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Supplementary appendix 1

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Outcomes at least 90 days since onset of myocarditis after mRNA COVID-19 vaccination in adolescents and young adults in the USA: a follow-up surveillance study

Appendix 1

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Case definition criteria

Centers for Disease Control and Prevention (CDC) definitions for probable and confirmed cases of myocarditis and myopericarditis (referred to as myocarditis) are shown in Table S1. CDC case definition criteria were applied to cases of myocarditis following mRNA COVID-19 vaccination as reported to the Vaccine Adverse Event Reporting System (VAERS) and as described in Oster et al.[1]

Patient and healthcare provider survey instruments

Contact information for healthcare providers was provided by patients completing the survey or through the submitted VAERS report. Initial cardiac imaging or biomarker test results were also taken from medical records.[1] The healthcare provider survey collected information on patient cardiac biomarkers, cardiac function tests and cardiac imaging including troponin, cardiac magnetic resonance imaging (cMRI), echocardiogram, electrocardiogram, exercise stress testing and ambulatory rhythm monitoring including the dates of the test and the assessment of function. We categorized troponin levels as normal or elevated based on each laboratory's reference range. Electrocardiograms were categorized as normal or baseline, or abnormal (borderline or abnormal), based on any one of the following: atrial, supraventricular or ventricular arrhythmia; ST elevation or ST abnormalities, T-wave abnormalities or abnormal repolarization, PR depression without reciprocal ST depression, conduction delays or blocks, or frequent atrial or ventricular ectopy. Echocardiograms were categorized as normal or baseline, or abnormal based on decreased left ventricular function. cMRIs were categorized as normal or baseline, or abnormal based on the presence of any one of the following: wall motion abnormalities, late gadolinium enhancement, or evidence of continued inflammation or edema, using either T2-weighted imaging or parametric mapping. We applied modified Lake Louise

criteria to findings from abnormal cMRIs to identify ongoing myocarditis.[2] Exercise stress tests were categorized as normal or baseline, or abnormal based on the presence of any one of the following; arrhythmia, coronary perfusion abnormality, other cardiac concern on exercise test, or a non-cardiac concern on exercise test. Ambulatory rhythm monitoring was categorized as normal or baseline, or abnormal based on the presence of any one of the following: atrial, supraventricular or ventricular arrhythmia; conduction delay or block, or frequent atrial or ventricular ectopy.

Patients ages 12 to 19 years were classified as obese based on national reference standards for body mass index (BMI) and patients ages 20 to 29 years were classified as obese if BMI was greater than 30.0 kg/m^2.[3]

Patient and healthcare provider outreach and interviews

Patient call lists included all VAERS reports of myocarditis following mRNA COVID-19 vaccination in persons aged 12–29 years and for whom 90 days had elapsed since the onset of myocarditis symptoms that met the CDC case definition (Table S1). The call list was periodically updated during the surveillance period (August 2021 through November 2021) as additional patients reached the 90-day period following the onset of myocarditis. VAERS records, including identifiers (e.g., date of birth, demographics, and contact information) were maintained in a secure call tracking log in DCIPHER (a cloud-based data integration and management platform used by federal agencies and partners and state, local, tribal, and territorial public health jurisdictions that requires secure access). Because data fields in VAERS (e.g., contact information) are not required for report submission, complete information was not available for all cases. Surveys were administered during August 2021–January 2022.

Letters were mailed to 707/836 (85%) eligible patients with an available street address, which included information about the public health surveillance activity and encouraged patients and/or parents or guardians to contact the CDC. For those with available contact information, CDC outreach staff attempted to contact patients by telephone. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at CDC.[4,5] Standard language was included for obtaining verbal consent for either adult case-patients or parents/guardians of minor case-patients. Patients received up to three telephone call attempts. If after three attempts, interviewers were unable to reach a patient, they were classified as unreachable. At each outreach attempt, interviewers would leave a standard voice mail as well as send a standard text message with information on how to contact CDC. Patients who were minors and had parents or guardians answer the survey were able to be present during the interview with permission from the parent or guardian. If the minor was present, survey questions, which collected information on quality of life based on the EuroQol 5-dimension, 5-severity level (EQ-5D-5L) questionnaires and EuroQol-visual analogue scale (EQ-VAS), were directed specifically to the minor to answer.

Additional efforts to contact cases classified as unreachable were made via the state vaccine coordinators. CDC staff provided each coordinator with a list of cases in their jurisdiction who were unreachable. State vaccine coordinators attempted to contact each unreachable patient.

For cases defined as minors (i.e., a case who had not reached the age of majority/age of legal adulthood, as defined by their state of residence on the date of interview), parents or guardians were verbally consented and interviewed.

Weighted patient self-reported quality of life measure

Value weights were applied to patient responses to the EQ-5D-5L questionnaires across five dimensions: mobility (ability to walk), self-care (ability to wash or dress), pain or discomfort, usual activities, and anxiety or depression and each of the five levels of severity: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5). Weights corresponding to each level and dimension in a patient health profile were used to create an index value and are shown in Table S2. A high weight indicates the population from which those weights were derived believe it has a higher impact on their quality of life. The index is calculated by taking one minus the linear summation of these weights resulting in a value ranging from 0 (a state as bad as death) to 1 (full health), with negative values representing health states considered worse than death. Health dimensions with a severity level of 1 (i.e., no problems) have a weight of zero.

Subsequent Hospital Admissions

For patients who reported on the patient survey that they had a subsequent hospitalization after the time of their initial myocarditis diagnosis, medical records were obtained from the respective hospital and reviewed to determine the reason for the hospitalization and if any cardiac abnormalities were identified during cardiac evaluation. Patients hospitalized because of an adverse event to myocarditis treatment or with any cardiac abnormality identified are summarized in the manuscript text and in Supplemental Results (Table S6).

Sensitivity Analysis

To examine proportion of patients considered recovered who had symptom onset ≤7 days from the last COVID-19 vaccine dose and no alternative etiology identified by their healthcare provider, we conducted a sensitivity analysis. We excluded patients with a provider survey who suggested a possible alternative infectious, immunological toxicological, hypersensitivity, or

radiation-therapy induced etiology (n=15). Additionally, we excluded patients with a provider survey and a symptom onset greater than 7 days after their last COVID-19 vaccine dose (n=22); 90% of the myocarditis events occurred within 7 days of vaccination in the Oster et al study.[1]

SUPPLEMENTARY RESULTS

Sensitivity Analysis

In the sensitivity analysis restricted to the 360/393 (92%) patients with symptom onset ≤7 days from last mRNA COVID-19 vaccine dose and no alternative etiology identified by their healthcare provider, the proportion of patients considered recovered (82%) was similar to the overall survey population.

Subsequent Hospital Admissions

Of 357 persons with patient survey completed, a total of 6 [2%] patients had a subsequent hospital admission for either an adverse reaction to myocarditis treatment, or a cardiac concern with an abnormality on cardiac evaluation. Three of the 6 were re-hospitalized because of an adverse reaction to intravenous immune globulin (2 for headache, 1 for hemolytic anemia and headache). Two other patients (Patients A and B in Table S6) were re-hospitalized 1 time for cardiac concerns and had ≥1 abnormality on cardiac evaluation. One other patient (Patient C in Table) was re-admitted twice for pericarditis (for total of 3 hospital admissions for this patient).

Table S1. Centers for Disease Control and Prevention case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis as described in Gargano et al.[6]

Condition	Definition	
Acute myocarditis	**Probable case**	**Confirmed case**
	Presence of ≥1 new or worsening of the following clinical symptoms: * • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy AND ≥1 new finding of • troponin level above upper limit of normal (any type of troponin) • abnormal ECG or rhythm monitoring findings consistent with myocarditis[§] • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis[¶] AND • No other identifiable cause of the symptoms and findings	Presence of ≥1 new or worsening of the following clinical symptoms:* • chest pain, pressure, or discomfort • dyspnea, shortness of breath, or pain with breathing • palpitations • syncope OR, infants and children aged <12 years might instead have ≥2 of the following symptoms: • irritability • vomiting • poor feeding • tachypnea • lethargy AND ≥1 new finding of • Histopathologic confirmation of myocarditis[†] • cMRI findings consistent with myocarditis[¶] in the presence of troponin level above upper limit of normal (any type of troponin) AND • No other identifiable cause of the symptoms and findings
Acute pericarditis**	Presence of ≥2 new or worsening of the following clinical features: • acute chest pain[††] • pericardial rub on exam • new ST-elevation or PR-depression on ECG • new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis	

cMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram. * Persons lacking listed symptoms but who meet other criteria may be classified as subclinical myocarditis (probable or confirmed). † Using the Dallas criteria.[7] Autopsy cases may be classified as confirmed clinical myocarditis on the basis of meeting histopathologic criteria if no other identifiable cause. § To meet the ECG or rhythm monitoring criterion, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias or 3) atrioventricular nodal conduction delays or intraventricular conduction defects. ¶ Using either the original or the revised Lake Louise criteria.[2,8] †† Typically described as pain made worse by lying down, deep inspiration, or cough, and relieved by sitting up or leaning forward, although other types of chest pain might occur.

Table S2. EuroQol 5-dimension, 5-severity level weights used to create a weighted index value from patient health profiles.[9]

Quality of life dimension and severity level	Value weight
Mobility — severity level 2	-0.096
Mobility — severity level 3	−0.122
Mobility — severity level 4	−0.237
Mobility — severity level 5	−0.322
Self-care — severity level 2	−0.089
Self-care — severity level 3	−0.107
Self-care — severity level 4	−0.220
Self-care — severity level 5	−0.261
Usual activity — severity level 2	−0.068
Usual activity — severity level 3	−0.101
Usual activity — severity level 4	−0.255
Usual activity — severity level 5	−0.255
Pain or discomfort — severity level 2	−0.060
Pain or discomfort — severity level 3	−0.098
Pain or discomfort — severity level 4	−0.318
Pain or discomfort — severity level 5	−0.414
Anxiety or depression — severity level 2	−0.057
Anxiety or depression — severity level 3	−0.123
Anxiety or depression — severity level 4	−0.299
Anxiety or depression — severity level 5	−0.321

Table S3. Characteristics of patient survey and non-survey respondents.

Characteristic	Respondents (n=519)	Non-respondents (n=317)	P-value
Sex — no. (%)			0.70
Male	457 (88)	276 (87)	
Female	61 (12)	41 (13)	
Unknown	1 (0)	0	
Age — median (IQR)	17 (15–22)	18 (15–22)	0.30
Race and ethnicity — no. (%)			
White – non-Hispanic	274 (53)	147 (46)	0.069
Black – non-Hispanic	16 (3)	12 (4)	0.75
Asian – non-Hispanic	25(5)	20 (6)	0.47
Multiple races – non-Hispanic	10 (3)	2 (<1)	0.14
Other race – non-Hispanic	12 (2)	6 (2)	0.81
Hispanic	98 (19)	54 (17)	0.17
Unknown	84 (16)	76 (24)	
Census region – no. (%)			0.76
West	133 (26)	74 (23)	
Midwest	94 (18)	44 (13)	
South	126 (24)	65(21)	
Northeast	112 (22)	67 (21)	
Unknown or international	54 (10)	67 (22)	
Initial echocardiogram	n=385	n=227	0.090
Normal or baseline	263/385 (68)	139/227 (61)	
Abnormal	122/385 (32)	88/227 (39)	
VAERS reporter type			
Healthcare provider	431 (83)	259 (82)	0.053
Patient	38 (7)	14 (5)	
Other	50 (10)	44 (14)	

Table S4. Abnormal cardiac magnetic resonance imaging (MRI) findings, at healthcare provider follow-up, in patients with myocarditis after COVID-19 mRNA vaccination.

Abnormal cardiac MRI finding	**Number of patients with an abnormal cardiac MRI finding (%) n=81**
Wall motion abnormality only	2 (2)
Late gadolinium enhancement only	47 (56)
Edema only	1 (1)
Wall motion abnormality and late gadolinium enhancement	3 (4)
Wall motion abnormality and edema	0
Late gadolinium enhancement and edema	20 (25)
Wall motion abnormality and late gadolinium enhancement and edema	1 (1)
Unknown abnormality or abnormal finding not provided	7 (8)

The denominator consists of 151 patients who received a follow-up cardiac MRI. Seven patients had a follow-up cardiac MRI but did findings were not available. Of these, 81/151 (54%) had an abnormal cardiac MRI finding. Of the patients with an abnormal finding, 20/151 (13%) had evidence of ongoing myocarditis indicated by the presence of edema and late gadolinium enhancement using modified Lake Louise criteria.

Table S5. Time from myocarditis onset to follow-up abnormal cardiac biomarker or test result

Cardiac biomarker test or imaging	Days from myocarditis onset to follow-up abnormal test result, Median (IQR)
Echocardiogram, n=17	72 (31–125)
Cardiac MRI, n=80	91 (24–143)
Late gadolinium enhancement and edema, n=20	26 (9—94)
Late gadolinium enhancement only, n=47	109 (58—163)
Electrocardiogram, n=47	24 (15—54)
Troponin, n=16	6 (3—17)

Table S6. Subsequent hospital admissions with any cardiac abnormality identified, among patients who completed the patient survey

Patient	Number of days from vaccination to original symptom onset	Number of days from original hospital discharge to subsequent admission	Duration of subsequent hospitalization, days	Diagnosis or cardiac findings during subsequent hospitalization	Recovery status per provider survey
A	0	5	4	Myocarditis, decreased ejection fraction	Fully recovered
B	4	17	3	Chest pain, elevated troponin	NA, no provider survey
C	18	10	6	Pericarditis (normal cardiac MRI)	NA, no provider survey
		18	2	Pericarditis (normal cardiac evaluation)	

Three of the 6 were re-hospitalized because of an adverse reaction to intravenous immune globulin (2 for headache, 1 for hemolytic anemia and headache).

Table S7. Proportion of patients and healthcare provider determination of myocarditis patient recovery status by vaccine manufacturer.

Vaccine	All eligible patients, n=836 (%)	Patients with information collected, n=519 (%)	Patients considered fully or probably fully recovered*, n=320 (%)
Pfizer-BioNTech	632 (76)	393 (76)	244 (76)
Moderna	204 (24)	126 (24)	76 (23)

*The total denominator for patients that received a determination of cardiac recovery was taken from the healthcare provider survey (n=393). Of the 393 patients, 320 (81%) were considered probably fully or fully recovered. Of the 320 patients considered fully or probably fully recovered, 244/302 (81%) patients received the Pfizer-BioNTech vaccine and 76/91 (84%) received the Moderna vaccine. There was no statistically significant difference (χ^2=0.01, p=0.92) in the proportion of patients considered fully or probably fully recovered who received either the Pfizer-BioNTech or Moderna vaccine.

Table S8. Characteristics of patients with evidence of late gadolinium enhancement (LGE) or ongoing myocarditis on cardiac magnetic resonance imaging

Characteristic	LGE (n=47)	Ongoing myocarditis* (n=20)
Median age in years (IQR)	16 (15–19)	16 (15–19)
Age group — no. (%)		
12–14 years	6 (13)	3 (15)
15–19 years	32 (68)	13 (65)
20–24 years	5 (11)	1 (5)
25–29 years	4 (9)	3 (15)
Sex — no. (%)		
Male	42 (89)	19 (95)
Female	4 (9)	1 (5)
Unknown	1 (2)	0
Cardiac Recovery status — no. (%)		
Fully recovered	18 (38)	12 (60)
Probably fully recovered, but awaiting additional information	11 (23)	2 (10)
Improved, but not fully recovered	18 (38)	6 (30)
Same cardiac status as at the initial myocarditis diagnosis	0	0
Abnormal follow-up echocardiogram — no. (%)	2 (4)	3 (15)
Abnormal follow-up troponin — no. (%)	5 (11)	0
Abnormal follow-up electrocardiogram — no. (%)	14 (30)	0
Cleared for physical activity — no. (%)	24 (51)	13 (65)
Highest level of care — no. (%)		
Hospitalized with no ICU care	34 (72)	12 (60)
Hospitalized with ICU care	10 (21)	6 (30)
Not hospitalized, managed as outpatient	1 (2)	1 (5)
ICU care ECMO	0	0
Unknown	2 (4)	1 (5)
Prescribed medication at last provider follow-up — no. (%)	13 (28)	8 (40)

Healthcare provider reported patient symptoms — no. (%)		
Chest pain	13 (28)	4 (20)
Fatigue	2 (4)	2 (10)
Shortness of breath	3 (6)	1 (5)
Heart palpitations	4 (9)	1 (5)
Health related quality-of-life from EQ-5D-5L — no. (%)	n=14	n=4
Problems with anxiety depression	5/14 (36)	2/4 (50)
Problems with pain or discomfort	3/14 (21)	2/4 (50)
Problems preforming usual activities	1/14 (7)	1/4 (25)
Problems with self-care	0	1/4 (25)
Problems with mobility	0	0
Visual analogue scale — median (IQR)	90 (78–95)	83 (58–96)

* Evidence of ongoing myocarditis, defined by both late gadolinium enhancement and edema using modified Lake Louise criteria.[2]

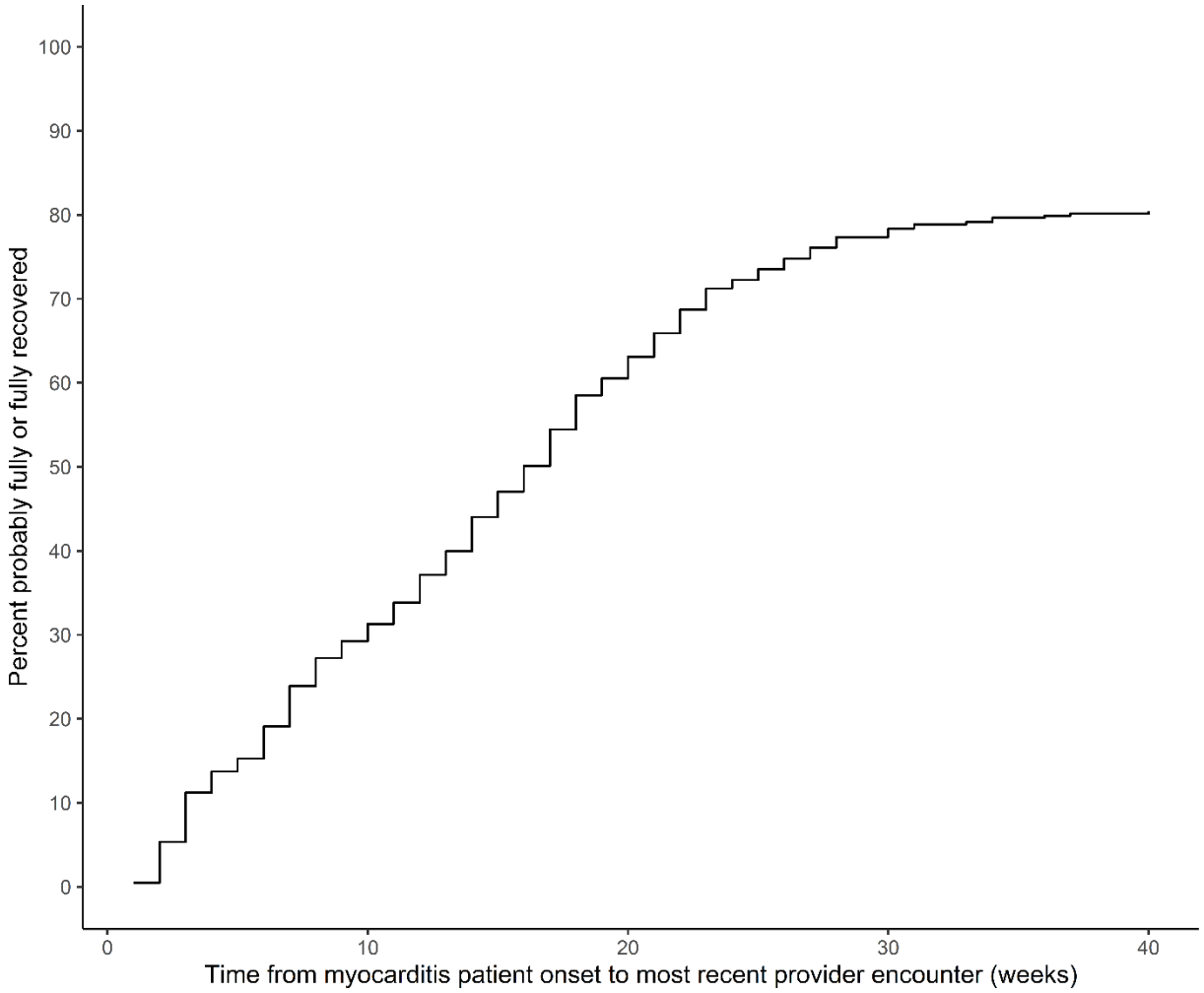

Figure S1. Cumulative proportion of patients with myocarditis after mRNA COVID-19 vaccination who were considered by their healthcare provider to be recovered fully or probably fully recovered (n=320) based on time since the patient last healthcare provider encounter. The denominator is taken from the healthcare provider survey completed by 393 providers as shown in Figure 1. In four patients considered fully or probably fully recovered the healthcare provider did not provide the date of their last encounter.

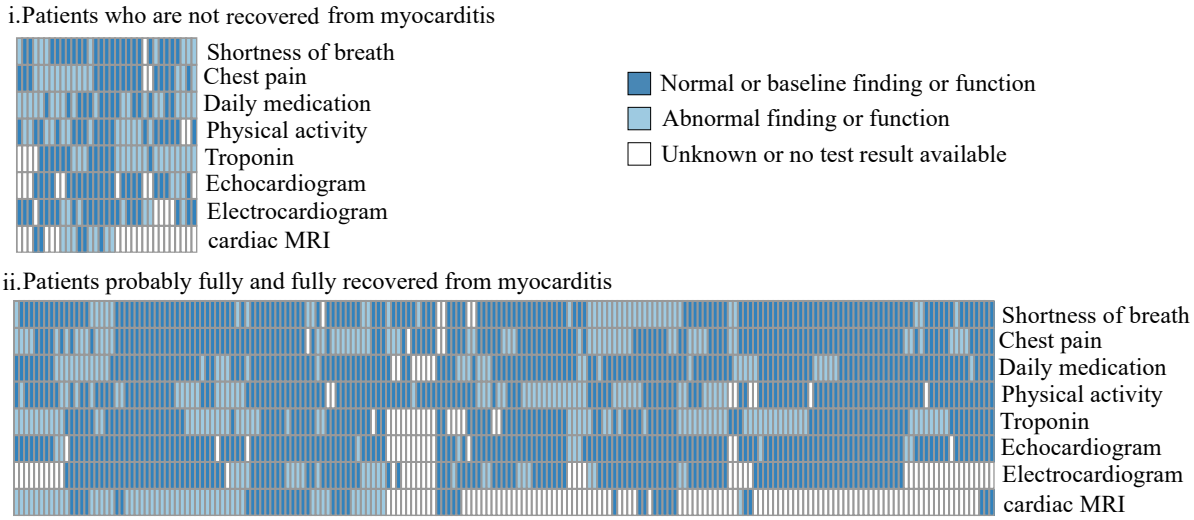

Figure S2. Cardiac biomarker, imaging and functional status at the individual patient level, by myocarditis recovery status. Each column represents a patient, and each row represents a diagnostic test, cardiac imaging or patient functional status. Symptoms are self-reported by the patient. The denominator is taken from linked patient and provider surveys and included 33 patients who are not recovered, and 195 patients considered probably fully or fully recovered.

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