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Myopericarditis After COVID-19 mRNA Vaccination Among Adolescents and Young Adults
A Systematic Review and Meta-analysis

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IMPORTANCE Published data on COVID-19 mRNA vaccine–associated myopericarditis in adolescents and young adults have been derived from small case series, national population-based studies, or passive reporting systems. Pooled evidence from a larger, international cohort is scarce.

OBJECTIVE To investigate the clinical features and early outcomes associated with myopericarditis after COVID-19 mRNA vaccination in a heterogeneous population of adolescents and young adults.

DATA SOURCES PubMed and EMBASE were searched through August 2022. Language restrictions were not applied.

STUDY SELECTION Observational studies and case series describing COVID-19 vaccine–associated myopericarditis in adolescents and young adults aged 12 to 20 years and reporting clinical characteristics and early outcomes were included.

DATA EXTRACTION AND SYNTHESIS Two independent investigators extracted relevant data from each study. One-group meta-analysis in a random effects model was performed. The Preferred Reporting Items for Systematic Reviews and Meta-analysis and Meta-analysis of Observational Studies in Epidemiology reporting guidelines were followed.

MAIN OUTCOMES AND MEASURES The primary outcomes were clinical features and early outcomes for COVID-19 mRNA vaccine–associated myopericarditis, including incident rate, cardiac findings, hospitalization, intensive care unit (ICU) admission, and in-hospital mortality.

RESULTS A total of 23 observational studies were identified, including 854 individuals (mean age, 15.9 [95% CI, 15.5-16.2] years) with COVID-19 vaccine–associated myopericarditis. Male sex was predominant, at 90.3% (95% CI, 87.3%-93.2%) of individuals. The incident rate was higher after the second dose than the first dose, with 74.4% (95% CI, 58.2%-90.5%) of events occurring after the second dose. Most patients (84.4% [95% CI, 80.5%-88.3%] of patients) had preserved left ventricular (LV) function. Of the 15.6% (95% CI, 11.7%-19.5%) of patients with LV systolic dysfunction (LV ejection fraction [LVEF] <55%), most (14.1% [95% CI, 10.2%-18.1%]) were mild (ie, LVEF 45%-54%), and only 1.3% (95% CI, 0%-2.6%) of patients had severe LV systolic dysfunction (ie, LVEF<35%). Interestingly, cardiac magnetic resonance imaging revealed late gadolinium enhancement in 87.2% (95% CI, 79.8%-94.7%) of patients. Although 92.6% (95% CI, 87.8%-97.3%) of patients were hospitalized and 23.2% (95% CI, 11.7%-34.7%) of patients required ICU admission, inotropes were used in only 1.3% (95% CI, 0%-2.7%) of patients, no patients died or required mechanical support, and the hospital length of stay was 2.8 (95% CI, 2.1-3.5) days.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found low incidence rate and largely favorable early outcomes of COVID-19 mRNA vaccine–associated myopericarditis in adolescents and young adults from a wide range of populations. These findings are reassuring but continued follow-up is warranted.

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Supplemental content

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The COVID-19 global pandemic began in December 2019.[1] The introduction of the messenger RNA (mRNA) vaccine against SARS-CoV-2 has resulted in a significant decline in COVID-19–related morbidity and mortality all over the world.[2-4] COVID-19 mRNA vaccines are the current standard approach to contain the pandemic and the Emergency Use Authorizations for these vaccines were recently extended to children aged 6 months and older in the US. Since the emergency use was authorized, the association of the mRNA-based COVID-19 vaccine with myopericarditis, which is a rare but serious adverse event, has been reported.[5,6] Cases of myopericarditis following COVID-19 mRNA vaccination have been reported worldwide, especially in adolescents and young adults. In addition, in June 2021, the Centers for Disease Control and Prevention (CDC) observed a rate of postvaccine myopericarditis that was higher in young males after the second mRNA vaccine doses.[7] Previous studies reported largely favorable outcomes in adults with myocarditis following COVID-19 mRNA vaccination, demonstrating resolution of clinical symptoms, preservation of cardiac function, and no complications.[8-11] However, data on the clinical features and outcomes of myopericarditis after COVID-19 vaccination in adolescents and young adults are scarce compared with adults and often consist of small case series. Most large-scale studies on COVID-19 vaccine–associated myopericarditis among adolescents and young adults are derived from national population-based studies that contain homogeneous populations or from surveillance networks that rely on passive reporting. In this study, we conducted a systematic review and meta-analysis to investigate the clinical spectrum and outcomes of COVID-19 vaccine–associated myopericarditis in adolescents and young adults from an international population.

Key Points

Question What are the frequency, clinical features, and early outcomes associated with myopericarditis after COVID-19 mRNA vaccination in adolescents and young adults?

Findings In this systematic review and meta-analysis of 23 studies, including 854 patients aged 12 to 20 years with vaccine-associated myopericarditis, the incidence of myopericarditis was higher in males after the second dose. Although 15.6% of patients had left ventricular (LV) systolic dysfunction, only 1.3% had severe LV systolic dysfunction (ejection fraction <35%); late gadolinium enhancement was found in 87.2% and 23.2% required intensive care unit admission; however, no in-hospital mortality was observed.

Meaning These findings suggest largely favorable outcomes of COVID-19 vaccine–associated myopericarditis in adolescents and young adults.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline[12] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.[13] The protocol was registered in PROSPERO (CRD42022335550).

Information Sources and Search Strategy

All observational studies and case series including adolescents and young adults with myopericarditis after COVID-19 vaccination were identified using a 2-level strategy. First, databases, including PubMed and EMBASE, were searched through August 25, 2022. Search terms included *COVID-19* OR *SARS-CoV-2*, *vaccination* OR *vaccine*, *myocarditis* OR *myopericarditis*, and *adolescent* OR *children* OR *child* OR *pediatric* OR *young adult* OR *young adults*. The search strategies specific to each database are shown in eTable 1 and eTable 2 in the Supplement. Second, we performed an additional manual search of secondary sources, such as references of initially identified studies, reviews, and commentaries, to collect relevant articles comprehensively. No restrictions on language, publication date, or publication status were applied.

Eligibility Criteria

Included studies met the following criteria: (1) observational studies or case series published in a peer-reviewed journal, (2) the study population was adolescents and young adults (aged 12-20 years) with myopericarditis after COVID-19 vaccination, and (3) the study reported the clinical characteristics and outcomes of myopericarditis following COVID-19 vaccination. Case reports that only included 1 patient with vaccine-associated myopericarditis were excluded.

Data Extraction

Two independent authors (J.Y. and K.M.) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria and assessed the eligibility for each study. After screening the articles based on title and abstract, the full texts of potentially eligible studies were retrieved for further review.

Risk of Bias Assessment

The risk of bias in the observational studies was evaluated using the assessment of risk of bias in prevalence studies.[14] Furthermore, the risk of bias for prevalence studies as well as case series was assessed using the Joanna Briggs Institute guidance for the appropriate checklist.[15] The overall quality of each study was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations approach.[16]

Data Items

The following information was extracted: author, year of publication, country of the study, sample size, age, sex, and race and ethnicity. We assessed race and ethnicity because the racial and ethnic differences in the frequency and outcomes of myopericarditis after COVID-19 mRNA vaccination are unclear. Race and ethnicity were categorized as African American, American Indian or Alaskan Native, Asian, Hispanic, White, and other, which included individuals reported as other race and ethnicity in the reviewed studies. Regarding the COVID-19 vaccine, the type of vaccine, dose of vaccine, and symptoms were collected, including

BNT162b2 (Pfizer-BioNTech) vaccine and mRNA-1273 (Moderna). Furthermore, the symptoms, outcomes (hospitalization, intensive care unit [ICU] admission, and death), treatment, laboratory values, electrocardiogram, echocardiogram, and cardiac magnetic resonance (CMR) findings of vaccine-associated myopericarditis were extracted. In addition, the incidence rate of vaccine-associated myopericarditis was collected in each study. The primary outcomes of this study were the clinical features and early outcomes of myopericarditis in adolescents and young adults following COVID-19 vaccination, including incidence, cardiac findings, in-hospital mortality, hospitalization, ICU admission, and treatments. The definition of myopericarditis followed each study. Left ventricular (LV) systolic dysfunction was defined as LV ejection fraction (LVEF) less than 55%; mild LV systolic function, as LVEF 45% to 54%; moderate, as LVEF 35% to 44%; and severe, as LVEF less than 35%.

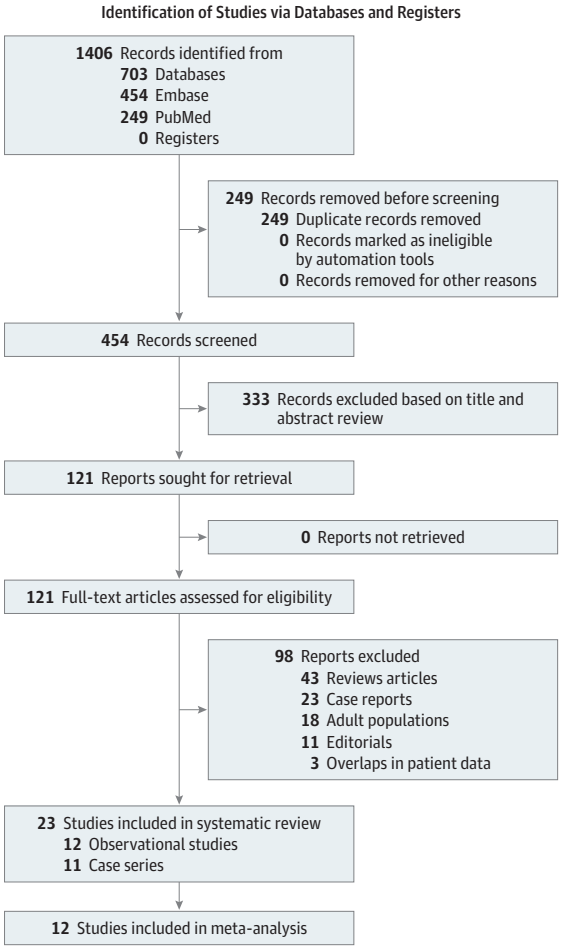
Statistical Analysis

We performed 1-group meta-analysis in a random effects model using the DerSimonian-Laird method for continuous values and Wald method for discrete values with the OpenMetaAnalyst version 12.11.14 (Brown University), in which pooled estimates of baseline characteristics were calculated as the inverse variance-weighted mean with 95% CIs. Case series were excluded from the meta-analysis because case series are prone to selection bias, limiting generalizability to larger patient populations, and the data in case series can be exceptionally divergent. Measuring the degree of heterogeneity attributable to actual between-study differences was used to quantify heterogeneity, with I^2 greater than 50% indicating substantial heterogeneity. Publication bias was assessed by Egger test and funnel plot of the clinical characteristics and early outcomes of COVID-19 vaccine-associated myopericarditis in each study.[17] The Duval and Tweedy trim-and-fill method was also performed.[18] All analyses were conducted using Comprehensive Meta-Analysis version 2 (Biostat). There was no transformation that was conducted for meta-analysis of proportions. We performed subgroup analyses specifically including the studies with only patients with myocarditis after COVID-19 mRNA vaccination. P values were 2-sided, and statistical significance was set at $P < .05$. Statistical analyses were conducted on September 10, 2022.

Results

We identified 454 articles by the initial database search and subsequent manual search. After removing 333 records based on the title and abstract, we retrieved 121 articles for full-text review. Of those, 98 articles were excluded based on the article type (clinical guidelines, consensus documents and conference proceedings, reviews), conference abstracts, population (adult patients with COVID-19, individuals without myopericarditis after the vaccines), and irrelevant topic. Furthermore, 3 articles were excluded because they were likely to have overlapping patient data with other studies based on the author list, institution, country, and study period. A total of 23 studies[19-41] met the inclusion criteria and were analyzed for the systemic review and meta-analysis (**Figure 1**).

Figure 1. Flowchart of Study Selection



Of 454 identified articles, 23 studies[19-41] reporting clinical characteristics and outcomes of myopericarditis following COVID-19 vaccination in adolescents and young adults were included for a systematic review and meta-analysis.

There were 12 retrospective or prospective cohort studies[19-30] and 11 case series.[31-41] Across all 23 studies, we included a total of 854 patients with myopericarditis following COVID-19 vaccination. There were 6 observational studies from the US (494 patients),[20,22,24,27,28,30] 2 from Israel (43 patients),[21,25] and 1 each from Hong Kong (15 patients),[19] South Korea (40 patients),[29] Denmark (15 patients),[26] and Europe (193 patients).[23] There were 5 case series from the US (21 patients),[33-37] 3 from Poland (10 patients)[31,38,39] and 1 each from Italy (5 patients),[32] Germany (2 patients),[41] and Iraq (3 patients).[40]

Baseline Characteristics

The baseline characteristics are summarized in **Table 1**, with characteristics in the observations studies provided eTable 3 in the Supplement , and characteristics in the case series provided in eTable 4 in the Supplement. The pooled estimates from

Table 1. Characteristics of the Studies Included in the Meta-analysis

Source	Country	Cohort size, No.	Age, mean (SD), y	Patients, No. (%)						Onset after vaccination, mean (SD), d	LV systolic dysfunction, No. (%)[a]				Outcomes, No. (%)					
				Female	Male	BNT162b2	mRNA-1273	First dose	Second dose		Mild	Moderate	Severe	LGE	Hospitalization	Hospital LOS, mean (SD), d	ICU admission	Inotropes	ECMO	Death
Li et al,[19] 2022	Hong Kong	43	14.9 (1.5)	NA	NA	43 (100)	0	7 (16.3)	36 (83.7)	NA	NA	NA	NA	NA	43 (100)	NA	NA	NA	NA	NA
Krug et al,[20] 2022	US	253	NA	23 (9.1)	230 (90.9)	253 (100)	0	129 (51.0)	124 (49.0)	NA	NA	NA	NA	NA	220 (87)	NA	NA	NA	NA	NA
Mevorach et al,[21] 2022	Israel	13	NA	1 (0.8)	12 (92.3)	13 (100)	0	1 (7.7)	12 (92.3)	NA	NA	NA	NA	NA	13 (100)	3.1	NA	0	NA	NA
Truong et al,[22] 2022	US	139	15.8 (14.5-17.0)[b]	13 (9.4)	126 (90.6)	131 (94.2)	5 (3.6)	12 (8.6)	128 (91.4)	2 (1-3)[b]	22 (16.0)	2 (1.4)	2 (1.4)	74 (76.3)	NA	2 (2-3)[b]	26 (18.7)	2 (1.4)	0	0
Foltran et al,[23] 2022	148 countries	193	15.9 (1.3)	21 (10.9)	172 (89.1)	185 (95.9)	8 (4.1)	31 (16.1)	58 (30.1)	3	NA	NA	NA	NA	172 (89.1)	NA	NA	NA	NA	NA
Jain et al,[24] 2021	US	63	15.6 (1.8)	5 (7.9)	58 (92.1)	59 (93.7)	4 (6.3)	1 (1.6)	62 (98.4)	2.1 (1.3)	9 (14.0)	0	0	49 (88.0)	NA	3 (1.4)	27 (42.9)	0	0	0
Amir et al,[25] 2022	Israel	15	17 (1.0)	0	15 (100)	15 (100)	0	1 (6.7)	14 (92.3)	4.4 (6.7)	2 (13.3)	0	0	14 (93.0)	13 (86.7)	4.8 (1.6)	7 (46.7)	0	NA	NA
Nygaard et al,[26] 2022	Denmark	15	16 (1.2)	2 (13.3)	13 (86.7)	15 (100)	0	8 (53.3)	7 (46.7)	NA	2 (13.0)	0	1 (6.7)	NA	15 (100)	3.7 (2.1)	1 (6.7)	NA	NA	NA
Chelala et al,[27] 2022	US	5	17.2 (1.0)	0	5 (100)	4 (80.0)	1 (20.0)	0	5 (100)	3.6 (0.5)	1 (20.0)	0	0	5 (100)	NA	4.4 (2.3)	NA	NA	NA	0
Das et al,[28] 2021	US	25	15.3 (1.4)	3 (12.0)	22 (88.0)	25 (100)	0	3 (12.0)	22 (88.0)	3.1 (3.6)	2 (8.0)	0	0	15 (93.8)	22 (88.0)	2.6 (1.2)	NA	NA	NA	0
Roh et al,[29] 2022	South Korea	40	16 (14.5-17)[b]	14 (35.0)	26 (65.0)	40 (100)	0	25 (62.5)	15 (37.5)	2 (1-5)[b]	6 (15.0)	0	0	NA	NA	1 (0-3)[b]	5 (12.5)	1 (2.5)	0	0
Patel et al,[30] 2022	US	9	15.5 (14.5-16.6)[b]	0	9 (100)	NA	NA	1 (11.1)	8 (88.9)	NA	NA	NA	NA	NA	9 (100)	2 (1-3)[b]	2 (22.2)	NA	0	0

Abbreviations: ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; ICU, intensive care unit; LGE, late gadolinium enhancement; LV, left ventricular; LOS, length of stay; NA, not available.

[a] LV systolic dysfunction was defined as LV ejection fraction (LVEF) less than 55%; mild LV systolic function, as LVEF 45% to 54%; moderate, as LVEF 35% to 44%; and severe, as LVEF less than 35%.

[b] Presented as median (IQR).

Table 2. Pooled Estimates of Characteristics and Outcomes of Myopericarditis After COVID-19 Vaccination in Adolescents and Young Adults

Characteristic	Pooled estimates, % (95% CI)	I^2, %	*P* value for heterogeneity
Age, y	15.9 (15.5-16.2)	83.6	<.001
Sex			
Female	9.7 (6.8-12.7)	33.6	.13
Male	90.3 (87.3-93.2)	33.6	.13
History of COVID-19	3.8 (1.1-6.4)	11.5	.34
Dose of vaccination			
First	20.7 (1.0-31.8)	95.7	<.001
Second	74.4 (58.2-90.5)	97.9	<.001
Type of vaccine			
BNT162b2 (Pfizer-BioNTech)	97.5 (95.7-99.2)	52.8	.02
mRNA-1273 (Moderna)	2.2 (0.6-3.7)	44.7	.06
Time from vaccination to symptom onset, mean (95% CI), d	2.6 (1.9-3.3)	89.0	<.001
Symptoms			
Chest pain	83.7 (72.7-94.6)	98.6	<.001
Fever	44.5 (16.9-72.0)	98.1	<.001
Headache	33.3 (8.6-58.0)	98.0	<.001
Dyspnea or respiratory distress	25.2 (17.2-33.1)	51.2	.07
Myalgia	17.8 (2.7-33.3)	90.9	<.001
Treatment			
NSAIDs	81.8 (75.3-88.3)	45.4	.09
Glucocorticoid	13.8 (6.7-20.9)	67.5	.005
IVIG	12.0 (3.8-20.2)	80.1	<.001
Colchicine	7.3 (4.1-10.4)	0	.62
Elevated troponin I	84.5 (75.1-94.5)	97.5	<.001
Electrocardiography findings			
ST-segment elevation or changes	53.0 (34.6-71.3)	91.5	<.001
T-wave changes	14.5 (5.1-24.0)	0	.80
Nonsustained VT	5.3 (2.5-8.1)	0	.75
Echocardiography findings			
LVEF, mean (95% CI), %	62.1 (59.1-65.1)	71.2	.03
LV systolic dysfunction[a]			
Any	15.6 (11.7-19.5)	0	.90
Mild	14.1 (10.2-18.1)	0	.94
Moderate	1.3 (0-2.6)	0	.98
Severe	1.3 (0-2.6)	0	.96
Pericardial effusion	5.1 (0.6-9.6)	45.2	.11
Cardiac magnetic resonance findings			
Presence of LGE	87.2 (79.8-94.7)	52.2	.08
Myocardial edema	58.0 (33.5-82.5)	92.3	<.001
Outcome			
Hospitalization	92.6 (87.8-97.3)	74.0	<.001
ICU admission	23.2 (11.7-34.7)	79.4	<.001
Inotropes	1.3 (0-2.7)	0	.93
Hospital length of stay, d	2.8 (2.1-3.5)	92.9	<.001

Abbreviations: ICU, intensive care unit; IVIG, intravenous immune globulin; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricle ejection fraction; NSAIDS, nonsteroidal anti-inflammatory drugs; VT, ventricular tachycardia.

[a] LV systolic dysfunction was defined as LVEF less than 55%; mild LV systolic function, as LVEF 45% to 54%; moderate, as LVEF 35% to 44%; and severe, as LVEF less than 35%.

1-group meta-analysis in a random-effects model are presented in **Table 2** and eFigure 1 in the Supplement. The pooled estimate of the mean age was 15.9 (95% CI, 15.5-16.2) years, and there was male preponderance, at 90.3% (95% CI, 87.3%-93.2%) of the population. The proportion of prior SARS-CoV-2 infection was 3.8% (95% CI, 1.1%-6.4%) of patients. There were no patients with prior history of myopericarditis or underlying cardiovascular disease, including cardiomyopathy. Notably, myopericarditis occurred more commonly after the second dose (74.4% [95% CI, 58.2%-90.5%] of patients) than after the first dose (20.7% [95% CI, 58.2%-90.5%] of patients). Among patients with vaccine-associated myopericarditis, 97.5% (95% CI, 95.7%-99.2%) received the BNT162b2 vaccine and 2.2% (95% CI, 0.6%-3.7%) received the mRNA-1273 vaccine. The incidence rate of myopericarditis was higher after the second dose (12.7-118.7 per million persons) than the

first dose (0.6-10.0 per million persons) (eTable 3 in the Supplement). The pooled estimate of the mean interval from vaccination to the onset of myopericarditis was 2.6 (95% CI, 1.9-3.3) days. The definition of myopericarditis in each study is summarized in eTable 5 in the Supplement. One study[22] used both the CDC criteria for myopericarditis and the Lake Louise CMR criteria for patients who had CMR data.[42,43] In 2 studies,[20,28] the CDC criteria were used. One study[19] used only *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and another[24] used only the Lake Louise criteria. In 3 studies,[25,29,30] vaccine-associated myocarditis was diagnosed clinically.

Clinical Features of Myopericarditis Following COVID-19 Vaccination

The most common presenting symptoms of myopericarditis were chest pain (83.7% [95% CI, 72.7%-94.6%] of patients), fever (44.5% [95% CI, 16.9%-72.0%] of patients), headache (33.3% [95% CI, 8.6%-58.0%] of patients) and dyspnea or respiratory distress (25.2% [95% CI, 17.2%-33.1%] of patients) (Table 2; eFigure 1 in the Supplement). The most common medication used for treatment was a nonsteroidal anti-inflammatory drug (81.8% [95% CI, 75.3%-88.3%] of patients), followed by glucocorticoid (13.8% [95% CI, 6.7%-20.9%] of patients) and intravenous immune globulin (12.0% [95% CI, 3.8%-20.2%] of patients). Colchicine was also used in 7.3% (95% CI, 4.1%-10.4%) of patients.

Troponin level was elevated in 84.5% (95% CI, 75.1%-94.5%) of patients (Table 2). Electrocardiography findings showed ST-segment elevation or depression in 53.0% (95% CI, 34.6%-71.3%) of patients, T-wave changes in 14.5% (95% CI, 5.1%-24.0%) of patients, and nonsustained ventricular tachycardia in 5.3% (95% CI, 2.5%-8.1%) of patients. As for echocardiography findings, mean LVEF was 62.1% (95% CI, 59.1%-65.1%), and 15.6% (95% CI, 11.7%-19.5%) of patients demonstrated LV systolic dysfunction (eFigure 1 in the Supplement). Notably, most patients with LV systolic dysfunction had mild dysfunction (14.1% [95% CI, 10.2%-18.1%] of patients), 1.3% (95% CI, 0%-2.6%) of patients had moderate dysfunction, and 1.3% (95% CI, 0%-2.6%) of patients had severe dysfunction (**Figure 2**). Pericardial effusion was seen in 5.1% (95% CI, 0.6%-9.6%) of patients. CMR was performed in 199 of 262 patients (80.7%) and the timing of CMR ranged between 3 to 28 days after the onset of myopericarditis. CMR revealed late gadolinium enhancement (LGE) in 87.2% (95% CI, 79.8%-94.7%) of patients (Figure 2). Myocardial edema, defined as abnormally high signal intensity on T2-weighted imaging or prolonged T2 relaxation time on T2 mapping, was seen in 58.0% (95% CI, 33.5%-82.5%) of patients (Table 2; eFigure 1 in the Supplement).

Early Outcomes

Overall, 92.6% (95% CI, 87.8%-97.3%) of patients were hospitalized and 23.2% (95% CI, 11.7%-34.7%) of patients required ICU admission, mainly for arrhythmia monitoring; however, inotropic support was used in only 1.3% (95% CI, 0%-2.7%) of patients (Table 2 and **Figure 3**; eFigure 1 in the Supplement). No patients received extracorporeal membrane oxygenation and no deaths were observed. In all the studies available, the pooled estimate of the hospital length of stay was 2.8 (95% CI, 2.1-3.5) days. Although the data are limited regarding LV systolic dysfunction at follow-up periods, some available cases showed improvement in LVEF from 45% at baseline to 50% to 54% at 3 months. The subgroup analyses including studies with only patients with myocarditis showed largely similar results (eTable 6 and eFigure 2 in the Supplement).

Bias Assessments

The risk of bias assessments for prevalence studies as well as case series are summarized in eTable 7, eTable 8, and eFigure 3 in the Supplement. The overall quality of each study is summarized in eTable 9 in the Supplement and the overall quality of evidence of most studies were graded low or moderate level of certainty.

Egger test revealed funnel plot asymmetry for hospitalization, which raised the possibility of publication bias (eTable 10 and eFigure 4 in the Supplement). However, the imputed 3 studies using the trim-and-fill method produced a symmetrical funnel plot (eFigure 5 in the Supplement), and the pooled analysis incorporating the 3 hypothetical studies did not substantively alter the results of the primary meta-analysis (eTable 11 in the Supplement).

Discussion

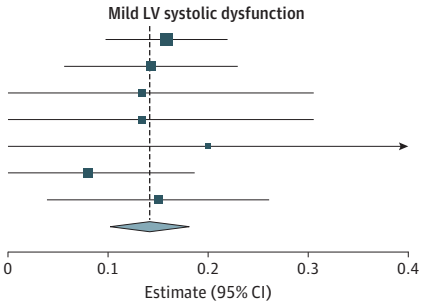
This systematic review and meta-analysis comprehensively summarized the available published literature and assessed the current situation regarding myopericarditis after COVID-19 vaccination in adolescents and young adults across a wide range of populations. There are 4 main findings of our study. First, COVID-19 vaccine–associated myopericarditis was predominantly observed in males after the second dose. Second, LV systolic dysfunction was identified in 15.6% of the patients; however, only 1.3% of patients had severe LV systolic dysfunction. Third, CMR showed LGE in 87.2% of patients. Fourth, although more than 90.0% of patients were hospitalized and 23.2% of patients were admitted to the ICU, inotropes were used in only 1.3% of patients, the duration of hospitalization was 2.8 days, and no patients died or required mechanical support during the hospitalization.

These findings are consistent with results from previous studies in adults, in which clinical course of COVID-19 vaccine-associated myopericarditis was typically mild, with complete resolution of symptoms and LV systolic dysfunction at presentation normalized within a few days.[44] Furthermore, recent systematic reviews have summarized the rate and clinical characteristics of myopericarditis after COVID-19 vaccination in children and adolescents (age <19 years).[45,46] They reported that echocardiographic findings were often normal, including pericardial effusion and borderline or mild depressed LV systolic function, and most patients recovered, with very few deaths reported. In contrast, compared with these reviews, the novelty of our study lies on providing the pooled estimates across the published observational studies with a

Figure 2. Forest Plots Showing the Prevalence of Echocardiogram and Cardiac Magnetic Resonance Findings

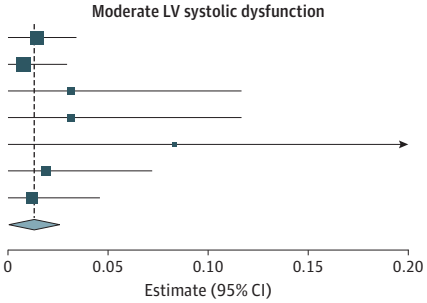
A Mild LV systolic dysfunction (LVEF 45-54%)

Studies	Events/total population, No.	Estimate (95% CI)
Truong et al,[22] 2022	22/139	0.158 (0.098-0.219)
Jain et al,[24] 2021	9/63	0.143 (0.056-0.229)
Amir et al,[25] 2022	2/15	0.133 (0-0.305)
Nygaard et al,[26] 2022	2/15	0.133 (0-0.305)
Chelala et al,[27] 2022	1/5	0.200 (0-0.551)
Das et al,[28] 2021	2/25	0.080 (0-0.186)
Roh et al,[29] 2022	6/40	0.150 (0.039-0.261)
Overall I^2 = 0% (P = .94)	44/302	0.141 (0.102-0.181)



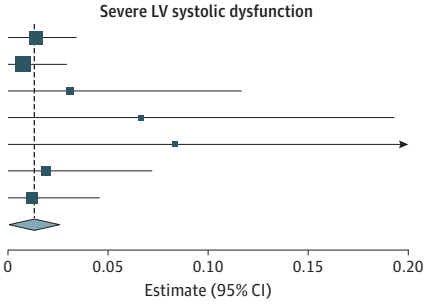
B Moderate LV systolic dysfunction (LVEF 35-44%)

Studies	Events/total population, No.	Estimate (95% CI)
Truong et al,[22] 2022	2/139	0.014 (0-0.034)
Jain et al,[24] 2021	0/63	0.008 (0-0.029)
Amir et al,[25] 2022	0/15	0.031 (0-0.117)
Nygaard et al,[26] 2022	0/15	0.031 (0-0.117)
Chelala et al,[27] 2022	0/5	0.083 (0-0.304)
Das et al,[28] 2021	0/25	0.019 (0-0.072)
Roh et al,[29] 2022	0/40	0.012 (0-0.046)
Overall I^2 = 0% (P = .98)	2/302	0.013 (0-0.026)



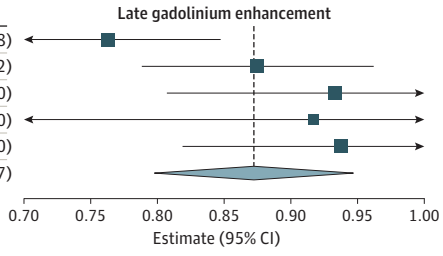
C Severe LV systolic dysfunction (LVEF<35%)

Studies	Events/total population, No.	Estimate (95% CI)
Truong et al,[22] 2022	2/139	0.014 (0-0.034)
Jain et al,[24] 2021	0/63	0.008 (0-0.029)
Amir et al,[25] 2022	0/15	0.031 (0-0.117)
Nygaard et al,[26] 2022	1/15	0.067 (0-0.193)
Chelala et al,[27] 2022	0/5	0.083 (0-0.304)
Das et al,[28] 2021	0/25	0.019 (0-0.072)
Roh et al,[29] 2022	0/40	0.012 (0-0.046)
Overall I^2 = 0% (P = .96)	3/302	0.013 (0-0.026)



D Late gadolinium enhancement

Studies	Events/total population, No.	Estimate (95% CI)
Truong et al,[22] 2022	74/97	0.763 (0.678-0.848)
Jain et al,[24] 2021	49/56	0.875 (0.788-0.962)
Amir et al,[25] 2022	14/15	0.933 (0.807-1.000)
Chelala et al,[27] 2022	5/5	0.917 (0.696-1.000)
Das et al,[28] 2021	15/16	0.938 (0.819-1.000)
Overall I^2 = 5216% (P = .87)	157/189	0.872 (0.798-0.947)



The pooled estimates of echocardiogram and CMR findings of myopericarditis after COVID-19 mRNA vaccination in adolescents and young adults were calculated using 1-group meta-analysis in random-effects model. LV indicates left ventricular; LVEF, left ventricular ejection fraction; diamond, total estimate with 95% CI.

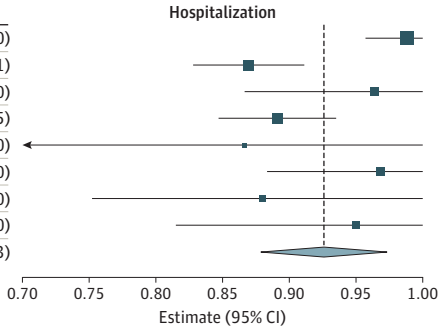
wide range of international population using 1-group meta-analysis. In particular, more detailed and specific data focusing on the clinical characteristics and outcomes, such as LV systolic dysfunction (mild, moderate, or severe), presence of LGE, myocardial edema, hospitalization, ICU admission, and hospital length of stay would be useful for a broad range of physicians as well as parents.

The overall incidence of COVID-19 mRNA vaccine-associated myocarditis was reported to be low, estimated as 0.3 to 5.0 cases per 100 000 vaccinated people in case series

Figure 3. Forest Plots Showing the Pooled Estimates of Early Outcomes

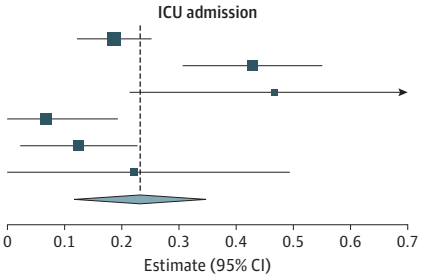
A Hospitalization

Studies	Events/total population, No.	Estimate (95% CI)
Li et al,[19] 2022	43/43	0.989 (0.957-1.000)
Krug et al,[20] 2022	220/253	0.870 (0.828-0.911)
Mevorach et al,[21] 2022	13/13	0.964 (0.867-1.000)
Foltran et al,[23] 2022	172/193	0.891 (0.847-0.935)
Amir et al,[25] 2022	13/15	0.867 (0.695-1.000)
Nygaard et al,[26] 2022	15/15	0.969 (0.883-1.000)
Das et al,[28] 2021	22/25	0.880 (0.753-1.000)
Patel et al,[30] 2022	9/9	0.950 (0.815-1.000)
Overall I^2 = 7402% (P < .001)	507/566	0.926 (0.878-0.973)



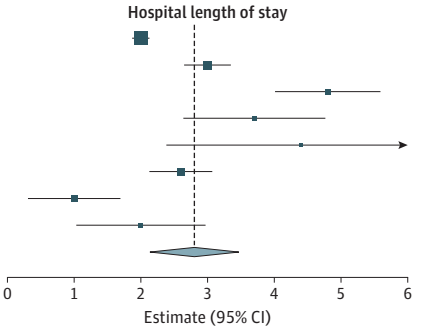
B ICU admission

Studies	Events/total population, No.	Estimate (95% CI)
Truong et al,[22] 2022	26/139	0.187 (0.122-0.252)
Jain et al,[24] 2021	27/63	0.429 (0.306-0.551)
Amir et al,[25] 2022	7/15	0.467 (0.214-0.719)
Nygaard et al,[26] 2022	1/15	0.067 (0-0.193)
Roh et al,[29] 2022	5/40	0.125 (0.023-0.227)
Patel et al,[30] 2022	2/9	0.222 (0-0.494)
Overall I^2 = 7937% (P < .001)	68/281	0.232 (0.117-0.347)



C Hospital length of stay

Studies	Estimate (95% CI)
Truong et al,[22] 2022	2.000 (1.877-2.123)
Jain et al,[24] 2021	3.000 (2.654-3.346)
Amir et al,[25] 2022	4.800 (4.011-5.589)
Nygaard et al,[26] 2022	3.700 (2.637-4.763)
Chelala et al,[27] 2022	4.400 (2.384-6.416)
Das et al,[28] 2021	2.600 (2.130-3.070)
Roh et al,[29] 2022	1.000 (0.312-1.688)
Patel et al,[30] 2022	2.000 (1.033-2.967)
Overall I^2 = 9294% (P < .001)	2.802 (2.136-3.467)



The pooled estimates of the prevalence of early outcomes of myopericarditis after COVID-19 mRNA vaccination in adolescents and young adults were calculated using 1-group meta-analysis in random-effects model. ICU indicates intensive care unit; diamond, total estimate with 95% CI.

studies from the US and Israel.[47-50] Myocarditis occurred primarily after the second vaccination in young males (1 case per 12 361 individuals in male adolescents vs 1 case per 144 439 individuals in female adolescents; 0.56 cases per 100 000 individuals after the first dose vs 8.09 cases per 100 000 individuals after the second dose in males).[48] Within the ages of 12 to 17 years, males were 7.2 times more likely to develop myocarditis following COVID-19 vaccination compared with females and myocarditis incidence was 6.8 times higher after the second dose than the first dose.[51] Our results are consistent with these reports, suggesting that myocarditis incidence after COVID-19 mRNA vaccination is rare and occurred mainly after the second dose in males. The incidence of myocarditis appears to be different among mRNA vaccines. In our study, almost all the cases of myocarditis were seen after the BNT162b2 vaccine. In contrast, a higher risk of myocarditis with mRNA-1273 compared with BNT162b2 has been observed in large observational studies.[52-54]

Importantly, the risk of developing myocarditis after SARS-CoV-2 infection is significantly higher than after COVID-19 mRNA vaccination. The incidence of myocarditis after SARS-CoV-2 infection is higher than after COVID-19 mRNA vaccination (11.0 events per 100 000 persons vs 3.2 events per 100 000 persons).[55] Furthermore, compared with cardiac complications associated with COVID-19, our study revealed largely favorable early outcomes of vaccine-associated myopericarditis.[56] Accordingly, the benefits of the mRNA COVID-19 vaccination are deemed to outweigh the potential risks. Despite the lack of severe complications commonly associated with COVID-19 mRNA vaccination, vaccine hesitancy remains high, and some parents still hesitate to vaccinate their children against COVID-19.[57] Our findings corroborate

the relatively low risks and good early outcomes for COVID-19 vaccine-associated myopericarditis across a wide population from multiple counties, improving understanding of myopericarditis following COVID-19 mRNA vaccination among adolescents and young adults and decision-making for parents with vaccine hesitancy.

The use of CMR is important in the noninvasive diagnosis and risk stratification of myocarditis. In particular, T2-weighted imaging is routinely performed to detect acute myocardial inflammation or edema. Similarly, LGE is widely used to detect necrosis and fibrosis and is incorporated into the original and revised Lake Louise criteria for diagnosis of acute myocarditis. In our study, the Lake Louise Criteria was used, and CMR was performed for making the diagnosis of myocarditis. However, a large proportion of patients with subclinical myocarditis might not have been diagnosed with myocarditis, leading to much lower hospitalization and ICU admission rates than currently reported. This would strengthen the argument that most cases of myocarditis are mild and possibly even underdiagnosed. Interestingly, our study found LGE in 87.2% of adolescents and young adults, while the clinical course was mild and no in-hospital mortality was observed. Although a previous study also detected LGE in 88.3% of patients (aged 14-70 years) with myocarditis after COVID-19 mRNA vaccination, all patients recovered and were discharged.[9] Unfortunately, the degree and extent of LGE was not reported, and follow-up studies with CMR have not been published, to our knowledge. The persistence of LGE indicates the potential myocardial fibrosis and could be a risk factor for adverse cardiac events, including arrhythmias, cardiac dysfunction, or recurrent myocarditis, in patients with myocarditis due to other causes.[58] While this is similar to other, non-vaccine-associated myocarditis, a clinical follow-up of cardiovascular events in patients with vaccine-associated myocarditis is essential. Further studies are needed to investigate the association of CMR findings and long-term outcomes.

Limitations

This study had several limitations to be noted. First, the available studies were observational studies or case series, subject to methodological biases or publication biases. Second, each study contained a small number of patients, potentially leading to substantial heterogeneity. Additionally, we excluded case reports, which may have included severe cases not reported in large observational studies. Furthermore, the retrospective designs of the included studies might have underestimated the complications. Third, it is difficult to identify a small number of overlaps in patient data between multicenter studies from the same countries, although we removed 1 study from Hong Kong and 2 single-center studies from the US that were likely to have overlapping patient data with other studies. Fourth, the lack of universal case inclusion criteria or diagnostic tests could lead to a misdiagnosis or underreporting of vaccine-associated myocarditis. Fifth, several variables were not available. For example, whereas an 8-week or longer interval has been associated with a lower risk of myopericarditis associated with COVID-19 mRNA vaccines in a population-based cohort study,[59] these variables were not obtainable across the included studies; the influence of the interval in adolescents and young adults remains uncertain. Sixth, our study did not find the association of symptoms with unfavorable outcomes in adolescents and young adults. Although a previous study reported that adult patients with gastrointestinal symptoms received more intensive care, risk factors of poor prognosis remain elusive.[60] Seventh, in this study, most of the types of vaccine were BNT162b2 vaccines, limiting the generalizability of findings to other COVID-19 vaccines, including the mRNA-1273 vaccine.

Conclusions

The findings of this systematic review and meta-analysis pooling data from multiple countries demonstrate low incidence rate and largely favorable early outcomes of COVID-19 vaccine-associated myopericarditis in adolescents and young adults from a wide range of populations. While mortality data are reassuring, a significant number of patients were reported to have acute LGE. Our findings could help improve understanding of myopericarditis among adolescents and young adults and decision-making for parents.

ARTICLE INFORMATION

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Drafting of the manuscript: Yasuhara, Masuda, Kuno.
Critical revision of the manuscript for important intellectual content: All authors.
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Administrative, technical, or material support: Yasuhara, Lee, Kuno.
Supervision: Yasuhara, Lee, Kuno.

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