events. Additionally, rare cardiovascular events such as hypertension, acute coronary syndrome, stress cardiomyopathy, arrhythmias, and cardiac arrest have also been reported. Although the relationship between these rare events and the vaccination is doubtful, the incidence of these rare side effects post vaccination in the absence of any other obvious cause in otherwise healthy individuals may suggest a causal relationship between the two[7].

When only focusing on myocardial infarction (MI), it is observed that after a person experiences an MI, there is a 20% chance of mortality in the 1st year and 10% thereafter[8]. According to Johansson *et al* [9], the relative risk of cardiovascular morbidity and mortality was 30% higher in those who suffered from MI compared to the general population. The aims of this review were to identify the pathophysiological links between MI and COVID-19 vaccination and investigate the doses and frequencies of COVID-19 vaccines, the types of MI, and mortality statistics linked with the vaccine administration in the available literature.

Table 1 Concept table for building the search strategy

Key concepts	Concept 1	Concept 2	Concept 3	Concept 4
	COVID-19	**Vaccines**	**Myocardial infarction**	**Link**
Free text terms		Vaccination	Heart attack	Relation
		Shot		Interrelation
		Jab		
		Dose		
		Booster		
Controlled vocabulary terms (MeSH terms, Emtree terms)	2019 novel coronavirus	Viral Vaccines	Anterior wall myocardial infarction	Association
	2019-nCoV disease	Immunization		
	2019-nCoV infection		Inferior wall myocardial infarction	
	COVID-19 pandemic		Non-ST elevated myocardial infarction	
	COVID-19 virus disease		ST elevation myocardial infarction	
	COVID-19 virus infection			
	SARS-CoV-2 infection			

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

MATERIALS AND METHODS

Databases and search strategy
This systematic review was conducted over a period of 6 mo. The databases searched were MEDLINE, EMBASE, and PakMediNet. MeSH and Emtree terms were used as well as free text words (Table 1) to develop a search strategy. Various concepts were identified and then searched using Boolean operators. "AND" was used to separate various concepts, and synonyms for a single concept were separated by "OR." The data was searched, and studies from the first delivery of COVID-19 vaccines in December 2020 until May 1, 2022 were included.

Eligibility criteria
Articles that mentioned COVID-19 vaccination along with MI as a vaccine complication were included. Case reports, case series, original research, and systematic reviews were also included.

Exclusion criteria
All studies that included COVID-19 cases but had no mention of vaccinations were excluded. Studies with no mention of MI as a complication of a COVID-19 vaccination were also excluded. Protocols and research based on animals and studies mentioning vaccinations for similar diseases, like influenza, were also excluded. Genetic studies involving COVID-19 without mention of vaccination and narrative reviews not identifying a link between MI and COVID-19 vaccination were further excluded (Figure 1).

Data extraction
The data was then extracted from the eligible studies by a structured data extraction form. Two independent researchers were engaged in both screening and data extraction, and data was analyzed for frequencies and percentages.

RESULTS

A total of 56 studies were identified, but only 29 were selected after applying the eligibility criteria (Table 2)[5-7,10-35]. The majority of these were case reports that reported the incidence of MI after COVID-19 vaccination but could not prove any causative relationship between the two. They also could not prove whether MI was due to vaccination-related changes in the body. The majority of side effects reported were from AstraZeneca followed by Pfizer and Moderna vaccines (Figure 2).

Based on the studies included in this report, patients usually suffered from MI after the first dose of the vaccine (69%). Of these studies, 53.3% of case reports reported MI within a few hours of vaccine

**Table 2 Analysis/summary of important findings in various studies**

Ref.	Study design	No. of cases reported	Type of vaccine given	Time during symptoms and vaccination	Dose of vaccine, 1st or 2nd	Type of MI	Patient outcome, dead or alive
Jabagi *et al*[10]	Cross sectional	6510/11113 (58.6%) after first dose, 4843/11113 (43.6%) after second dose of vaccine	Pfizer	Not given	1st and 2nd both	Not given	NA
Li *et al*[11]	Cohort study	Ages 35-74 incidence = between 1/100 and 1/1000 ages 75 and above incidence = between 1/10 and 1/100 patients	NA	Not given	NA	Not given	NA
Aye *et al*[12]	Cohort and systematic review	29 in cohort, 35 in systematic review	Pfizer 30/35 (86%), Moderna 1/35 (3%), AstraZeneca 4/35 (11%), Janssen 0%	Median of 1 d	2nd	STEMI 20/35 (57%) NSTEMI 15/35 (43%)	1 dead, remaining were alive
Maadarani *et al* [13]	Case report	1	AstraZeneca	1.5 h	1st	STEMI and NSTEMI	Alive
Fazlollahi *et al* [14]	Systematic review	3	2 Pfizer, 1 Moderna	Case 1: 6 h, case 2: 1 h, case 3: 30 min	1st	Case 1: NSTEMI, case 2: STEMI, case 3: STEMI	Case 1: alive, case 2: alive, case 3: dead
Şancı *et al*[15]	Case report	1	Pfizer	15 min	1st	STEMI	Alive
Chatterjee *et al* [16]	Case report	1	AstraZeneca	2 d	1st	STEMI	Alive
Jeet Kaur *et al* [17]	Cross sectional	Pfizer: 44, AstraZeneca: 1, Moderna: 3	Pfizer, AstraZeneca, and Moderna	NA	NA	NA	NA
Iqbal *et al*[18]	Case report	1	Moderna	90 min	1st	NSTEMI	Alive
Cari *et al*[19]	Cross sectional	Pfizer: 0.00044%, AstraZeneca: 0.00168%, Janssen: 0.00217%	Pfizer, AstraZeneca, Janssen	Not given	NA	NA	Dead Pfizer: 0.00013%, AstraZeneca: 0.0004%, Janssen: 0.00048%
Tajstra *et al*[20]	Case report	1	Pfizer	30 min	1st	STEMI	Dead
Flower *et al*[21]	Case report	1	AstraZeneca	8 d	1st	STEMI	Alive
Chiang *et al* [22]	Case report	1	AstraZeneca	8 d	1st	NSTEMI	Alive
Fialho *et al*[23]	Case report	1	AstraZeneca	20 min	1st	STEMI	Alive
Hsu *et al*[24]	Case report	1	AstraZeneca	9 d	1st	STEMI	Dead
Showkathali *et al*[25]	Cross sectional	37 (42%)	AstraZeneca was the most used vaccine-28 (76%), while 9 (24%) had Covaxin	< 1 wk: 9 (24%), 1-4 wk: 19 (52%), and > 4 wk: 9 (24%)	1st (65%), 2nd dose (35%)	STEMI and NSTEMI	NA
Whiteley *et al*	Cross sectional	Post vaccination < 28 d 3814/13787 (27.66%). Post	AstraZeneca and Pfizer	NA	1st	NA	Dead, < 28 d 16192/43766

[26]		vaccination > 28 d 2050/7758 (26.42%)					(37.00%), > 28 d 11738/19496 (60.21%)
Shiravi *et al*[5]	Narrative review	Not given	Pfizer, AstraZeneca, and Sinovac vaccines	15 min to 2 d	NA	NA	NA
Barda *et al*[27]	Cross sectional	59/892785 = 0.006%	Pfizer	Not given	NA	NA	NA
Barsha *et al*[6]	Case report	1	Moderna	12 h	1st	NSTEMI	Alive
Boivin *et al*[28]	Case report	1	Moderna	1 h	1st	STEMI	Alive
Hippisley-Cox *et al*[29]	Cross sectional	AstraZeneca: 0-7 d 1983/22079 (8.98%), 8-21 d 4028/22079 (18.23%), 22-28 d 1889/22.79 (8.55%). Pfizer: 0-7 d 1578/15124 (10.43%), 8-21 d 3457/15124 (22.83%), 22-28 d 1510/15124 (10.00%)	AstraZeneca and Pfizer	AstraZeneca: 0-7 d 1983, 8-21 d 4028, 22-28 d 1889, Pfizer: 0-7 d 1578, 8-21 d 3457, 22-28 d 1510	1st	Not given	Not given
Edler *et al*[30]	Case series	1	Pfizer	2 d	1st	Not given	Dead
Hana *et al*[7]	Systematic review	1644 cases total	AstraZeneca, Pfizer and Moderna	NA	NA	Not given	NA
Ho *et al*[31]	Systematic review	10	Pfizer, Moderna, AstraZeneca, Sinovac	NA	1st	STEMI and NSTEMI	Some dead, some alive
Sung *et al*[32]	Case series	2	Moderna	Case 1 < 24 h, case 2 < 12 h	1st	Case 1 STEMI, case 2 Not given	Alive
Pottegård *et al* [33]	Cross sectional	Incidence rate 1.04/1.21, no of cases 20	AstraZeneca	Not given	1st	Not given	NA
Agostino *et al* [34]	Case report	1	AstraZeneca	12 d	1st	Not given	Dead
Bardenheier *et al*[35]	Cross sectional	1	Pfizer	2 d	2nd	Not given	NA

MI: Myocardial infarction; NA: Not available; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; NA: Not Applicable.

administration and the rest within 10 d. Out of these patients, 44% of cases reported were of ST-segment elevation MI (STEMI), and 26% were non-ST-segment elevation MI (NSTEMI). The mortality rate was 29% (Figure 3). The most studies reported were from the United States, the United Kingdom, and India (Figure 4).

Possible mechanisms behind MI that have been identified after the literature review are as follows: (1) Kounis syndrome, which can cause MI through different mechanisms like allergic vasospasm and stent occlusion with a thrombus infiltrated by eosinophils or mast cells; (2) Vaccine-induced thrombotic thrombocytopenia; (3) Acute coronary syndrome after influenza vaccine administration as both influenza and COVID-19 vaccines share a common excipient (polysorbate 80); (4) Demand–supply mismatch ischemia, which can be caused by the stress of getting the vaccine in elderly people with other associated comorbidities; and (5) Myocarditis.
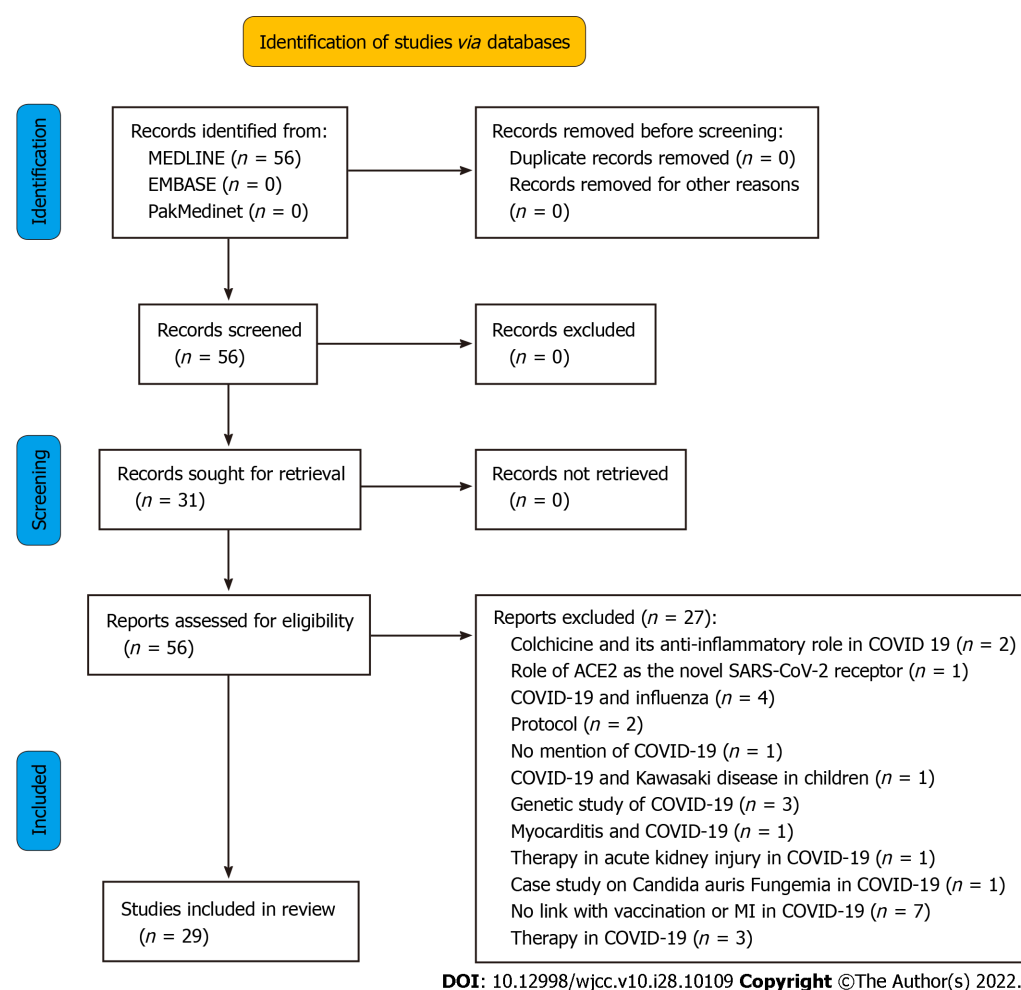
Figure 1 PRISMA flow chart showing the selection process. ACE2: Angiotensin-converting enzyme 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

DISCUSSION

Globally, 65.8% of people have received at least one dose of a COVID-19 vaccine, and 11.79 billion doses have been administered globally[36]. The doses of various vaccines administered through May 25, 2022 are as follows: Pfizer, 613 million; Moderna, 147 million; AstraZeneca, 67 million; Janssen, 19 million; Sputnik V, 1.85 million; Sinopharm, 2.31 million; Sinovac, 3737; and Covaxin, 44. Pakistan has administered at least 248672457 doses of COVID-19 vaccines so far. Assuming that every person needs two doses, that is enough to have vaccinated about 57.4% of the country's population[37].

MI remains one of the rare complications of a COVID-19 vaccination[7]. In this review, nearly 69% of the studies reported MI occurrence after the first dose, and 14% reported it after the second. It is a known fact that a subsequent or a booster dose of a vaccine is given to increase the antibody titer. This is especially crucial in those with a weakened immune response due to comorbidities[38]. A theory based on this finding is that since MI occurrence is higher after the first vaccine dose, immune response probably plays no role or only a minimal role in MI pathophysiology. If MI was due to overstimulation of the immune system, then the frequency of MI after the second dose would be higher.

A study showed that COVID-19 vaccination produces an optimum immune response in chronic inflammatory disease patients on immunosuppressive therapy, and the risk of adverse consequences is not higher than in the normal population[39]. No single inflammatory biomarker of systemic manifestations of vaccines has been identified but rather a battery of biomarkers, specifically, interleukin-6, C-reactive protein, and the interferon signaling pathway. A vaccine starts its action within minutes, starting from the injection site and spreading throughout the body. The factors known to affect the reactogenicity of various COVID-19 vaccines are age, gender, psychological/physical stressors, obesity, pre-existing immunity, vaccine characteristics (route, site, and method of vaccine administration), vaccine composition, antigen type, combination, and dose[40].

According to McManus *et al*[41], the incidence of STEMI compared to NSTEMI has reduced over the past few years. In the present research, patients with STEMI were present in 44% of the studies compared to 26% with NSTEMI after COVID-19 vaccination[41]. A recent case reported STEMI in a
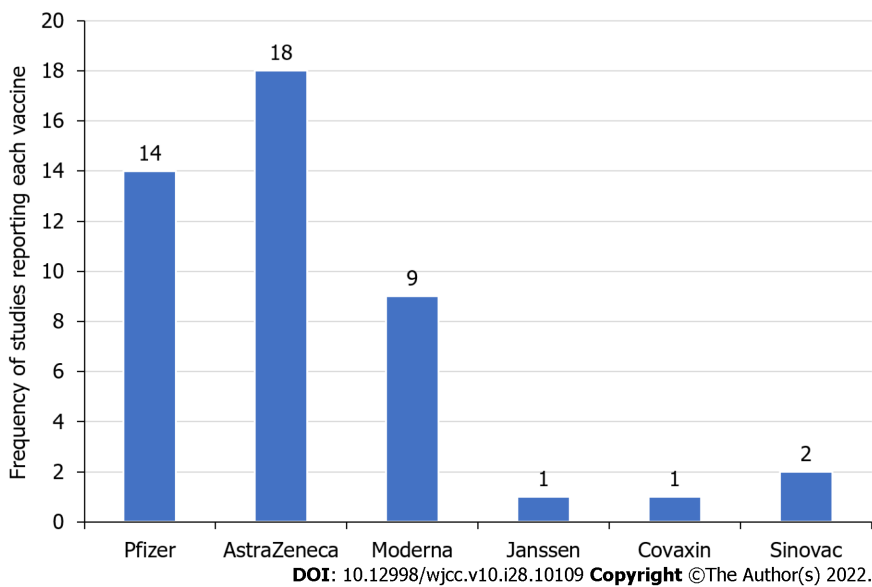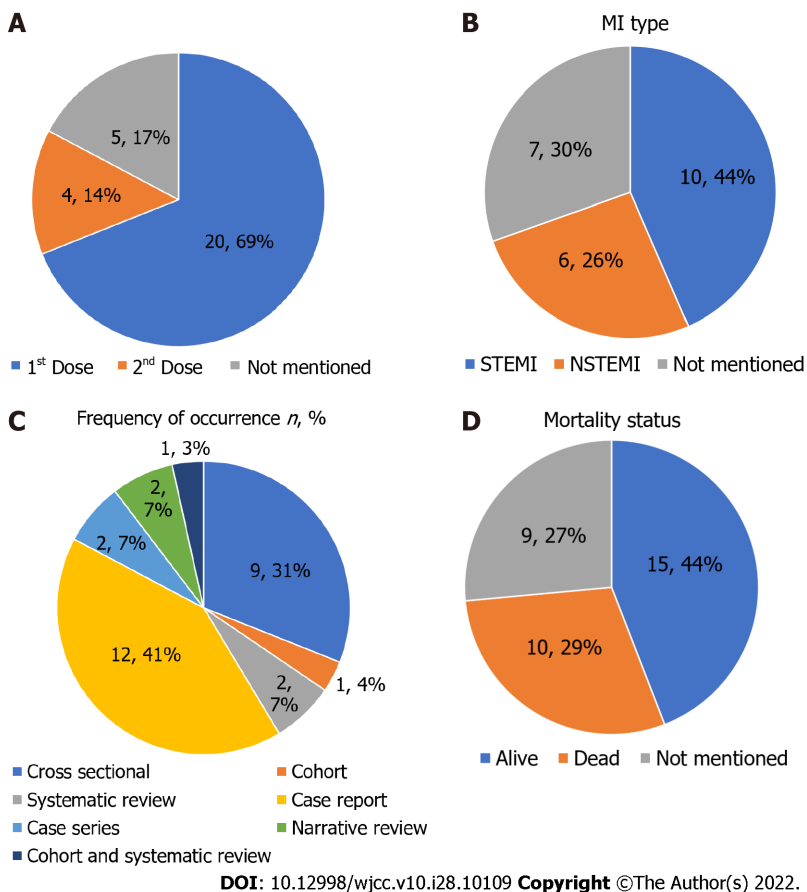
Figure 2 Frequency of vaccines given to subjects in each study.

Figure 3 Characteristics of research studies analyzed. A: Doses of vaccines given to subjects/participants in studies analyzed; B: Percentage/frequencies of types of myocardial infarction reported in studies analyzed; C: Type of studies analyzed; D: Mortality status of subjects/participants in various studies after suffering from myocardial infarction post-vaccination. MI: Myocardial infarction; STEMI: ST-segment elevated myocardial infarction; NSTEMI: Non-ST-segment elevated myocardial infarction.

post-COVID-19-vaccinated patient in April 2022, and the patient also had a history of myocarditis. A possible explanation was the transient atrial fibrillation or plaque rupture after the myocarditis[42]. Therefore, myocarditis on the one hand is a primary complication of COVID-19 vaccination and on the other hand is a secondary cause of MI development after COVID-19 vaccination.
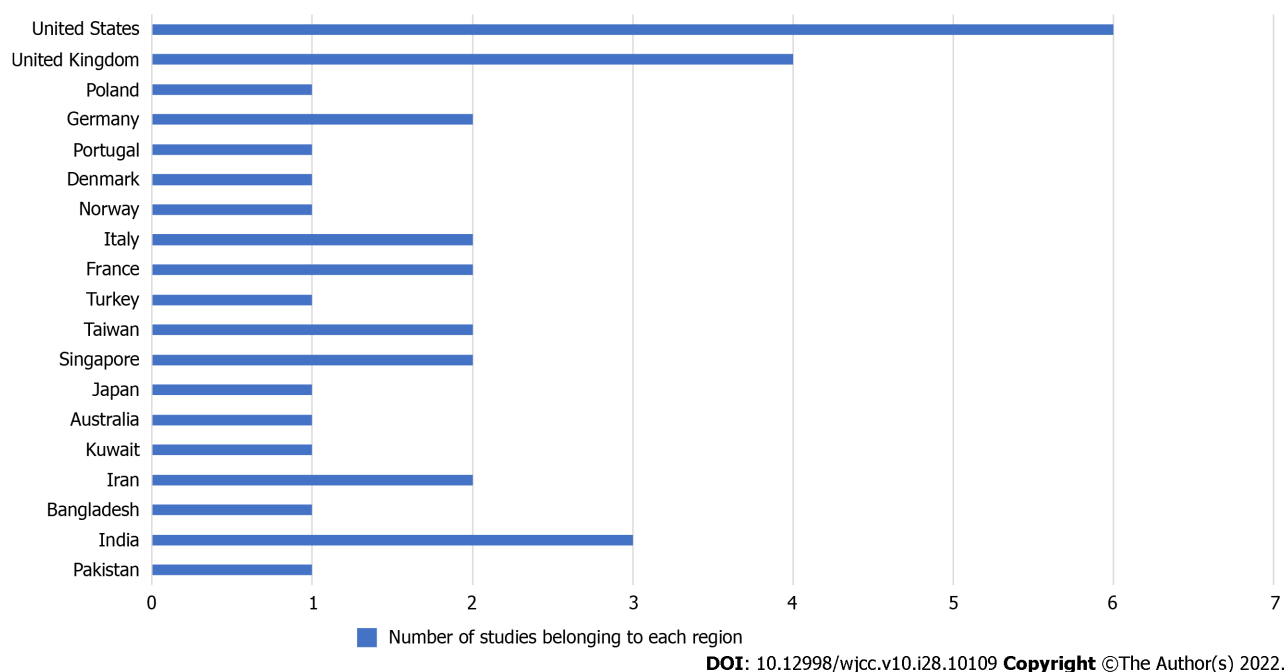
Figure 4 Frequency of studies reporting myocardial infarction after coronavirus disease 2019 vaccination in different countries.

In his blog, Labos wrote a critique in which he pointed out that in order to state the link between inflammation and MI after COVID-19 vaccination, the inflammatory biomarkers need to be measured before, soon after, and a month after vaccination[43]. Jabagi *et al*[10] proved that there was no association between increased risk of MI post Pfizer vaccination for COVID-19. He did a serial analysis 1 d, 1 wk, and 2 wk post vaccination[10].

Kounis syndrome is one of the mechanisms identified for the occurrence of MI post COVID-19 vaccination as it has been observed in various patients who received a COVID-19 vaccination (Pfizer, AstraZeneca, and Sinovac vaccines)[5,15]. It manifests as an acute coronary syndrome accompanied by mast cell activation due to hypersensitivity or an allergic or anaphylactic reaction[44]. It is more commonly linked with STEMI, which probably explains the higher percentage of STEMI cases after COVID-19 vaccination compared to NSTEMI in the present research.

Vaccine-induced thrombotic thrombocytopenia is another mechanism linking MI with COVID-19 vaccines. In vaccine-induced thrombotic thrombocytopenia, tetramers of platelet factor 4 crosslink with vaccine proteins to form multimolecular aggregates. The ethylenediamine tetraacetic acid in the vaccine possibly causes capillary leakage and dissemination of components in the blood. The multimolecular aggregates are recognized by immunoglobulin G antibodies, which activate platelets, neutrophils, and the complement system, resulting in massive coagulation system activation[45]. This can lead to MI and eventually mortality or long-term morbidity.

Polysorbate 80, an excipient in the AstraZeneca vaccine, is seen to trigger allergic reactions in those allergic to the compound. Similarly, polyethylene glycol is the excipient found in Pfizer and is a cause of severe anaphylaxis in those allergic to polyethylene glycol. However, polyethylene glycol allergy is very rare compared to polysorbate 80 allergy[46], which probably explains the increased number of MI cases reported in patients vaccinated with AstraZeneca compared to other vaccines.

The literature searched and analyzed in this study was quite diverse. Therefore, one of the challenges faced while compiling this review was to bring the results under one umbrella. It was observed that robust original research needs to be conducted to probe the mechanisms of and the association between MI and COVID-19 vaccination. Considering the amount of clinical evidence available linking MI with COVID-19 vaccination, it is a bit early to make definitive deductions regarding their link.

CONCLUSION

It can be concluded that there is a link between COVID-19 vaccinations and MI in temporal terms of occurrence. However, there is also a possibility that the link was found purely by chance as a majority of cases were reported within 1 d, which is too short a time for a build-up of definitive causative mechanisms for MI. This is due to the diversity of risk factors for MI, such as age, gender, body mass index, ethnicity, and physical/mental stressors. This link can be definitively proven by conducting research while considering the confounders. AstraZeneca was seen to induce the greatest amount of

coronary artery disease, with STEMI as the leading type, and this primarily followed the first vaccination dose.

ARTICLE HIGHLIGHTS

Research background
Coronavirus disease 2019 (COVID-19) was first identified November 2019 and subsequently caused a world pandemic. The development of vaccines was quickly achieved with the first vaccinations occurring in December 2020. From then on, a global campaign commenced to vaccinate the majority of the world's population. The implications of these vaccines have been researched abundantly.

Research motivation
The side effects of COVID-19 vaccines, particularly serious cardiovascular side effects, mention myocarditis. However, myocardial infarction (MI) and its link with COVID-19 vaccines remain unclear.

Research objectives
To investigate and pinpoint if any link exists between COVID-19 vaccination and MI amongst the vaccinated individuals.

Research methods
We devised a search strategy to search MEDLINE, EMBASE, and PakMediNet. All studies that reported MI after COVID-19 vaccine delivery were included in this research. A structured data extraction form was developed to extract the data from the eligible studies.

Research results
The majority of MI cases reported were after vaccination with the AstraZeneca vaccine. Out of all the studies, 69% reported MI cases after the first COVID-19 vaccination dose and 14% after the second. The majority (44%) of MI reported was STEMI.

Research conclusions
Many studies linked MI to COVID-19 vaccinations, but no definitive association could be found.

Research perspectives
More robust clinical trials in this regard could clarify the link between COVID-19 vaccinations and MI.

FOOTNOTES

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