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## **A Systematic Review of Myocarditis Associated with Covid-19 Mrna Vaccination among Adolescents**

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### **ABSTRACT**

The COVID-19 infection which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to severe respiratory illness especially in male adolescents. This systematic review article aimed to compile and illustrate clinical features, diagnostic findings, management, and outcomes manifesting in adolescents in myocarditis associated with mRNA Covid-19. A literature search was accomplished for published eligible articles with MEDLINE and PubMed. All eligible case reports and case series were included from around the world without any language restrictions. For this review, inclusion criteria were confirmed-confirmed SARS-CoV-2 infection cases reporting a diagnosis of myocarditis in adolescents. A total of 6 articles with a total number of 107 patients were included. Patients presented with fatigue, fever, headache, malaise and chest pain. The median age of these patients was 16.23 years. Cardiac biomarkers troponin was raised in almost 78.5% of patients. Elevated C-reactive protein levels were also reported in some of the patients. Electrocardiography results demonstrated ST-segment division while echocardiography showed normal in 4.67% of the studied patients and left ventricular systolic function in 3.74%. Hydroxychloroquine, antiviral therapy, corticosteroids, nonsteroidal anti-inflammatory drugs, intravenous immunoglobulin, and glucocorticoids were the most frequent used medications with no death recorded. Common available data on COVID-19 myocarditis among adolescents is limited. Further research is therefore needed to advance the understanding of COVID-19 myocarditis among adolescents.

**KEYWORDS:** Covid-19, myocarditis, adolescents, systematic review

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### **INTRODUCTION**

The COVID-19 which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first discovered in December 2019 in Wuhan city of China [1]. Since its identification in Wuhan, the virus has spread globally, resulting in the continuing 2019-2021 coronavirus pandemic. On January 30, 2020, the WHO declared the Covid-19 outbreak a global health emergency [2]. Scientists all over the world have examined different platforms for vaccine development, including viral-based and protein-based vaccines, in order to prevent infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or to reduce the severity of the disease, with an ultimate aim to reduce mortality and morbidity [3]. There is a precipitous rise in the production of COVID-19 vaccine; the conventional length of time that has always bedeviled vaccine approval was bypassed with an Emergency Use

Authorization by the Food and Drug Administration. Currently, there are more than 232 vaccine candidates [4].

Myocarditis is the inflammation of muscle of the heart with associated symptoms which can include shortness of breath, chest pain or the feeling of a rapid or abnormal heart rhythm and other non-cardiac symptoms such as fatigue, edema or cough [5]. The list of possible causes of triggers for myocarditis is broad and includes both infectious and non-infectious triggers [6]. Smallpox vaccination is the only vaccine that has ever been conclusively linked to myocarditis based on a significantly higher relative risk [7]. Myocarditis has also been associated with recent Covid-19 infections, specifically in young adults [8]. Recent research also has shown adolescents and young adults are at increased risk for myocarditis after receiving mRNA vaccinations (Pfizer-BioNTech and Moderna) for COVID-19 [9]. Cases were

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typically mild with no reported deaths, though many had evidence of continued heart inflammation [10].

The Center for Disease Control and Prevention (CDC) also noticed that the rate of postvaccine myocarditis was higher in adolescents and young adults than the expected baseline [4]. Pfizer-BioNTech messenger RNA COVID-19 vaccines authorized for emergency use administration on children between the ages of 12 and older was approved May 10, 2021. Reports showed that the vaccine was well tolerated without any serious adverse events; however, there have been few cases of myocarditis from several reports since after the approval. Most cases followed the second dose of vaccine, and chest pain was the most common presenting symptom. Patients came to medical attention a median of 2 days (range, <1-20 days) after receipt of Pfizer mRNA COVID-19 vaccination [11]. Several cases of myocarditis have also been identified from the vaccine Adverse Event Reporting System (VAERS), most commonly in male adolescents aged 16. An increasing numbers of adolescents are currently being vaccinated, it is important to understand the potential side effects, in order to appropriately counsel patients on the risks and benefits of the mRNA COVID-19 vaccination. The aim of this study is to conduct a systematic review of case reports and case series to summarize the cardiac complications associated with COVID-19 mRNA vaccines.

### METHODS

#### Study Design

In the following bibliographic databases, we carried out a thorough systematic search of literatures in PubMed/Embase, and MEDLINE. We searched for articles that are mostly relevant and that were published in English Language up to January 2022. The study included keywords such as COVID-19, severe acute respiratory syndrome coronavirus SARS-CoV-2, in combinations with myocarditis, cardiac injury, cardiomyopathies. In addition, all the references of the selected papers were searched manually for additional related articles. The present systematic review conforms to the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement. A total number of 32 studies were screened, 21 studies were accepted and 11 were rejected.

#### Eligibility Criteria

**Inclusion Criteria** – Only articles that reported myocardial inflammation or myocarditis is combination with COVID-19 were included. Articles that do not involve adolescents were not included.

**Exclusion Criteria** – Studies were excluded if; 1) Articles were not case reports, case series or observational studies, 2) Articles were reviewed appropriately, 3) Articles published before COVID-19 started were excluded. The language of publication was not an issue.

#### Information Sources and Search Strategies

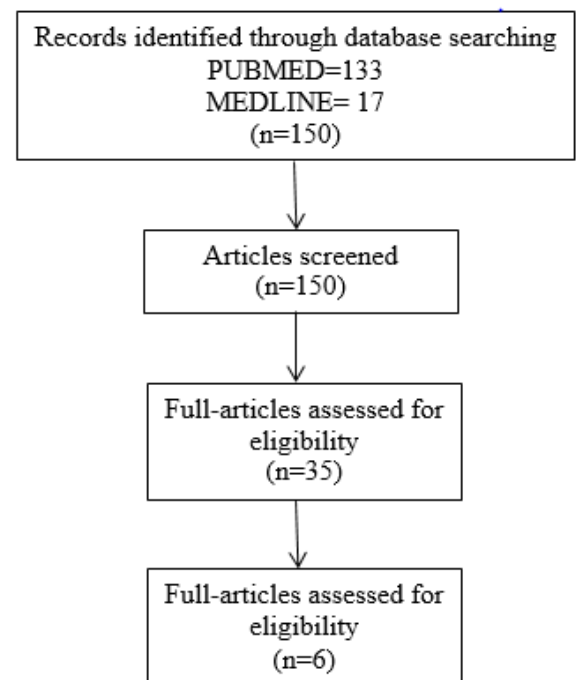
A comprehensive literature search was completed using Scopus, PubMed, Emebase, Google Scholar, and Web of science databases from December, 2019 to January 18, 2022, using the terms ‘Coronavirus’ or ‘COVID’ myocarditis.

#### Data Extraction

Data collection from articles included the first name of the author, year and country of publication and study design, study population. Patient variables including age, sex, and presenting complaints on admission were sought from all the studies. Myocarditis management approaches and patient outcomes, including complications, were acquired from case reports. Extracted data were critically looked at and reviewed.

### RESULTS

**Study Selection:** Two databases were used to find the 150 articles related to COVID-19 and myocarditis in adults. Seven studies were then deemed eligible for inclusion in this review. A PRISMA flow diagram detailing the process of identification, inclusion an exclusion of studies is shown in Figure 1.



**Figure 1:** Flow diagram of literature search and selection criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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### Study Results

In this review, 108 patients reported to be diagnosed with myocarditis were included from six published studies [10, 11, 12, 13, 14, 15]. The median age of included patients was 16.23 years (which ranged from 12-19 years) with 100% of them being made adolescent. All the eleven included articles were case reports and published in 2021. Four studies were conducted in USA and one was conducted in Poland, Italy, and Canada with USA producing the most articles. Table 1

compiles the patient demographic and clinical characteristic features of each case.

Chest pain and fever was the most prevalent presenting symptoms seen in all patients followed by fatigue and headache. Other atypical symptoms observed were sore throat, myalgias, shortness of breath, and body aches. In all the studies, only three patients had remarkable past history such as Von Willerbrand disease and Lennox-Gastaut syndrome [14], hyperactivity disorder and mild intermittent asthma and Obesity, Asthma, Spondylolysis [12].

**Table 1. Patient demographic and clinical characteristic features**

Author	Country	Study design	Covid-19 Status (diagnostic technique)	Sample size	Age (y)	Past medical history	Presenting symptoms	Physical examination findings on admission
Marshall <i>et al.</i> [11]	Portland	Case report	Positive (RT-PCR)	7	16yr	None	Fatigue, poor appetite, fever, chest and arm pains.	Temperature- 38.3°C
					19yr	None	Acute and chest pain, myalgias, fatigue, weakness and subjective low-grade fevers.	NA
					17yr	None	Chest pain associated with left arm pain and paresthesias	NA
					18yr	None	Chest pain, malaise, arthralgia and subjective fever	NA
					17yr	None	Chest pain, sore throat, headache, dry cough and body aches	NA
					16yr	None	Chest pain, malaise and subjective fever	Acute midsternal chest pain- 18 hrs
					14yr	None	Fever, pleuritic chest pain, shortness of breath.	Temperature-38.3°C

Author	Country	Study design	Covid-19 Status (diagnostic technique)	Sample size	Age (y)	Past medical history	Presenting symptoms	Physical examination findings on admission
Ambati <i>et al.</i> [12]	USA	Case report	Positive (RT-PCR)	2	16yr	Von Willerbrand disease and Lennox-Gastaut syndrome	Chest pain	NA

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Author	Country	Study design	Covid-19 Status (diagnostic technique)	Sample size	Age (y)	Past medical history	Presenting symptoms	Physical examination findings on admission
					17yr	Hyperactivity disorder and mild intermittent asthma	Fatigue, generalized body aches, headache and fever	Temperature-101 F
Jain <i>et al.</i> [13]	USA	Case report	Positive (RT-PCR)	23	12-19r	None	Chest pain, shortness of breath, headache, fatigue, myalgias, nausea and fever.	Temperature-100.4°F
Gnecchi <i>et al.</i> [15]	Italy	Case report	Positive (RT-PCR)	1	16yr	None	Chest and arm pain, fever	Temperature-38.5°C
Truong <i>et al.</i> [10]	US and Canada	Case report	Positive	73	12-16yrs	None	Chest pain, palpitations, syncope, dyspnea, pressure	NA

**Table 2. Laboratory analysis, electrocardiogram (ECG), and echocardiogram findings**

Author	Lab findings and imaging	Inflammation related markers	Cardiac biomarkers	Electrocardiogram (ECG)	Echocardiogram
Marshall <i>et al.</i> 2021	LGE (subepicardial) involving lateral lateral, myocardial edema of lateral L wall, left axillary adenopathy.	Mildly elevated, with D-dimer 1.52 µg/mL, erythrocyte sedimentation rate (ESR) of 43mm/hour and maximum C-reactive protein (CRP) of 12.3 mg/L (normal range:<1.0 mg/dL).	Elevated troponin I (2.59ng/mL)	Atrioventricular dissociation with junctional escape rhythm, ST elevation	Normal
	LGE involving mild LV wall, myocardial edema of basal inferolateral LV wall.	CRP (6.7 mg/dL)	High sensitivity troponin T: 232 (<14)	ST segment (diffuse)	Normal
	LGE (subepicardial) involving basal anterolateral and basal anterolateral and basal to midventricular inferolateral LV segments, myocardial edema, elevated extracellular volume fraction (29.2%)	N-terminal probrain natriuretic peptide (NT-proBNP) (376pg/mL) and CRP (253mg/L)	Troponin I: 5.55 (<0.045)	ST segment (diffuse), T- wave abnormally	Borderline basal lateral and basal posterior strain

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	Fibrosis, myocardial edema, hyperemia, mild mitral regurgitation (RF-18%)	N/A		Troponin T:1.09 (<0.01)	ST elevation	Normal
	LGE (epicardial) involving anterior and lateral LV wall, no myocardial edema	N/A		Troponin T: 3.2 (<0.01)	Sinus bradycardia, T-wave abnormality	Normal
	LGE, diffuse myocardial edema	N/A		Troponin T: 0.66 (<0.01)	ST elevation (diffuse)	Normal
	LGE (subepicardial) involving mid and apical LV free wall, myocardial edema, hyperemia	N/A		Troponin I: 22.1 (<0.045)	ST elevation, low voltage of extremity leads	Mildly depressed RV and LV systolic function (LVEF 47%)
Ambati <i>et al.</i> (2021)	N/A	Normal B type Natriuretic Peptide (BNP)		Elevated troponin I: 38 ng/mL	Diffuse segment elevations	ST N/A
	Negative viral respiratory panel			Elevated troponin I: 5 ng/mL	ST segment elevations	Mildly decreased left ventricular systolic function
		Normal ferritin and d-dimer with BNP of 121 pg/mL (mildly elevated) and CRP 95 mg/L (elevated), ESR 43 mm/hr (elevated).				
Jain <i>et al.</i> (2021)	Dysrhythmia	N/A		N/A	N/A	Left ventricular dysfunction
Trogen <i>et al.</i> (2020)	N/A	N/A		Elevated troponin levels	Abnormal	Decreased left ventricular ejection fraction
<b>Author</b>	<b>Lab findings and imaging</b>	<b>Inflammation related markers</b>	<b>Cardiac biomarkers</b>	<b>Electrocardiogram (ECG)</b>	<b>Echocardiogram</b>	
Gnecchi <i>et al.</i> (2020)	N/A	Creatine phosphokinase (671.0U/L), creatine phosphokinase (32.5 mg/L), and lactate dehydrogenase (276.0U/L) concentration	High-sensitivity cardiac troponin I (9449 ng/L)	Inferolateral ST segment elevation	Hypokinesia of the inferior and infolateral segments of the left ventricle, with a preserved ejection fraction of 52%.	

Truong <i>et al.</i> (2021)	Late gadolinium enhancement and myocardial edema	N/A	Elevated troponin I (8.2 ng/mL)	Abnormal ECGs and arrhythmias	Nonsustained ventricular tachycardia and left ventricular ejection fraction of 55%.
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**Diagnostic findings**

The most prominent etiology behind acute myocarditis is viral infections. Several cases of acute myocarditis associated with Covid-19 in adolescents have been described around the globe and are diagnosed in multiple ways. Cardiac biomarkers troponin and N-terminal (NT)-prohormone BNP (NT-proBNP) were elevated in almost all the patients. The level of inflammation related markers such as C-reactive protein was significantly increased, indicating an inflammatory process in the body. Table 2 summarizes laboratory findings, serology, ECG and echocardiogram findings.

**ECG findings**

ECG was normal in five (5) patients [11]. In other patients, ECG findings were viable and ranged from ST-elevations, T-wave abnormality and arrhythmias which included atrioventricular dissociation.

**Echogram findings**

Echocardiogram was performed on some of the patients, of which some exhibited decreased left ventricular systolic function. Other features observed were hypokinesia of the inferior and infolateral segments, depressed RV and LV systolic function and borderline basal lateral and basal posterior strain.

**CMRI findings**

CMR is the noninvasive gold standard technique for diagnosing myocarditis. It was reported in two studies [11, 14]. Common findings appreciated demonstrated myocardial edema and sub-epicardial late gadolinium enhancement.

**Management and outcomes**

The most frequent drugs targeted against SARS-CoV-2 among adolescents in this study were hydroxychloroquine and antiviral therapy which reduced the troponin concentration and returned the inflammatory markers to normal with a resolved ST-segment elevation. In other studies, patients were discharged home with normal echocardiogram and troponin 1 level on ibuprofen. Other patients also had normal ST segments and troponin levels when managed with derail troponins and supportive management with ibuprofen and narcotics for chest pain.

**DISCUSSION**

COVID-19 has resulted in organ involvement, and myocarditis are among the most significant complications of this rapidly emerging disease, causing more severe disease (Daniels *et al.*, 2021). In this review, we studied the cardiac

injuries among adolescent patients with COVID-19 that resulted in myocarditis. Echocardiographic results showed normal in 4.67% of the studied patients and left ventricular systolic function in 3.74%. In a cohort of 73 adolescent, Jain *et al.* [13] reported that four patients had significant dysrhythmia on echocardiography, which resolved on discharge while 88% met the diagnostic CMR Lake Louise criteria for myocarditis. Our review of published studies showed the most common abnormal laboratory finding in adolescent patients with myocarditis was elevated troponin, D-dimer and CRP. Some studies reported normal B type Natriuretic Peptide (BNP), ferritin and d-dimer. Our systematic review also showed that 78.50% of patients presented with elevated troponin levels that were investigated in 5 studies. Myocardial injury is a common condition in COVID-19 hospitalized, which is characterized by increased troponin levels [16]. Another definition of cardiac injury is reported as abnormality in cardiac biomarkers, electrocardiography, or echocardiography relative to the patient’s previous condition. In a cohort study of 139 adolescents, 34.2-52% of hospitalized patients cardiovascular injury.

There are different manifestations of cardiac involvement in COVID-19, including acute myocardial infarction, acute heart failure, cardiogenic shock, myocarditis, and fatal arrhythmias [17]. In order of prevalence, the clinical manifestations of the severe acute respiratory syndrome due to COVID-19 among adolescents are fatigue, fever, and headache. Typically, myocarditis presents with fever, malaise and/or chest pain, which hampers the recognition and clinical diagnosis of myocarditis during the COVID-19 pandemic. We have identified through this systematic review that adolescents with COVID-19 myocarditis will commonly present with fever, headache, fever, and malaise and chest pain. Besides these common symptoms, other symptoms identified in this review were poor appetite, neck pain, weakness, diarrhea, and palpitations. These findings are broadly consistent with other studies examining clinical signs in patients with COVID-19 [18].

The patient recovery rates were assessed and in one study, three patients were treated with nonsteroidal anti-inflammatory drugs only, and only 4 received intravenous immunoglobulin and corticosteroids (Marshall *et al.* 2021). In a cohort study involving 139 adolescents, suspected myocarditis occurred in 97.8% after mRNA vaccine [10]. Patients were treated with nonsteroidal anti-inflammatory drugs (81.3%), intravenous immunoglobulin (21.6%),



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glucocorticoids (21.6%), colchicine (7.9%), or no anti-inflammatory therapies (8.6%).

In this systematic review, one of the limitations that must be taken into account is that research related to COVID-19 and myocarditis among adolescents is rapidly evolving, these reports are small scale studies based on early restricted understanding; hence these data may not be decisive and relevant for the entire population. Since only case reports and case series studies have been selected for this review, this increases the potential risk of bias. Another issue is the small number of patients enrolled in the study. Further investigations are required to include a broader range of studies, including clinical trials in patients with COVID-19 and myocarditis.

### CONCLUSION

This systematic review summarizes clinical features, diagnostic findings, management, and myocarditis outcomes associated with COVID-19 among adolescent. We confined 107 infected patients diagnosed with myocarditis. An elevated level of troponin and N-terminal prohormone of brain natriuretic peptide (NT-BNP), together with elevated ST segment, can trigger suspicion. This study has also showed that myocarditis is common in COVID-19 patients who are adolescents; however, no mortality was associated in these patients. Common fatal conditions in these patients include fatal arrhythmias and cardiovascular injury. Therefore, diagnostic measures of COVID-19 among adolescents should consist of underlying comorbidities. History, signs, symptoms of cardiovascular injury should be considered in evaluating these patients early in the course of this diseases and prompt therapeutic measures for the prevention of exuberating cardiac condition should be sought. Data are presently limited, therefore more research, particularly epidemiological type, is needed to improve our understanding of COVID-19 among adolescents.

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