

Overview of SARS-CoV-2 infection and vaccine associated myocarditis compared to non-COVID-19-associated myocarditis: A systematic review and meta-analysis

Yoshiko Ishisaka ^{a,1}, Atsuyuki Watanabe ^{a,1}, Tadao Aikawa ^{b,1}, Koshiro Kanaoka ^{c,1}, Hisato Takagi ^{d,1}, Jose Wiley ^{e,1}, Jun Yasuhara ^{f,1}, Toshiki Kuno ^{g,h,1,*}

^a Department of Internal Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, NY, New York, USA

^b Department of Cardiology, Hokkaido Cardiovascular Hospital, Sapporo, Japan

^c Department of Medical and Health Information Management, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

^d Division of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan

^e Section of Cardiology, Department of Medicine, Tulane University School of Medicine, LA, USA

^f Department of Cardiology, The Royal Children's Hospital, Melbourne, Victoria, Australia

^g Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, NY, New York, USA

^h Division of Cardiology, Jacobi Medical Center, Albert Einstein College of Medicine, NY, New York, USA

ARTICLE INFO

Keywords:
COVID-19
mRNA vaccine
Myocarditis
SARS-CoV-2

ABSTRACT

Background: Previous literature suggests that both SARS-CoV-2 infection and COVID-19 mRNA vaccine are associated with myocarditis, in which the incidence is higher in the infection group. COVID-19 mRNA vaccine-related myocarditis is noted to have a more benign course. Despite these findings, there is a need for a larger population systematic review that compares the outcomes to pre-pandemic acute myocarditis to better understand the extent of the current post-COVID state.

Methods: We performed a literature search with PubMed and EMBASE and identified studies investigating COVID-19 and its vaccinated population, and the population prior to the pandemic (control group) who had myocarditis. We performed a one-group meta-analysis of the incidence, baseline demographics, and outcomes of myocarditis for each group.

Results: The incidence in the SARS-CoV-2 infection group was 2.76 per thousand (95% CI, 0.85–8.92), 19.7 per million (95% CI, 12.3–31.6) in the vaccine group, and 0.861 per million (95% CI, 0.04–16.7) in the control group. The majority of patients were male, with the highest proportion in the vaccine group. The mean age was the youngest in the vaccine group (24.8, 95% CI, 19.1–30.6). The vaccine group had the lowest mortality (2.0%, 95% CI, 1.3–2.7) followed by the control and the SARS-CoV-2 infection group. The vaccine group had the lowest proportion of immunoglobulin and glucocorticoid use, mechanical circulatory support, and cardiogenic shock.

Conclusion: Our study showed favorable outcomes of myocarditis in patients with COVID-19 mRNA vaccination, despite a higher incidence than pre-COVID controls. Further studies with standardized myocarditis diagnostic criteria assessing long-term outcomes are necessary.

1. Introduction

The relationship between myocarditis and SARS-CoV-2 infection or COVID-19 mRNA vaccines has been an area of investigation. Prior literature suggested that SARS-CoV-2 infection was associated with

myocarditis, with a higher prevalence among younger (<16 years) and older (≥ 50 years) age groups, and in the male population [1–3]. The incidence rate of SARS-CoV-2 infection related myocarditis may vary depending on the severity of the disease from 0.01% to 7.7%, whereas mortality has been reported from 13.7% to as high as 33% [4]. COVID-

* Corresponding author at: Division of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th St, Bronx, NY 10467–2401, USA.

E-mail address: tkuno@montefiore.org (T. Kuno).

¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

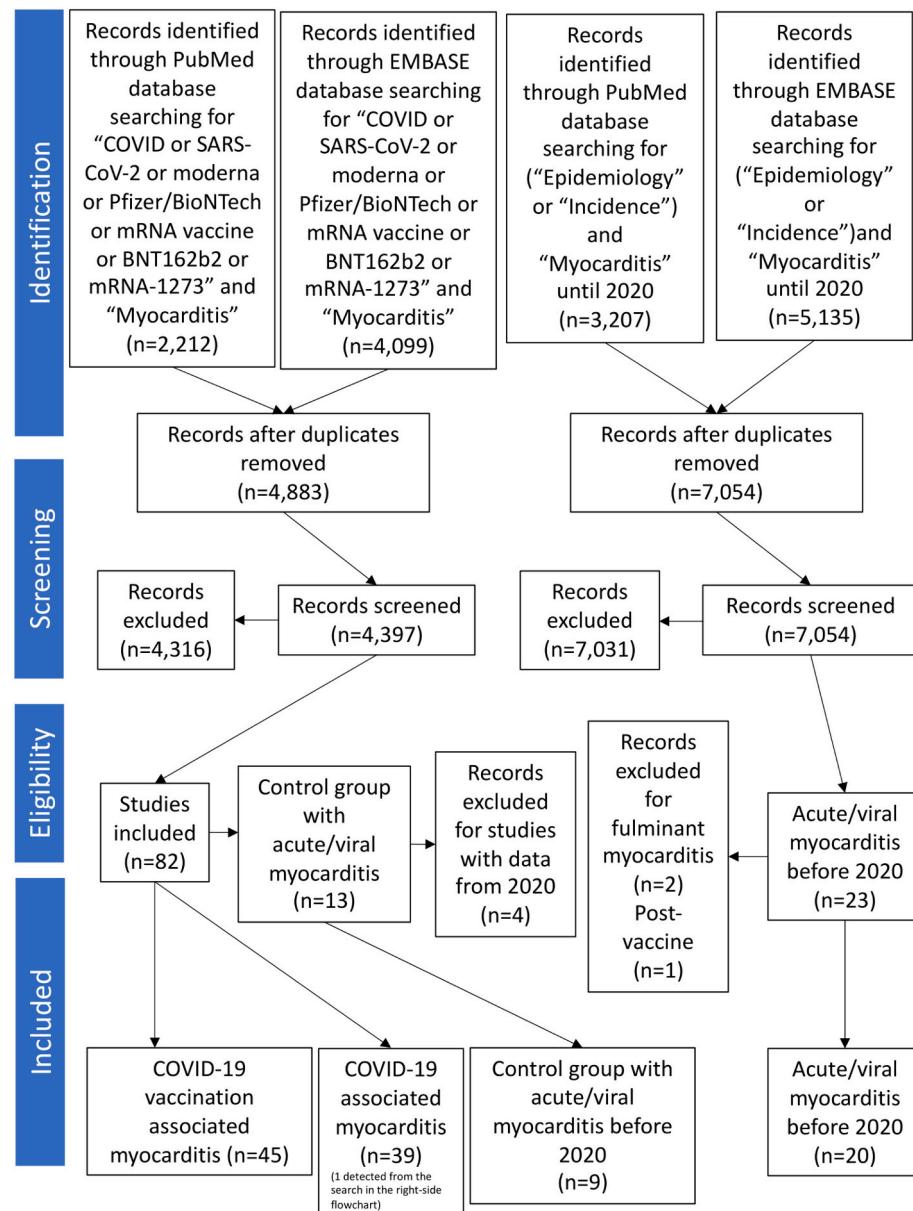


Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of study selection.

Table 1

SARS-CoV-2 infection group baseline characteristics.

First author	Year	Country/region	Frequency	Age ^(a)	Male (%) ^(a)
Daniels	2021	USA	Clinical: 9/9225 Subclinical: 28/9225	N/A	N/A
Ammirati	2022	USA, Europe	54/54963	38 [25–53]	33 (61)
Karlstad	2022	Norway	73/ (N/A)	N/A	42 (58)
			Incidence rate ratio: Male 0.568 /1000 person-year Female 0.437/1000 person-year		
Moulson	2021	USA	21/3018	20 ± 1	11 (52)
Eiros	2021	Spain	35/ (N/A)	Myocarditis: 53[49–58] Myopericarditis: 50[44–61]	5/35 (14)
Weckbach	2021	Germany	7/116	N/A	N/A
Luchetti	2022	Italy	1/584	N/A	N/A
Kildegaard	2022	Denmark	0/74611	N/A	N/A
Lagana	2021	Italy	12/1169 (1%)	76 ± 11.34	5 (42)
Maestrini	2021	Italy	14/152	N/A	N/A
Zeng	2020	China	34/416	N/A	N/A
Mahmoud	2022	USA	1/100	N/A	N/A
Linschoten	2020	UK	3/3011	N/A	N/A
Murk	2021	USA	49/70288	N/A	N/A
			OR 8.17, 95% CI 3.58–18.62, absolute risk 0.1%		
Buckley	2021	UK	35,820/718365	47.4 ± 21.1	15,592 (44)
Daugherty	2021	USA	16/193113	N/A	N/A
Hiroi	2022	Japan	19/19853	60.2 ± 17.84	14 (74)
Kunal	2020	India	3/108	N/A	N/A
Rubens	2022	USA	578/164417	N/A	356 (62)
Boehmer	2021	USA	2116/1452773	N/A	1274 (60)
Petersen	2021	USA	10	53 [44–72]	6 (60)
Priyadarshni	2022	USA	79/107699	N/A	N/A
Bemtgen	2022	Germany	443/(N/A)	53.4 ± 22.4	284 (64)
Cates	2020	USA,	23/3948	N/A	N/A
Wang	2022	China	711/690892	N/A	N/A
Annie FH	2021	USA	383/259352	47.5 ± 21.4	226 (59)
Davis	2022	USA	6455/1659040	N/A	3963 (57)
Tuvali	2022	Israel	9/196992	36.4 ± 19.7	8 (89)
Joy	2021	UK	3/74	N/A	N/A
Brito		USA	0/54	N/A	N/A
Clark	2021	USA	2/59	N/A	N/A
Malek	2021		0/26	N/A	N/A
Starekova	2021	USA	2/145	N/A	N/A
Szabo	2022	Hungary	1/147	N/A	N/A
Vladislav	2021	Serbia	8/ (N/A)	N/A	N/A
Tanacli	2021	Italy	3/ (N/A)	N/A	N/A
Aquaro	2022	Italy	67/ (N/A)	41 ± 19	51 (76)
			Incidence rate ratio: 5.9/100000 year		
Puttegowda	2021	India	52/ (N/A)	N/A	N/A
Husby	2023	Nordic countries	109/(N/A)	N/A	N/A
Rinaldi	2022	Italy	2/701	N/A	N/A
Fronza	2022	USA	10/(N/A)	51 ± 14	3 (30)

(a) Of all myocarditis patients

Age presented with mean ± standard deviation, or median [interquartile range].

HS: high-sensitivity, Tn: troponin.

19 mRNA vaccine-associated myocarditis has been reported in the summary of product characteristics of each vaccine [5,6]. It is more commonly seen in males, in the age range of 17–39 years old, within <2 weeks after vaccination [4,7]. The highest risk is recognized after the second vaccine dose [7–9]. Regarding the vaccine type, several studies show a higher risk of myocarditis in mRNA-1723 compared to BNT162b2 [8]. Current evidence demonstrates a low incidence of mRNA vaccine-associated myocarditis with fewer than 20 cases per million, and largely benign clinical outcomes [3,10–14].

Currently, the Center for Disease Control (CDC) and advisory committee on immunization practices as well as the U.S. Food and Drug Administration recommends COVID-19 vaccination for patients ≥6 months old and concludes that the benefit of mRNA vaccine in preventing SARS-CoV-2 infection and its overall severe outcomes overweighs the risk of myocarditis [15,16]. The risk of myocarditis is shown to be seven-fold higher in patients with SARS-CoV-2 infection compared to those after COVID-19 vaccination [17]. However, the difference in

outcomes of myocarditis between SARS-CoV-2 infection and COVID-19 vaccination remains unknown.

Although there is accumulating information regarding myocarditis associated with SARS-CoV-2 infection and its vaccination, there are few large studies that compared both the incidence and outcomes. The data comparing outcomes of myocarditis after SARS-CoV-2 infection or mRNA vaccination with non-COVID causes of acute myocarditis is also sparse. In addition, a comparison with pre-pandemic controls would facilitate understanding the extent of the disease as well as the efficacy of vaccination.

To our knowledge, there has not been any pooled evidence that compared both myocarditis occurrence and outcomes between patients infected with SARS-CoV-2, patients vaccinated with COVID-19, and the acute myocarditis population excluding SARS-CoV-2 infection or COVID-19 vaccination. In this study, we conducted a systematic review and meta-analysis to synthesize the current literature and investigate the incidence and clinical outcomes of myocarditis in SARS-CoV-2 infection,

Table 2

COVID-19 mRNA vaccination group baseline characteristics.

First author	Year	Country/ region	Frequency	Dose 1	Dose 2	Booster	Age ^(a)	Male (%) ^(a)
Lai	2022	Hong Kong	119/8896843	28	68	8	N/A	82 (69)
Patone	2022	UK	1615/38615491 (Hospitalized or deceased cohort)	N/A	N/A	N/A	N/A	N/A
Diaz	2021	USA	20/2000287	4	16	N/A	36 [26–48]	15 (75)
Husby	2021	UK	269/4931775	N/A	N/A	N/A	N/A	196 (73)
Patone	2022	UK	2861/42842345 (hospitalized or deceased cohort)	ChAdOx1: 140 BNT1627: 124 mRNA-1273: 11	ChAdOx1: 90 BNT162b2: 119 mRNA-1273: 40	BNT162b2: 85 mRNA- 1273: 8	53.8 ± 19.7	1333 (59)
Karlstad	2022	Norway	1077/1356457	BNT162b2: 105 mRNA-1273: 15	BNT162b2: 115 mRNA-1273: 60		N/A	N/A
Mouch	2021	Israel	6/ (N/A)	1	5	N/A	25.1 ± 9.89	6 (100)
Barda	2021	Israel	21/884828	N/A	N/A	N/A	N/A	N/A
Kim	2021	USA	4	N/A	100%	N/A	N/A	N/A
Foltran	2022	France	193/4942	31	58	N/A	15.9 ± 1.3	172 (90)
Montgomery	2021	USA	23/2810000	N/A	20/23	N/A	20[20–51]	23 (100)
Moureira	2022	International	0/5055	N/A	N/A	N/A	N/A	N/A
Marshall	2021	USA	7	7	0	0	16.7 ± 0.148	7 (100)
Rosner	2021	USA	7	1	6	N/A	27.4 ± 7.8	7 (100)
Larson	2021	USA	8	1	7	N/A	31.6 ± 11.2	8 (100)
Levin	2021	Israel	7	0	7/7	N/A	20.4 ± 1.92	7 (100)
Choe	2022	Korea	N/A	N/A	N/A	N/A	N/A	N/A
Yap	2022	Singapore	25/7183889	9	16	N/A	23	20 (80)
			Myopericarditis: 11				[12–55]	
			Myocarditis: 14					
Anastassopoulou	2022	Greece	2016/406570875	539	1078	13	N/A	1508 (75)
Naveed	2022	Canada	7 days: 99/10255385 21 days: 141/10255385	7 days: 7/99 21 days: 26/141	7 days: 74/99 21 days: 88/141	7 days: 18/ 99 21 days: 27/ 141	Male 31 ± 17, Female 49 ± 22	7 days: 80 (80.8) 21 days: 105 (74.5)
Massari	2022	Italy	441/5109231	N/A	N/A	N/A	N/A	302 (69)
Tan	2021	Singapore	3/127081	N/A	N/A	N/A	N/A	N/A
Sharff	2022	USA	6/65785	0	0	6/6	N/A	4 (67)
Naveed	2022	Canada	59/3204555	N/A	59	N/A	N/A	44 (75)
Niesen	2022	USA	1/47999	0	0	1/1	N/A	N/A
Corrao	2022	Italy	120/25242528	48/4392516	69/5593884	3/556116	N/A	N/A
Perez	2022	USA	7/ (N/A)	1	6	N/A	44	6 (86)
							[22–71]	
Le Vu	2022	France	534/32153452	141/24084447	393/21927002	N/A	N/A	N/A
Hatziantoniou	2022	Europe and USA	4877/581440261 (Europe), 1784/400260000 (USA)	N/A	N/A	N/A	N/A	N/A
Chua	2022	China	33/305406	6	27	N/A	15.1 ± 1.55	29 (87.9)
Goddard	2022	USA	18/4694765	N/A	N/A	N/A	N/A	N/A
Oster	2022	USA	1626/354100845	361	1265	N/A	N/A	1334 (82)
Buchan	2022	Canada	212/19740741 (myocarditis 105, myopericarditis 107)	52/212	160/212	N/A	N/A	N/A
				Myocarditis: 31/ 105	Myocarditis: 74/105			
				Myopericarditis: 107	Myopericarditis: 86/ 107			
Mevorach	2022	Israel	28/3944797	N/A	N/A	28	N/A	N/A
Farahmand	2021	USA	10/268320	3	7	N/A	42.9 ± 15.2	Myocarditis: 5 (50) Myopericarditis: 0
			Myocarditis: 9	Myocarditis: 2				
			Myopericarditis: 1	Myopericarditis:1				
Lai	2022	Hong Kong	N/A	8/138141	30/119644	N/A	N/A	N/A
Chouchana	2022	France	1408/ (N/A)	N/A	N/A	N/A	N/A	N/A
Witberg	2022	Israel	9/182605	1	8	N/A	14 [13–14]	8 (89)
Mevorach	2021	Israel	136/10568331	19/5442696	117/5125635	N/A	N/A	118 (87)
Witberg	2021	Israel	54/2558421	17/156816	37/2401605	N/A	27[21–35]	51 (94)
Friedensohn	2022	Israel	N/A	N/A	N/A	8/126029	N/A	8 (100)
Nygaard	2022	Denmark	12/261334	7	6	N/A	N/A	11 (92)
			10 myocarditis 2 myopericarditis					
Truong	2022	USA	139/ (N/A)	12	127	N/A	15.8[14.5–17]	126 (91)
Patel	2022	USA	9/ (N/A)	1/9	8/9	N/A	15.7[14.5,16.6]	9 (100)
Husby	2022	Nordic countries	530/(N/A)	N/A	N/A	N/A	N/A	413 (77.9)
Strauss	2022	USA	3017/568668391	N/A	N/A	N/A	N/A	2263 (75)
Ozen	2022	Turkey	9/(N/A)	N/A	N/A	N/A	15.5 ± 0.92	9 (100)

(continued on next page)

Table 2 (continued)

First author	Year	Country/ region	Frequency	Dose 1	Dose 2	Booster	Age ^(a)	Male (%) ^(a)
Shiyovich Schauer	2021 2022	Israel USA	15/(N/A) 16/(N/A)	N/A N/A	N/A N/A	N/A N/A	32 (22.5–40) 15 years (range, 12–17 years)	15 (100) 15 (94)
Liao Fronza Evertz	2022 2022 2022	Taiwan USA Switzerland	14/(N/A) 21/(N/A) 15/(N/A)	2 N/A N/A	12 N/A N/A	N/A N/A N/A	15 (13–17) 31 ± 14 25.5 (21.8–33.5)	11 (79) 17 (81) 10 (100)
Amir	2022	Israel	15/(N/A)	N/A	N/A	N/A	17 ± 1 (median 17.2, range 14.9–19)	100%
Shauer	2021	USA	13/(N/A)	N/A	N/A	N/A	15.1 ± 1.25	14/15

(a) Of all myocarditis patients

Tn: troponin.

Age and continuous values presented as mean ± standard deviation or median [interquartile range].

COVID-19 vaccination, and control group with non-COVID-19 causes.

2. Methods

2.1. Data sources and search strategy

We performed a comprehensive literature search through PubMed and EMBASE on January 3rd, 2023. The search term was (“COVID or SARS-CoV-2” or “Moderna” or “Pfizer/BioNTech” or “mRNA vaccine” or “BNT162b2” or “mRNA-1273”) and “Myocarditis”, for the COVID-19, COVID-19 mRNA vaccination group, and part of the control group, and literature before December 2019 with search terms (“Epidemiology” or “incidence”) and “myocarditis” for the control group. We then reviewed related articles and collected relevant information. The systematic review and meta-analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [18] and enrolled in PROSPERO (ID: CRD42023397478). An institutional review board/ethics exemption was granted for the innocuousness of the study.

We included studies that investigated COVID-19 mRNA vaccination-associated myocarditis, SARS-CoV-2 infection-associated myocarditis, and myocarditis prior to the COVID-19 pandemic before December 2019. We allocated each study to three groups; the SARS-CoV-2 infection group, the COVID-19 mRNA vaccination group, and the control group. In the control group, we used studies that investigated the background of acute or viral myocarditis population before December 2019. There was no restriction regarding sample size or the age of included patients. We included studies regardless of the definition or diagnostic criteria of myocarditis and summarized the definition/criteria of each study in a table. We excluded studies that only investigated fulminant cases, or post-vaccination myocarditis except for COVID-19 mRNA vaccines. We also excluded pericarditis/myopericarditis/perimyocarditis cases as we aimed to specifically investigate the myocarditis incidence and outcome. The treatment would differ between each disease entity, thus we decided to focus only on identifying features regarding myocarditis in this study. No restrictions on language and publication date were applied.

Two authors (Y.I. and A.W.) screened the eligibility of initial search results. Initially, we filtered through the titles and abstracts, and then a full-text review was performed on any potentially relevant studies. The same investigators performed the data extractions, and discrepancies were solved upon discussion.

2.2. Outcomes

For our primary outcome, we investigated the proportion of myocarditis cases in each group. In the SARS-CoV-2 infection group, the incident was calculated as patients with myocarditis per SARS-CoV-2 positive patients included in the entire cohort. In the vaccination

group, we defined the incident as myocarditis cases divided by the number of vaccines administered. In the control group, the number of patients with myocarditis was divided by the number of patients in the total cohort. Specifically, cohorts utilizing the population that was enrolled in a certain health plan during a period prior to December 2019 or population in a single area were deemed eligible for analysis. We excluded studies that only included inpatient cases for analysis of the incidence, as this would only limit the incidence to severe cases which require hospitalization and does not capture the entire myocarditis cases in the general population including those not requiring inpatient level of care. When available, we also collected data on the incidence rate ratio divided by time. We excluded the studies that focused on only the fulminant cases.

Our secondary outcomes focused on patients diagnosed with myocarditis in each patient group. These included in-hospital mortality rate, the occurrence of heart failure, the use of intravenous immunoglobulin (IVIG), the use of glucocorticoids, the use of mechanical circulatory support (MCS) including extracorporeal membranous oxygenation (ECMO) and ventricular assist device (VAD), and the occurrence of cardiogenic shock.

2.3. Data extraction

The following details from each study were extracted and tabulated: study characteristics (publication year, study design, cohort size), number of myocarditis cases, baseline cohort characteristics (age, sex and comorbidities), mortality, use of IVIG or steroids, and use of mechanical cardiac support. We also collected data regarding the number of vaccine administrations for each patient in the vaccination group. The risk of bias for non-randomized studies was assessed using a tool for assessing the risk of bias for non-randomized studies of interventions [19], while the Cochrane Collaboration’s tool was used for randomized studies [20].

2.4. Summary measures and synthesis of results

The proportion of mortality, mechanical cardiac support (MCS), and use of IVIG and steroids were collected. We collected mean values and standard deviation for continuous variables. We performed a study-level one-group meta-analysis in a random-effects model using the DerSimonian-Laird method for continuous values and the Wald method for discrete values using OpenMetaAnalyst version 21.11.14. The frequency and incidence of the outcomes were calculated by summation of events divided by the number of total patients from all studies whose information is available for each value. We performed a logarithmic transformation for the analysis of myocarditis incidence because of the low proportion. We calculated the 95% confidence interval (CI) for each variable. We assessed heterogeneity using I^2 and defined >50% as substantial.

Table 3
Control Group Baseline Characteristics.

First Author	Year	Country/region	Frequency	Age ^(a)	Male (%) ^(a)
Lai	2022	Hong Kong	866/(N/A)	N/A	457 (60)
Daugherty	2021	USA	2,972,2381 (2019 cohort) 15/165,5907 (lower respiratory tract infection cohort)	N/A N/A	N/A N/A
Farahmand	2021	USA	1/235,343	37	N/A
Petersen	2021	USA	45/(N/A)	40[19–89]	23 (51)
Priyadarshni	2022	USA	29/77,499 (admitted patients) 39/74,888 (admitted patients)	N/A N/A	N/A N/A
Bemtgen	2022	Germany	24,474/(N/A) 0.052 per 10,000 person-month	N/A	N/A
Cates	2020	USA	11/5,453 (admitted patients)	N/A	N/A
Patel	2022	USA	43/(N/A)	14.7 [9.0, 16.6]	31 (72)
Aquaro	2022	Italy	92/(N/A)	38 ± 18	63 (69)
			Incidence rate ratio: 8.1 per 100,000 person-year		
Park	2021	Korea	119/(N/A) 2010: 0.34 per 1000 in-patients 2019: 1.25 per 1000 in-patients	N/A	N/A
Nasreen	2022	Canada	Incidence rate ratio per 100,000 (95% CI) per year 2015: 2.54 (2.28, 2.82) 2016: 2.88 (2.60, 3.17) 2017: 3.38 (3.08, 3.69) 2018: 2.58 (2.32, 2.86) 2019: 2.93 (2.66, 3.22) 2020: 2.42 (2.18, 2.69)	N/A	N/A
Aljohani	2022	USA	29/(N/A)	4.2[1.4–14]	18 (62)
			Incidence ratio 2015: 9.82[9.3–10.36]/100,000 person-year 2016: 10.22 [9.69–10.77]/100,000 person-year 2017: 12.4 [11.8–13]/100,000 person-year 2018: 11.9 [11.3–12.4]/100,000 person-year 2019: 12.0 [11.4–12.6]/100,000 person-year Mean: 11.3 [11.0–11.5]/100,000 person-year		
Vasudeva	2021	USA	6371/603,900,000 (admitted patients)	12 [11–13]	4205 (66)
Kyto	2013	Finland	3198/(N/A)	33 [16–96]	2458 (77)
Younis	2020	USA	322/(N/A)	37 ± 14	272 (84)
Arola	2017	Finland	213/88,2253 (admitted patients)	N/A	163 (77)
			Incidence rate ratio 1.95/100,000 person-year		
Shah	2019	USA	27,129/(N/A)	37.3 ± 18.8	17,921 (66)
Matsuura	2016	Japan	221/(N/A)	6.5 ± 3.3	
Pahuja	2019	USA	36,967/(N/A)	N/A	N/A
Barfuss	2019	USA	75/(N/A)	15.5 [13.6–16.6]	50 (67)
Klugman	2010	USA	216/42,7615 (admitted patients)	N/A	94 (44)
Ukimura	2013	Japan	25/(N/A) 4/(N/A)	39 ± 21 45 ± 15	17 (68) 3 (75)
English	2004	USA	45/(N/A)	median 2.2 years	21 (51)
Mahrholdt	2006	Germany	128/(N/A)	N/A	N/A
Herskowitz	1993	USA	49/(N/A)	43 ± 16	28 (57)
Baselga-Moreno	2019	International	Influenza negative: 2/7245 Influenza positive: 1/2895	N/A	N/A
Ukimura	2010	Japan	15/ (N/A)	42.5 ± 20.1	9 (75)
McCarthy	2000	USA	Acute myocarditis: 132/ (N/A) Fulminant myocarditis: 15/ (N/A)	Acute myocarditis: 43 ± 13 Fulminant myocarditis: 35 ± 16	Acute myocarditis: 84 (64) Fulminant myocarditis: 11 (73)
Wang	2021	International	3,071,000/(N/A) Age standardized incidence rate: 39.2/100,000 persons	N/A	N/A

(a) Of all myocarditis patients

Age and continuous values presented as mean ± standard deviation or median [interquartile range].

Table 4

Summary of results of one group meta-analyses.

	COVID-19	SARS-CoV-2 mRNA vaccine	Control
Incidence	2.76×10^{-3} 37,225/2,380,858 per COVID-19 positive patients [95% CI: 8.56×10^{-4} , 8.92×10^{-3}] $I^2 = 99.9\%$	1.97×10^{-5} 15,795/2,456,227,389 per vaccine doses [95% CI: 1.23×10^{-6} , 3.16×10^{-5}] $I^2 = 99.9\%$	8.61×10^{-7} 3/9,957,724 per included population [95% CI: 4.45×10^{-8} , 1.67×10^{-5}] $I^2 = 83.6\%$
Age	51.8 [95% CI: 47.6–56.1] $I^2 = 94.5\%$	24.8 [95% CI: 19.1–30.6] $I^2 = 99.9\%$	36.4 [95% CI: 23.7–49.3] $I^2 = 99.9\%$
Male percentage	58.1% 21,948/46,213 [95% CI: 51.1–64.7%] $I^2 = 98.4\%$	84.1% 8285/11,839 [95% CI: 78.9–89.4%] $I^2 = 97.3\%$	66.4% 25,920/38,773 [95% CI: 62.9–69.8%] $I^2 = 93.8\%$
Mortality	12.1% 2975/43,933 [95% CI: 4.9–26.7%] $I^2 = 99.6\%$	2.0% 612/18,694 [95% CI: 1.3–2.7%] $I^2 = 94.5\%$	6.5% 3071/90,035 [95% CI: 4.5–9.5%] $I^2 = 98.2\%$
Immunoglobulin use	27.2% 16/80 [95% CI: 8.3–60.5%] $I^2 = 77.0\%$	12.5% 125/937 [95% CI: 7.3–17.6%] $I^2 = 57.1\%$	44.1% 256/564 [95% CI: 26.3–63.6%] $I^2 = 93.8\%$
Glucocorticoid use	55.4% 257/459 [95% CI: 44.5–65.9%] $I^2 = 43.0\%$	11.4% 126/1517 [95% CI: 6.9–18.1%] $I^2 = 63.3\%$	20.1% 155/918 [95% CI: 12–31.6%] $I^2 = 89.5\%$
Mechanical circulatory support	5.8% 187/6983 [95% CI: 2.0–16%] $I^2 = 89.4\%$	2.7% 1/1575 [95% CI: 1.5–4.8%] $I^2 = 0\%$	10.3% 1876/28,436 [95% CI: 5.4–18.7%] $I^2 = 95.4\%$
Cardiogenic shock	18.7% 773/7203 [95% CI: 12.1–27.9%] $I^2 = 86.7\%$	3.3% 18/2257 [95% CI: 1.9–5.6%] $I^2 = 29.2\%$	20.0% 58/339 [95% CI: 10–35.8%] $I^2 = 86.0\%$

3. Results

We identified 2096 articles on PubMed, and 3717 articles on EMBASE by the search term (“COVID or SARS-CoV-2” or “Moderna” or “Pfizer/BioNTech” or “mRNA vaccine” or “BNT162b2” or “mRNA-1273”) and “Myocarditis”, and 91 studies were identified for our review (Fig. 1). There were 38 articles investigating SARS-CoV-2 infection-associated myocarditis and 44 articles investigating COVID-19 mRNA vaccine-associated myocarditis, and out of these studies, nine studies had control groups that consisted of non-COVID-19 acute/viral myocarditis patients before the pandemic. All references to the included studies are listed in the Supplemental file. We identified 3207 articles on PubMed, and articles on EMBASE by the search term (“Epidemiology” or “Incidence”) and “Myocarditis”, and 20 studies were identified for our review (Fig. 1). Details of inclusion criteria and definition of myocarditis in the included studies are listed in Supplemental Tables 1–3. Some studies used the Brighton criteria, Lake Louise criteria, and other clinical criteria for diagnosis, however, many of the studies, especially those with a wide population, included patients based on the ICD-10 codes or the Medical Dictionary for Regulatory Activities codes, and did not specify what criteria was used for diagnosis of myocarditis.

41 studies were from the United States, 30 were from Europe, 16 were from Asia, 10 were from Israel, and five were from Canada. All baseline characteristics of each group are listed in Tables 1–3, and the outcomes are listed in Supplemental Tables 4–6. The risk of bias graph and summary are in Supplemental Fig. 1. The summary of the results of the one-group meta-analyses is in Table 4.

3.1. Incidence

The incidence of myocarditis in each group is summarized in Fig. 2. The studies with inclusion criteria of hospitalized patients were excluded from the incidence analysis in each group. Myocarditis incidence in the SARS-CoV-2 infected group was 37,225/2,380,858 cases,

2.76 per thousand (95% CI, 0.85–8.92; $I^2 = 99.9\%$) after analysis by logarithmic transformation. In the COVID-19 mRNA vaccination group, the incidence was 15,795/2,456,227,389 doses (19.7 per million; 95% CI, 12.3–31.6; $I^2 = 99.9\%$). Incidence in the control group was 3/9,957,724 cohort enrolled population (0.861 per million; 95% CI, 0.0445–16.7; $I^2 = 83.6\%$).

Several studies in the vaccine and control group reported the incidence rate. However, we were unable to perform a meta-analysis because the vaccination group outcome varied in terms of the observation period.

We also investigated the incidence stratified by age group and vaccine type/doses, which was calculated from studies that reported total vaccine doses and myocarditis cases in each group. The results are in Supplemental table 7. The proportion of patients who had myocarditis in the second dose of vaccination was 1.39×10^{-5} , 95% CI [1.06×10^{-6} – 1.82×10^{-5}] compared to 1.36×10^{-5} , 95% CI [3.24×10^{-6} – 5.71×10^{-5}] in those who only had the first dose. The proportion of myocarditis was higher in the younger population.

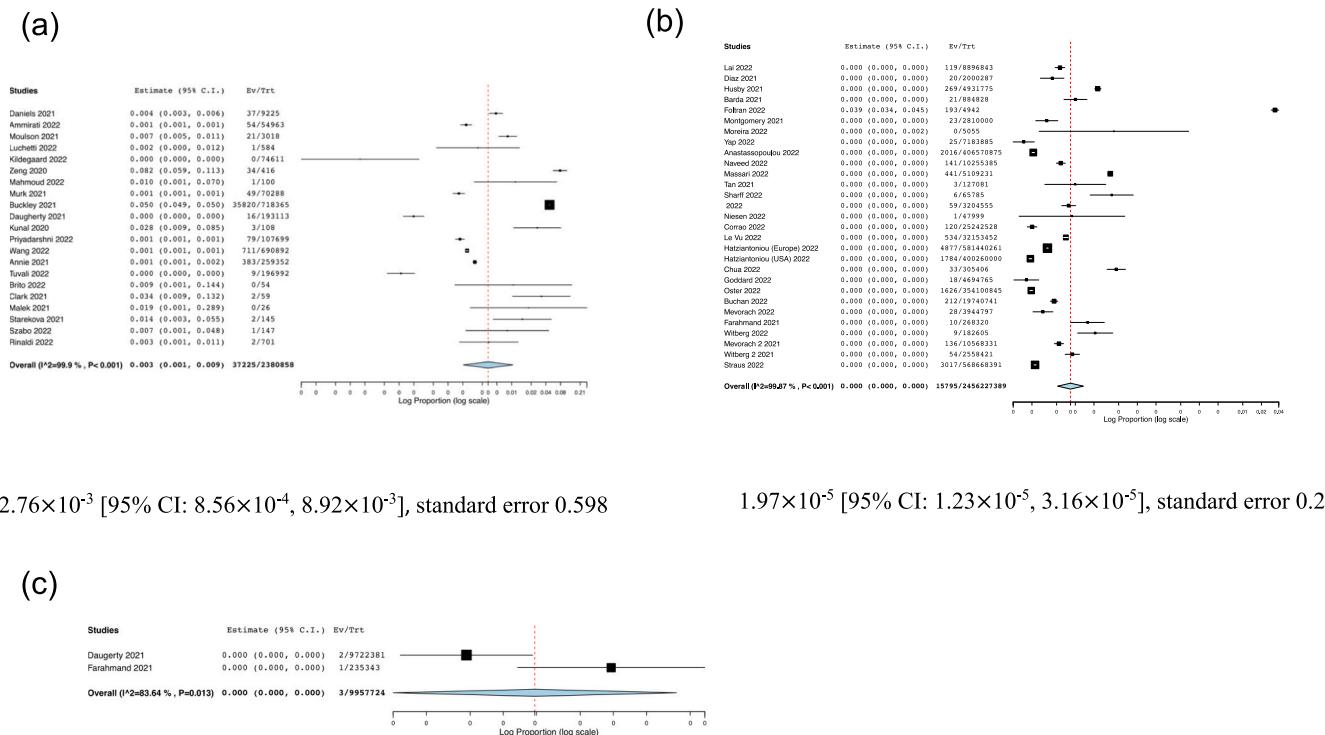
3.2. Demographics

The forest plots are shown in Supplemental Fig. 3. Regarding the mean age of patients with myocarditis, the SARS-CoV-2 infection group was 51.8 years (95% CI: [47.6–56.5], $I^2 = 95.3\%$), the COVID-19 mRNA vaccination group was 24.8 years (95% CI: [19.1–30.6], $I^2 = 99.9\%$), and the control group was 36.4 years (95% CI [23.7–49.3], $I^2 = 99.9\%$).

Supplemental Fig. 4 shows the proportions of male patients. All groups were likely to have more male population, especially in the COVID-19 mRNA vaccination group 8285/11,839 [84.1%, 95% CI: 78.9–89.4%, $I^2 = 97.3\%$].

3.3. Mortality

The highest myocarditis mortality was noted in the SARS-CoV-2

**Fig. 2.** One Group Meta-Analysis of Incidence of Myocarditis.

infection group, which was 2975/43,933 patients (12.1%, 95% CI: [4.9–26.7%], $I^2 = 99.6\%$). COVID-19 mRNA vaccination group 612/18,694 (2.0%, 95% CI: [1.3–2.7%], $I^2 = 94.5\%$) had the lowest mortality, followed by the control group 3071/90,035 (6.5%, 95% CI: [4.5–9.5%], $I^2 = 98.2\%$) (Figs. 3, 4).

3.4. Treatment/management

IVIG was most commonly used in pre-COVID myocarditis patients with 44.1% (256/564 patients, [95% CI: 26.3–63.6%], $I^2 = 93.8\%$) and the least used in the COVID-19 mRNA vaccine-associated myocarditis patients with 125/937 patients (12.5%, 95% CI: [7.3–17.6%], $I^2 = 57.1\%$) (Supplemental Fig. 5). Glucocorticoid was most used in patients with myocarditis in the SARS-CoV-2 infection group with 257/459 (55.4%, 95% CI: [50.1–60%], $I^2 = 43\%$) and the least used in the COVID-19 mRNA vaccination group with 11.4% (126/1517, 95% CI: [6.9–18.1%], $I^2 = 63.3\%$) (Supplemental Fig. 6).

Regarding MCS and cardiogenic shock with vasopressor requirement for myocarditis patients, these were most frequently used in the control group and least in the COVID-19 mRNA vaccination group (Supplemental Figs. 7 and 8).

4. Discussion

We summarized the incidence of myocarditis and assessed the baseline characteristics and outcomes between the SARS-CoV-2 infection, COVID-19 mRNA vaccination, and the control group. By investigating the proportion of myocarditis, we could assume that the SARS-CoV-2 infection group is associated with a higher risk compared to the COVID-19 mRNA vaccination group, and was even higher than the control group. COVID-19 mRNA vaccine-associated myocarditis was observed predominantly in young patients in their twenties with overall

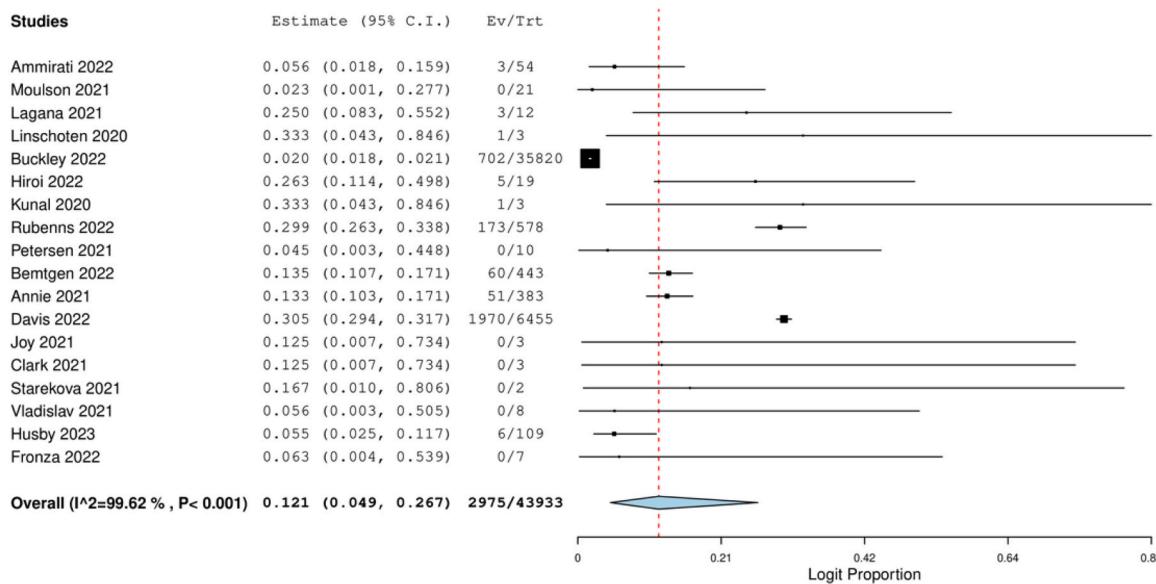
low mortality, lower use of IVIG or glucocorticoids, lower needs for MCS, and lower incidence of cardiogenic shock.

Our study showed a low incidence of COVID-19 mRNA vaccine-related myocarditis. Although we did not measure any risk ratio, the incidence rate was higher in the COVID-19 infection group compared to the COVID-19 mRNA vaccine group, which is consistent with prior meta-analysis [17]. It is conceivable that the benefit of vaccination outweighs the risks of myocarditis, supporting the current CDC advisory [15]. Another interesting finding of our study was that there was a higher proportion of patients with COVID-19 mRNA vaccination who developed myocarditis compared to the pre-pandemic population. Previously, one study observed this association [21], but to our knowledge, no further studies have investigated this topic. Although there may be more patients with myocarditis post-vaccination, there is still a benefit to being vaccinated for COVID-19 considering the worse outcome of myocarditis in non-vaccinated patients.

We also demonstrated relatively better mortality, cardiogenic shock, and MCS outcomes in the COVID-19 mRNA vaccination group, and the net benefit outweighs the risk as the adverse outcomes of myocarditis would have a benign course. The worse outcomes in SARS-CoV-2 infection-associated myocarditis could be attributed to the other hallmark findings such as pneumonia, but there has been a study that showed no difference in terms of MCS requirement and mortality between SARS-CoV-2 infected patients with and without pneumonia [22]. Thus, we could assume that there could be another underlying mechanism causing worse cardiac-related outcomes other than inflammation secondary to pneumonia in SARS-CoV-2 infection.

SARS-CoV-2 infection-associated myocarditis group also had worse outcomes than the control group, which consisted mostly of acute viral myocarditis patients. The difference in clinical outcomes may be related to different baseline characteristics of patients who had SARS-CoV-2 infection compared to those with viral myocarditis prior to the

(a)



(b)

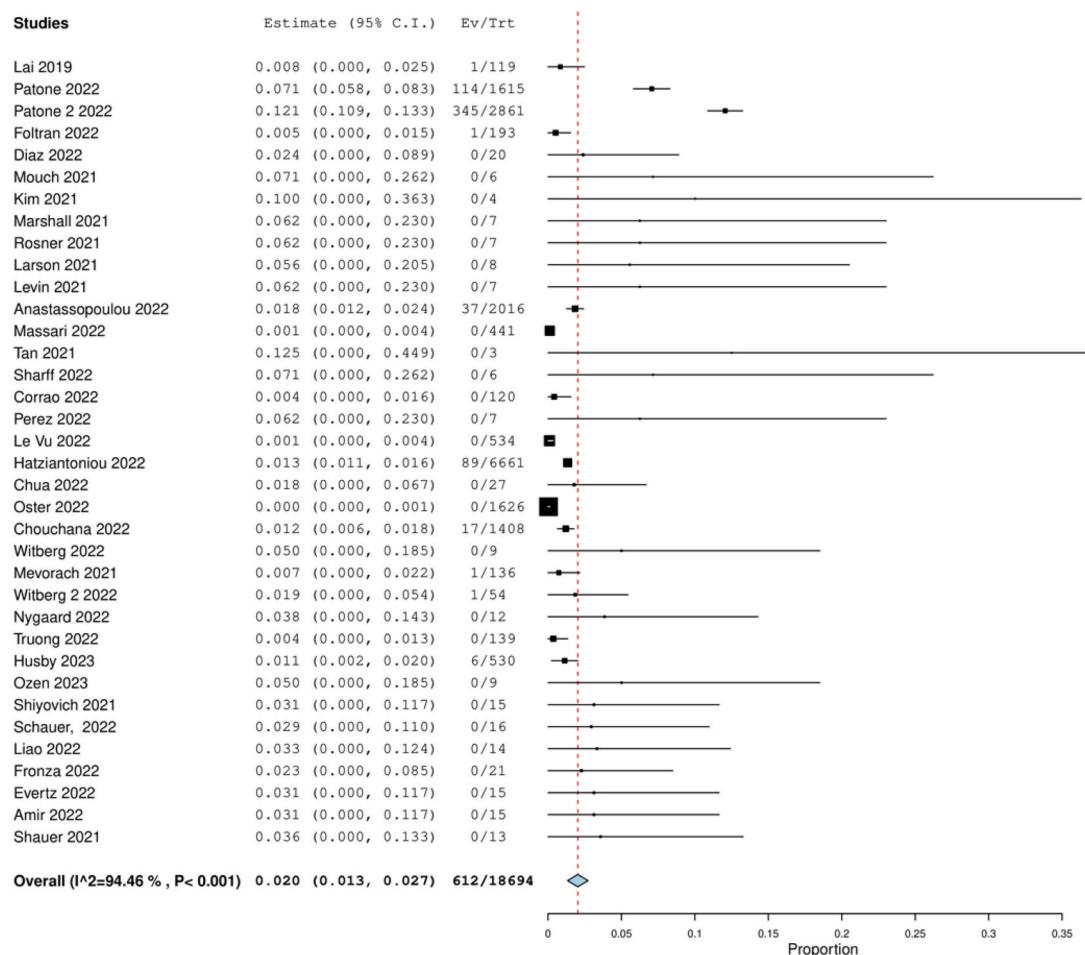


Fig. 3. One Group Meta-Analysis of Mortality of Myocarditis: (a) SARS-CoV-2 infection-associated myocarditis, (b) COVID-19 mRNA vaccination-associated myocarditis, (c) Control myocarditis

(C)

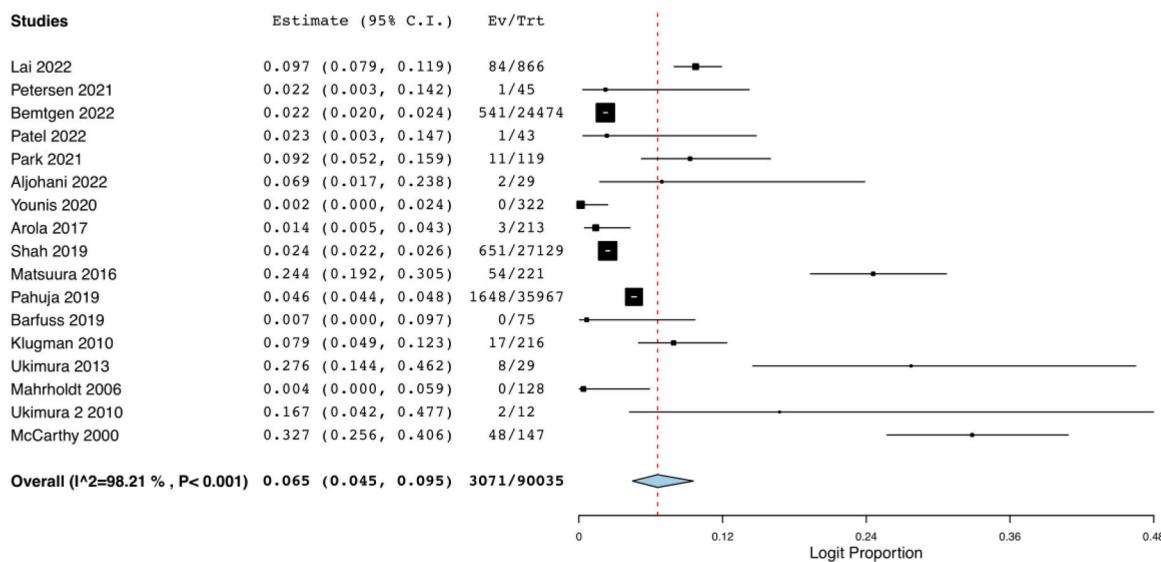


Fig. 3. (continued).

pandemic [23]. The age of SARS-CoV-2 infection related myocarditis patients was older in our study, and the underlying cardiovascular risk factors of patients included in each group were different, thus could possibly influence the outcome.

There are several hypothesized mechanisms of COVID-19 mRNA vaccine-associated myocarditis explained by a hyperimmune or inflammatory response. If this hypothesis is true, the lower mortality of COVID-19 mRNA vaccine-associated myocarditis compared to SARS-CoV-2 infection-related myocarditis or viral myocarditis can be explained by its shorter exposure to stimuli [24]. However, the symptoms are rather localized to be a hypersensitivity reaction, and the observed gender difference in the incidence is incoherent with this hypothesis [3].

SARS-CoV-2 infection-related myocarditis is thought to be caused by immune or inflammatory responses, direct viral invasion, microvascular angiopathy, demand ischemia, or hypoxia. Although COVID-19 mRNA has been detected in the myocardium in 25–50% of the COVID-19 autopsy cases, the virus has also been detected in the subendothelium. Pathologic findings have not shown the commonly found lymphocyte infiltrating, necrosis pattern that is seen in viral myocarditis, but rather a macrophage infiltration pattern [25]. Thus, due to the lack of a clear explanation of all the above hypotheses, the exact mechanism is yet to be established.

The strength of our study is that we were able to summarize results from prior studies or case series which had multiple patients enrolled. Most of the previous meta-analysis literature on SARS-CoV-2 infection or COVID-19 mRNA vaccine-associated myocarditis included individual case reports for analysis. Our study enabled a generalized overview due to a larger sample. Another prominent feature of our study is that we performed a meta-analysis of the control group. To our knowledge, most of the previous systematic reviews did not compare outcomes with the background population before the COVID-19 pandemic. The comparison with control groups enables us to understand the risk of SARS-CoV-2 infection-related myocarditis and its vaccine.

4.1. Limitations

Our study has several limitations. First, this study was not a direct comparison between each group. Thus, we could not assess the

statistical significance between frequency or mean values. Second, the diagnostic criteria for myocarditis differed between each study, although we specified the definition in each study. Some studies did not clarify the clinical diagnostic criteria and included myocarditis cases solely based on the international classification of disease codes on chart review. Further studies with standardized diagnostic criteria are required for further investigation. Third, although numerous studies were included, only a few were assessed for each outcome, and there was significant heterogeneity between the studies. In terms of the included studies, only a few were eligible for assessment for the incidence outcome since many of the sample groups were hospitalized patients. Hence, the results were based on a smaller sample size than the included studies altogether and have a risk of overgeneralization. The I^2 was high in each outcome, thus we must be cautious when applying the integrated result of each study to a generalized population. Fourth, we could not exclude the influence of baseline condition or age in terms of incidence or outcomes in each group. Patients who have viral or SARS-CoV-2 infection could have a worse underlying health condition, and we did not take that under consideration. Additionally, we were unable to assess the information bias in identifying myocarditis pre- and post-pandemic, thus the baseline characteristics in each period may differ and cause a difference in detection as well as outcomes of myocarditis. During the pandemic, the entire public became more aware of testing and being vaccinated for COVID-19, which could highly likely influence our outcomes. Fifth, in the COVID-19 mRNA vaccine group analysis, we attempted to stratify proportions of events by age groups, vaccine type, and vaccine doses. We were also unable to clarify if any of the vaccinated population had SARS-CoV-2 infection prior to being immunized, and thus could lead to a confounding bias. Furthermore, given the lack of an actual control group without influence of any infectious etiologies of myocarditis, we could not conclude that there is a causal link between vaccination and myocarditis [26]. Finally, we could not assess the long-term outcomes of myocarditis. Each study reported short-term outcomes, and the evaluation of long-term cardiac complications or longer dose intervals has not been evaluated. This could be partially due to the acute disease course of myocarditis, which makes the clinical impact of long-term outcomes less significant. We were unable to summarize the person-year incidence as well, thus we were unable to provide incidence and outcomes in a standardized timeframe.

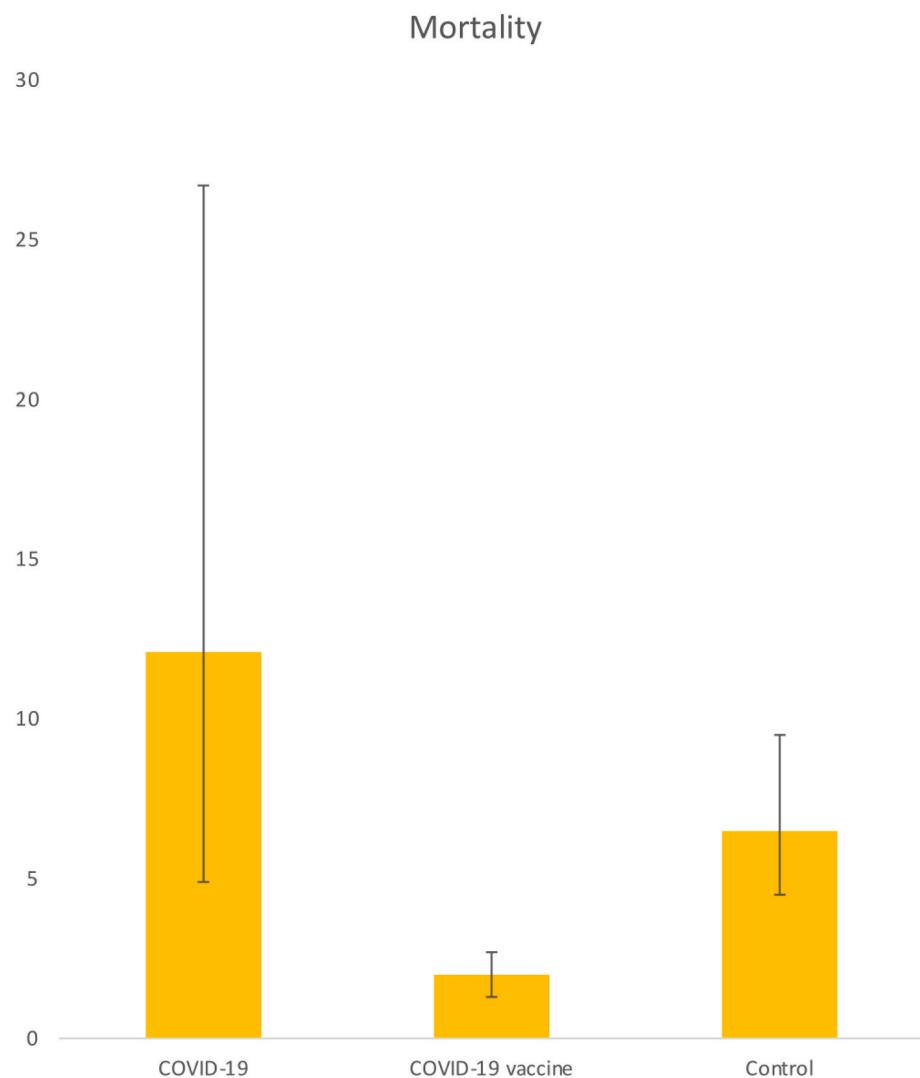


Fig. 4. Mortality of Myocarditis with 95% confidence interval: (a) SARS-CoV-2 infection-associated myocarditis, (b) COVID-19 mRNA vaccination-associated myocarditis, (c) Control myocarditis.

5. Conclusion

Our systematic review and meta-analysis showed favorable outcomes of myocarditis in patients with COVID-19 mRNA vaccination compared to SARS-CoV-2 infection-related myocarditis and myocarditis pre-pandemic, despite a higher incidence of myocarditis than pre-COVID controls. Further studies with standardized myocarditis diagnostic criteria investigating the long-term consequences and the longitudinal effects of additional booster vaccination doses are necessary.

Declaration of Competing Interest

None.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2023.131401>.

References

- [1] J. Liu, A. Deswal, U. Khalid, COVID-19 myocarditis and long-term heart failure sequelae, *Curr. Opin. Cardiol.* 36 (2) (2021 Mar 1) 234–240.
- [2] T.K. Boehmer, L. Kompaniyets, A.M. Laverty, J. Hsu, J.Y. Ko, H. Yusuf, et al., Association between COVID-19 and myocarditis using hospital-based administrative data - United States, march 2020-January 2021, *MMWR Morb. Mortal. Wkly Rep.* 70 (35) (2021 Sep 3) 1228–1232.
- [3] J. Pillay, L. Gaudet, A. Wingert, L. Bialy, A.S. Mackie, D.I. Paterson, et al., Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review, *BMJ.* 378 (2022 Jul 13), e069445.
- [4] A. Rout, S. Suri, M. Vorla, D.K. Kalra, Myocarditis associated with COVID-19 and its vaccines - a systematic review, *Prog. Cardiovasc. Dis.* 74 (2022 Oct 22) 111–121.
- [5] European Medicines Agency, Summary of Product Characteristics, 2023 Aug 10. Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf.
- [6] European Medicines Agency, Summary of Product Information, 2023 Aug 24. Available from: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf.
- [7] B. Knudsen, V. Prasad, COVID-19 vaccine induced myocarditis in young males: a systematic review, *Eur. J. Clin. Investigig.* 53 (4) (2023 Apr), e13947.
- [8] G. Corrao, M. Franchi, D. Cereda, F. Bortolan, O. Leon, E. Vignati, et al., Increased risk of myocarditis and pericarditis and reduced likelihood of severe clinical outcomes associated with COVID-19 vaccination: a cohort study in Lombardy, Italy, *BMC Infect. Dis.* 22 (1) (2022 Nov 12) 844.

- [9] M. Patone, X.W. Mei, L. Handunnetthi, S. Dixon, F. Zaccardi, M. Shankar-Hari, et al., Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex, *Circulation*. 146 (10) (2022 Sep 6) 743–754.
- [10] H.M. Salah, J.L. Mehta, COVID-19 vaccine and myocarditis, *Am. J. Cardiol.* 157 (2021 Oct 15) 146–148.
- [11] A. Matta, R. Kunadharaju, M. Osman, C. Jesme, Z. McMILLER, E.M. Johnson, et al., Clinical presentation and outcomes of myocarditis post mRNA vaccination: a meta-analysis and systematic review, *Cureus*. 13 (11) (2021 Nov), e19240.
- [12] A. Cordero, D. Cazorla, D. Escribano, M.A. Quintanilla, J.M. López-Ayala, P. P. Berbel, et al., Myocarditis after RNA-based vaccines for coronavirus, *Int. J. Cardiol.* 353 (2022 Apr 15) 131–134.
- [13] I. Bellos, V. Karageorgiou, D. Viskin, Myocarditis following mRNA Covid-19 vaccination: a pooled analysis, *Vaccine*. 40 (12) (2022 Mar 15) 1768–1774.
- [14] J. Yasuhara, K. Masuda, T. Aikawa, T. Shirasu, H. Takagi, S. Lee, et al., Myopericarditis after COVID-19 mRNA vaccination among adolescents and young adults: a systematic review and meta-analysis, *JAMA Pediatr.* [Internet]. (2022 Dec 5), <https://doi.org/10.1001/jamapediatrics.2022.4768>.
- [15] J.W. Gargano, M. Wallace, S.C. Hadler, G. Langley, J.R. Su, M.E. Oster, et al., Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices - United States, June 2021, *MMWR Morb. Mortal. Wkly Rep.* 70 (27) (2021 Jul 9) 977–982.
- [16] U.S. Food and Drug Administration, Coronavirus (COVID-19) Update: FDA Takes Key Action by Approving Second COVID-19 Vaccine, 2022 Jan 31. Available from: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine>.
- [17] N. Voleti, S.P. Reddy, P. Ssentongo, Myocarditis in SARS-CoV-2 infection vs. COVID-19 vaccination: A systematic review and meta-analysis, *Front. Cardiovasc. Med.* 9 (2022 Aug 29) 951314.
- [18] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, *BMJ*. 372 (2021 Mar 29) n71.
- [19] J.A. Sterne, M.A. Hernán, B.C. Reeves, J. Savović, N.D. Berkman, M. Viswanathan, et al., ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions, *BMJ*. 355 (2016 Oct 12) i4919.
- [20] J.P.T. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials [internet], *BMJ*. Vol. 343 (2011), <https://doi.org/10.1136/bmj.d5928> p.
- [21] R. Farahmand, C.A. Trottier, J.P. Kannam, K.K.L. Ho, Incidence of myopericarditis and myocardial injury in coronavirus disease 2019 vaccinated subjects, *Am. J. Cardiol.* 164 (2022 Feb 1) 123–130.
- [22] E. Ammirati, L. Lupi, M. Palazzini, N.S. Hendren, J.L. Grodin, C.V. Cannistraci, et al., Prevalence, characteristics, and outcomes of COVID-19-associated acute myocarditis, *Circulation*. 145 (15) (2022 Apr 12) 1123–1139.
- [23] X. Bemtgen, K. Kaier, J. Rilinger, F. Rottmann, A. Supady, Mühlen C. von Zur, et al., Myocarditis mortality with and without COVID-19: insights from a national registry, *Clin. Res. Cardiol.* 24 (2022 Dec) 1–7.
- [24] F.T.T. Lai, E.W.W. Chan, L. Huang, C.L. Cheung, C.S.L. Chui, X. Li, et al., Prognosis of myocarditis developing after mRNA COVID-19 vaccination compared with viral myocarditis, *J. Am. Coll. Cardiol.* 80 (24) (2022 Dec 13) 2255–2265.
- [25] R. Kawakami, A. Sakamoto, K. Kawai, A. Gianatti, D. Pellegrini, A. Nasr, et al., Pathological evidence for SARS-CoV-2 as a cause of myocarditis: JACC review topic of the week, *J. Am. Coll. Cardiol.* 77 (3) (2021 Jan 26) 314–325.
- [26] B. Heidecker, N. Dagan, R. Balicer, U. Eriksson, G. Rosano, A. Coats, et al., Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC Working Group on Myocardial and Pericardial Diseases, *Eur. J. Heart Fail.* 24 (11) (2022 Nov) 2000–2018.