Cardiac MRI Findings in Symptomatic Post Covid Patients with Suspected Myocarditis

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ABSTRACT

Background: Cardiovascular magnetic resonance (CMR) imaging, considered the gold standard for myocarditis diagnosis, presented conflicting results on the prevalence of COVID-19-associated myocarditis.

Objective: This study aimed to describe CMR findings in patients with active COVID-19 infection within three months of infection and who had suspected acute myocarditis. **Patients and Methods:** This was a multi-center cross-sectional study that comprised adult patients with COVID-19 and clinical suspicion of associated myocarditis. Evaluation encompassed history, clinical examination, laboratory investigations, ECG, echocardiography, and CMR using the revised Lake Louise Criteria 2018 for myocarditis diagnosis. Participants (n=100) were divided into three groups based on CMR findings (Group I (n = 6); no myocarditis, Group II (n = 63); suspected myocarditis, and Group III; proved myocarditis. Notably, Group III (n = 31) exhibited distinct characteristics.

Results: A multivariate analysis showed that chest pain, ferritin levels, and LAVI significantly predicted proved myocarditis after adjusting the other confounding factors.

Conclusions: Active COVID-19 infection within three months showed a high prevalence of suspected and proved myocarditis, with specific characteristics in the proved myocarditis group.

Keywords: Cardiac MRI Findings, Symptomatic Post Covid Patients, Suspected Myocarditis.

INTRODUCTION

The pathophysiology of COVID-19 related myocarditis is thought to be a combination of direct viral injury and cardiac damage due to the host's immune response. COVID-19 myocarditis diagnosis should be guided by insights from previous coronavirus and other myocarditis experience. The clinical findings include changes in magnetic resonance imaging, electrocardiogram, cardiac biomarkers, and impaired cardiac function [1]. Cardiovascular complications of COVID-19 have received less medical attention; nevertheless, the first case of myocarditis in COVID-19 patients have been reported and myocarditis has been recognized as the cause of death in some of them. Pathology is usually focal within the myocardium, but there is a risk of arrhythmia as well as progression to fulminant heart failure and cardiogenic shock [2].

According to the U.S. Centers for Disease Control and Prevention, the risk of myocarditis after infection with COVID-19 is much higher, at 146 cases per 100,000. The risk is higher for males, older adults (ages 50+) and children under 16 years old. Over 80% of myocarditis cases not related to COVID-19 or COVID-19 vaccination resolve spontaneously, while 5% of patients die or require a heart transplant within 1 year of diagnosis [3].

Adults who develop myocarditis from COVID-19 have poorer outcomes than non-myocarditis COVID-19 cases, including a higher risk of death. It should be noted that myocarditis associated with SARS-CoV-2 infection is just one of several heart conditions linked to COVID-19 with outcomes that are worse than non-COVID-19 cases [4]. Cardiac MRI is the most important non-invasive cardiac modality for the diagnosis, follow-up, and risk stratification of patients with non-ischemic myocardial inflammation, with unparalleled ability to characterize myocardial tissue.

According to the 2021 American Heart Association/American College of Cardiology/American Society of Echocardiography/ American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance Guideline for the Evaluation and Diagnosis of Chest Pain, cardiac MRI is useful in distinguishing myocarditis from other causes of acute chest pain in patients with myocardial injury who have non-obstructive coronary arteries at anatomic testing [5]. Cardiac MRI is also useful in patients with suspected myocarditis or myopericarditis if there is a diagnostic uncertainty or to determine the presence and extent of myocardial or pericardial inflammation and fibrosis [6]. The aim of this study is to describe cardiac MRI findings in participants with active COVID-19 infection within three months of infection and had suspected acute myocarditis.

PATIENTS AND METHODS

This multi-centre cross-sectional study was carried out on 100 adult COVID-19 patients within 3 months of infection, of both sexes with clinical suspicion of associated myocarditis, who were recruited consequently from the Cardiovascular Medicine Department, Benha University Hospital and Kobry El Kobba Military Complex in the duration between January 2021 to December 2021. **Exclusion criteria** were patients with acute coronary syndrome, structural heart disease (valvular or congenital heart disease) and those who needed mechanical ventilator.

Participants (n=100) were subdivided into three groups based on cardiovascular magnetic resonance (CMR) findings (Group I (n= 6); no myocarditis, Group II (n= 63); suspected myocarditis, and Group III (n= 31); proved myocarditis. All patients were subjected to:

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full history taking [Personal history: (name, age, sex, residence, occupation, telephone number, smoking), Other medical history (any chronic disease such as diabetes mellitus, hypertension, and drug allergy), and clinical examination: Full general examination to exclude any systemic disease, including checking for level of consciousness and complexion (pallor, jaundice and cyanosis), vital signs (heart rate, respiratory rate, blood pressure and temperature), and signs of respiratory distress. Detailed cardiologic and chest examination included inspection, palpation, percussion, and auscultation.

Laboratory examination included blood sample (after overnight fasting, seven millilitres of venous blood were drawn under aseptic conditions, complete blood count, creatinine, C-reactive protein (CRP), serum ferritin analysis, and D-dimer level.

Electrocardiogram (ECG) assessment:

To assess ST-segment, T wave changes, and to detect any arrhythmia.

Echocardiography assessment:

The patient was prepared for the echocardiography examination by providing information about the procedure, and the patient was positioned comfortably on an examination table, typically lying on their left side. The examination was done using Philips EPIQ5, Philips IU Elite (Australia), with a cardiac 5 to 10 MHz probe transducer. The transducer was placed on the patient's chest at specific locations, known as acoustic windows, and multiple views, including parasternal, apical, and subcostal views, were acquired to obtain comprehensive images of the heart. Images of the heart were acquired in 2D mode, allowing visualization of cardiac structures and motion, color Doppler and spectral Doppler modes were used to assess blood flow patterns and velocities. Pulsed Doppler was used to assess E, A velocity and E/A ratio. Tissue Doppler was used to assess septal, lateral e velocity. Measurements of cardiac parameters, such as ejection fraction (EF), were obtained as needed. The echocardiographic images and data were analyzed, and findings were interpreted in the context of the patient's clinical history to make a diagnosis and determine the appropriate treatment plan.

Tricuspid annular plane systolic excursion (TAPSE) is a scoring system that is used with non-invasive Doppler echocardiography to determine right ventricular (RV) function. TAPSE is a widely recognized, clinically useful, and feasible marker of RV dysfunction, and it has been proven to be a valuable prognostic marker in various cardiac diseases, including heart failure. TAPSE refers to an apical four-chamber view with an M-mode ultrasound technique to measure the displacement of the tricuspid ring in the longitudinal direction of the RV. It is the most commonly used method to evaluate RV systolic functions, which is one of the most in-depth studies of echocardiographic parameters. The TAPSE measurement method is simple and has low dependence on the ultrasound image quality, requires no specific ultrasound equipment and analysis software, and has high repeatability [7].

Cardiac MRI assessment:

The patients were welcomed, and the MRI procedure was explained to them. The patients were asked to change into a hospital gown and remove any metallic objects or jewellery. Patients were examined with closed superconductive 1.5 T magnet (MAGNETOM Aera, Siemens Healthcare. Germany), the MRI machine was ensured to be in proper working condition, and the availability of appropriate MRI coils was verified. The patient was positioned on the MRI examination table, usually lying supine, careful positioning was essential to achieve optimal imaging planes and minimize motion artifacts. ECG leads were placed on the patient's chest to synchronize cardiac gating with MRI acquisition, ensuring accurate cardiac imaging. An IV line was established to administer contrast agents for dynamic cardiac imaging. The MRI technician selected the appropriate imaging planes, including short-axis, long-axis, and four-chamber views, based on the clinical indication, and parameters such as field of view, slice thickness, and acquisition timing were configured on the MRI scanner.

Cardiac gating was employed to acquire images at specific phases of the cardiac cycle, usually during end-expiration and breath-holding, and the patient was instructed to hold their breath as needed during image acquisition to reduce motion artifacts. A gadolinium-based contrast agent was injected intravenously, and post-contrast images were acquired to assess myocardial perfusion and tissue characterization. The MRI technician initiated the scan, and the patient remained still during the imaging process, and multiple sequences were acquired to capture various aspects of cardiac structure and function. After image acquisition, post-processing software was used to analyse and reconstruct the MRI data, and image reconstruction allowed for the generation of cardiac cine loops, perfusion maps, and tissue characterization. The acquired images were reviewed by a radiologist or cardiologist for interpretation and diagnosis.

The primary outcome of the study was the percentage of proved myocarditis. The secondary outcome was the association of clinical, laboratory, ECG, echocardiographic, and the cardiac MRI signs with the proved COVID-19-associated myocarditis.

Diagnosis of myocarditis according to the revised Lake Louise Criteria 2018:

In the setting of clinically suspected acute myocarditis, CMR findings were consistent with myocardial inflammation if both T1- and T2- based criteria are present, as follows:

T2-based imaging: regional or global increase in myocardial T2 signal, either on T2-weighted imaging or T2-mapping; T1-based imaging: regional or global increase in myocardial T1 signal, either on native myocardial T1-mapping, extracellular volume (ECV) quantification, or LGE imaging in a predominantly non-

ischaemic pattern; and supportive criteria include: (i) the presence of pericardial effusion in cine CMR images or high signal intensity (SI) of the pericardium in LGE images, T1-mapping or T2-mapping, and (ii) systolic LV wall motion abnormality in cine CMR images [8].

Ethical considerations: An informed written consent was obtained from the patient. The study was done after approval from the Ethical Committee, Benha University Hospitals (Approval code: RC 9-1-2021). The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Statistical analysis was done by SPSS v28 (IBM Inc., Armonk, NY, USA). Shapiro-Wilk test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) utilizing ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) were analysed utilizing the Chi-square test. Multivariate logistic regression was also used to estimate the relationship between more independent variables. A two tailed P value < 0.05 was considered statistically significant.

RESULTS

Demographic, clinical, laboratory data, ECG, echocardiography, and cardiac MRI findings of all 100 patients are represented in **table 1.**

Table 1: Data of all studied population

			Study patients (n = 100)	
Demographic data	**Age in years**	**Mean ± SD**	29.5 ± 12.1	
		Median (IQR)	24 (22-36)	
			N	**%**
	Gender	**Male**	90	90
		Female	10	10
	Residence	**Urban**	40	40
		Rural	60	60
	Comorbidities	**Hypertension**	12	12
		Diabetes mellitus	15	15
	Smoker		29	29
Clinical data	**Time of presentation of suspicious symptoms of myocarditis in days**	**Mean ± SD**	55.41 ± 14.58	
		Median (IQR)	51 (45-68)	
	Clinical presentation	**Cough**	63	63
		Myalgia	37	37
		Dyspnea	43	43
		Chest pain	26	26
		Diarrhea	22	22
		Palpitations	57	57
	ICU admission		33	33
	Medications	**Steroids**	33	33
		Antiviral	61	61
		Antibiotics	100	100
		Supportive treatment and vitamins	100	100
Laboratory data	**Platelets (*10^3/µL)**	**Median (IQR)**	13.2 (12.8 – 14.2)	
	TLC (*10^3 cells/µL)	**Median (IQR)**	7.7 (6.8 – 9.4)	
	Lymphocytes (*10^3/µL)	**Median (IQR)**	2.41 (1.17 – 3.53)	
	CRP (mg/L)	**Median (IQR)**	5.45 (1.7 – 7.2)	
	Ferritin (ng/mL)	**Median (IQR)**	229 (153 - 748)	
	Creatinine (mg/dL)	**Median (IQR)**	0.9 (0.8 – 1.1)	
	D-Dimer		36	36
ECG finding	**Heart Rate**	**Mean + SD**	88.7 ± 18.5	
	Rhythm	**Regular sinus**	91 (91%)	
		Others	9 (9%)	
	PR duration	**Normal**	94 (94%)	
		No P wave	6 (6%)	
	QT	**Normal**	94 (94%)	
		Shortened	6 (6%)	
	QRS duration	**Normal**	97 (97%)	
		Prolonged	3 (3%)	

			Study patients (n = 100)
	ST segment	**Normal**	54 (54%)
		Abnormal	46 (46%)
	T wave	**Normal**	58 (58%)
		Abnormal	42 (42%)
Echocardiography findings	**IVSD (mm)**	**Mean ± SD**	7.62 ± 0.61
		Median (IQR)	7.7 (7.1 – 8.2)
	LVPWD (mm)	**Mean ± SD**	7.66 ± 0.44
		Median (IQR)	7.45 (7.3 – 8.1)
	LVEDV (mL)	**Mean ± SD**	49.55 ± 5.32
		Median (IQR)	47.8 (46 – 50.4)
	LVESV (mL)	**Mean ± SD**	31.75 ± 4.08
		Median (IQR)	31 (29 – 33.4)
	EF (Modified Simpson, %)	**Mean ± SD**	57.81 ± 12.14
		Median (IQR)	61.24 (51.42 – 66.67)
	IVC diameter (cm)	**Mean ± SD**	1.26 ± 0.52
		Median (IQR)	1.1 (0.8 – 1.7)
	LAVI (mL/m^2)	**Mean ± SD**	20.7 ± 7.34
		Median (IQR)	20.5 (17.15 - 23)
	TAPSE (mm)	**Mean ± SD**	19.36 ± 3.13
		Median (IQR)	19.9 (16.2 – 21.9)
	E velocity (cm/s)	**Mean ± SD**	57.88 ± 12.23
		Median (IQR)	55 (47 - 64)
	A velocity (cm/s)	**Mean ± SD**	54.24 ± 14.24
		Median (IQR)	55 (41 - 66)
	Pulsed wave Doppler septal e (cm/s)	**Mean ± SD**	9.17 ± 1.95
		Median (IQR)	8.3 (7.8 – 11.3)
	Pulsed wave Doppler lateral e (cm/s)	**Mean ± SD**	14.36 ± 3.55
		Median (IQR)	14 (12 – 16.35)
	E/A	**Mean ± SD**	1.15 ± 0.35
		Median (IQR)	1.31 (0.76 – 1.47)
	RSWMA		39 | 39
Cardiac MRI findings	**LVEF, %**	**Mean ± SD**	55.98 ± 11.91
		Median (IQR)	59.7 (45 – 62.2)
	LVEDV, ml	**Mean ± SD**	76.99 ± 18.17
		Median (IQR)	78.1 (62 – 88.5)
	LVESV, ml	**Mean ± SD**	38.7 ± 16.7
		Median (IQR)	38.2 (23 – 45.9)
	RVEF, %	**Mean ± SD**	48.09 ± 11.08
		Median (IQR)	54.1 (36.8 - 57)
	T2 relaxation time	**> 60 msc**	70 (70%)
		< 60 msc	30 (30%)
	LGE		55 (55%)
	Affected segment	**Apical**	57 (57%)
		Mid-ventricular	49 (49%)
		Basal	6 (6%)
	Pericardial enhancement		56 (56%)
	Pericardial effusion > 10 mm		6 (6%)

Data are presented as mean ± SD, median (IQR), or frequency (%). IQR: Interquartile range, ICU: Intensive care unit, TLC: Total leukocyte count, CRP: C reactive protein, IQR: Interquartile range, ECG: electrocardiogram, QT: Q and T waves, ST: the part of an electrocardiogram between the QRS complex and the T wave, IVSD: Interventricular septum thickness, LVPWD: Left ventricular posterior wall, LVEDV: left ventricular end diastolic volume, LVESV: Left ventricular end-systolic volume, EF: Ejection fraction, IVC: Inferior vena cava, LAVI: Left atrial volume index, TAPSE: Tricuspid annular plane systolic excursion, RSWMA: Regional wall motion abnormality, RVEF: right ventricular ejection fraction, LGE: Late gadolinium enhancement.

Patients with proved myocarditis had significantly lower prevalence of myalgia and higher prevalence of dyspnea and palpitations. The prevalence of chest pain, treatment with steroids, CRP and ferritin levels were significantly higher in patients with suspected and proved myocarditis than those without myocarditis. While mean Hb level was significantly lower in patients with proved myocarditis compared to those with suspected myocarditis. There were no statistically significant differences among the studied groups regarding age, gender hypertension, DM, cough, diarrhea, need for ICU admission, antiviral drugs, TLC, lymphocytes count, platelet, creatinine, and D-dimer level **(Table 2)**.

Table 2: Comparison of the participants' demographic, clinical, and laboratory data according to the presence of myocarditis

		No myocarditis (N=6)		Suspected myocarditis (N=63)		Proved myocarditis (N=31)		P
Demographic data								
Age in years		34 ± 8.76		30.675 ± 13.35		26.26 ± 9.26		0.163
		N	**%**	**N**	**%**	**N**	**%**	p
Gender	**Male**	6	100.0%	56	88.9%	28	90.3%	0.685
	Female	0	0.0%	7	11.1%	3	9.7%	
Residence	**Urban**	3	50.0%	25	39.7%	12	38.7%	0.872
	Rural	3	50.0%	38	60.3%	19	61.3%	
Comorbidities	**Hypertension**	0	0.0%	9	14.3%	3	9.7%	0.525
	DM	0	0.0%	9	14.3%	6	19.4%	0.462
Smoker		0	0.0%	16	25.4%	13	41.9%	0.068
Clinical data								
Time of presentation in days								
Mean ± SD		**50 ± 6.57**		60.17 ± 15.66		46.77 ± 7.54		<0.001*
Clinical presentation	**Cough**	**6**	100.0%	39	61.9%	18	58.1%	0.144
	Myalgia	6	100.0%	25	39.7%	6	19.4%	<0.001*
	Dyspnea	3	50.0%	16	25.4%	24	77.4%	<0.001*
	Chest pain	0	0.0%	23	36.5%	3	9.7%	0.007*
	Diarrhea	3	50.0%	12	19.0%	7	22.6%	0.216
	Palpitations	3	50.0%	27	42.9%	27	87.1%	<0.001*
ICU admission		0	0.0%	23	36.5%	10	32.3%	0.191
Medications	**Steroids**	0	0.0%	20	31.7%	3	9.7%	0.022*
	Antiviral	3	50.0%	44	69.8%	14	45.2%	0.059
	Antibiotics	6	100.0%	63	100.0%	31	100.0%	--
	Supportive treatment and vitamins	6	100.0%	63	100.0%	31	100.0%	--
Laboratory data								
Hb (g/dL)		13.25 ± 0.6		13.58 ± 1.3#		12.77 ± 0.9*		0.007*
TLC (*10^3 cells/µL)		4.75 ± 1.37		8.31 ± 3.24		8.44 ± 1.46		0.082
Platelets (*10^3/µL)		301 ± 10.3		328.8 ± 106.9		324.6 ± 94.6		0.112
Lymphocytes (*10^3/µL)		3.1 ± 0.3		2.2 ± 1.3		2.4 ± 0.8		0.137
CRP (mg/L)		**2.35 (1.7 – 3)**		**3.3 (1.6 – 6.4)**		7.2 (7.1 – 7.4) *		<0.001*
Ferritin (ng/mL)		**146.5 (28 - 265)**		**213 (153 - 748)**		587 (248 - 775) *		0.027*
Creatinine (mg/dL)		1.1 ± 0.11		0.99 ± 0.2		0.92 ± 0.23		0.115
D-Dimer		0	0.0%	23	36.5%	13	41.9%	0.145

Data are presented as mean ± SD, median (IQR), or frequency (%). IQR: Interquartile range, ICU: Intensive care unit, TLC: total leukocyte count, CRP: C reactive protein, *: significant P value.

There was significantly higher prevalence of prolonged QRS duration in the patients with proved myocarditis and significantly higher prevalence of abnormal ST segment in patients with suspected and proved myocarditis. According to the patients' echocardiographic findings, participants with proved myocarditis had significantly higher LVESV, lower TAPSE, septal e, lateral e, and E/A ratio compared to those with suspected myocarditis and those without myocarditis. Notably, participants with proved myocarditis had a significantly higher LAVI, and A velocity compared to those with suspected myocarditis. There was also significantly higher prevalence of RSWMA in patients with suspected and proved myocarditis.

According to the cardiac MRI findings, the LVEF was significantly lower in participants with proved myocarditis compared to those with suspected myocarditis and those without myocarditis. Patients with proved myocarditis had significantly higher LVEDV, LVESV, and the presence of apical and mid-ventricular involvement. No significant difference between groups regarding heart rate or rhythm, corrected QT interval, abnormal T wave, RVEF, pericardial enhancement, and pericardial effusion > 10 mm **(Table 3)**.

Table 3: Comparison of the participants' ECG, echocardiography, and cardiac MRI findings according to the presence of myocarditis

		No myocarditis (N=6)		Suspected myocarditis (N=63)		Proved myocarditis (N=31)		P
ECG findings								
Rate		78.5 ± 3.8		89 ± 17.9		90.1 ± 21		0.366
		N	**%**	**N**	**%**	**N**	**%**	
Regularity	**Regular**	6	100.0%	57	90.5%	28	90.3%	0.729
	Irregular	0	0.0%	6	9.5%	3	9.7%	
Rhythm	**Sinus**	6	100.0%	57	90.5%	28	90.3%	0.729
	Others	0	0.0%	6	9.5%	3	9.7%	
QTc	**Normal**	6	100.0%	60	95.2%	28	90.3%	0.523
	Shortened	0	0.0%	3	4.8%	3	9.7%	
QRS duration	**Normal**	6	100.0%	63	100.0%	28	90.3%	0.032*
	Prolonged	0	0.0%	0	0.0%	3	9.7%	
ST segment	**Normal**	6	100.0%	34	54.0%	14	45.2%	0.048*
	Abnormal	0	0.0%	29	46.0%	17	54.8%	
T wave	**Normal**	6	100.0%	34	54.0%	18	58.1%	0.92
	Abnormal	0	0.0%	29	46.0%	13	41.9%	
Echocardiography findings								
IVSD		7.45 ± 0.27		7.64 ± 0.61		7.6 ± 0.64		0.743
LVPWD		7.65 ± 0.44		7.66 ± 0.48		7.66 ± 0.44		0.993
LVEDV		46.7 ± 1.5		49.3 ± 4.8		50.7 ± 6.5		0.176
LVESV		27.7 ± 0.49		32.3 ± 4.2		31.4 ± 3.9		0.022*
EF (Modified Simpson)		65.9 ± 1.5		58.7 ± 12.4		54.4 ± 11.9		0.061
IVC Diameter		1.2 ± 0.55		1.24 ± 0.52		1.31 ± 0.54		0.801
LAVI		16 ± 9.3		20.6 ± 3.1		22 ± 5.6		<0.001*
TAPSE		23.7 ± 0.55		19.4 ± 3.4		18.4 ± 2		<0.001*
E velocity		63.5 ± 9.3		56.7 ± 14		59 ± 8		0.367
A velocity		45.5 ± 3.8		52 ± 14.7		61.1 ± 15.5		0.006*
Septal e		10.3 ± 1.4		9.2 ± 2		8.5 ± 1.6		0.003*
Lateral e		19 ± 0.77		14.6 ± 3.3		13 ± 3.6		<0.001*
E/A		1.4 ± 0.09		1.2 ± 0.4		1.04 ± 0.3		0.042*
RSWMA		0	0.0%	22	34.9%	17	54.8%	0.023*
Cardiac MRI findings								
LVEF, %		63.8 ± 2.8		57.3 ± 12		51.7 ± 11.7		0.024*
LVEDV, ml		59.3 ± 3.1		76.3 ± 20.4		87.9 ± 10.3		0.004*
LVESV, ml		21.4 ± 0.38		39.1 ± 18.1		41.2 ± 13.1		0.025*
RVEF, %		50.9 ± 3.7		49.4 ± 10		44.9 ± 13.4		0.146
Affected segment	**Apical**	0	0.0%	33	52.4%	24	77.4%	0.001*
	Mid-ventricular	0	0.0%	32	50.8%	17	54.8%	0.044*
	Basal	0	0.0%	9	14.3%	7	22.6%	0.320
Pericardial enhancement		3	50.0%	40	63.5%	13	41.9%	0.135
Pericardial effusion > 10 mm		0	0.0%	3	4.8%	3	9.7%	0.523

Data are presented as mean ± SD, or frequency (%). ICU: intensive care unit, TLC: Total leukocyte count, CRP: C reactive protein, IVSD: Interventricular septum thickness, LVPWD: Left ventricular posterior wall, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end-systolic volume, EF: Ejection fraction, IVC: Inferior vena cava, LAVI: Left atrial volume index, TAPSE: Tricuspid annular plane systolic excursion, RSWMA: Regional wall motion abnormality.

A univariate binary logistic regression analysis that included all the clinically relevant statistically parameters showed that the statistically significant predictors for myocarditis were myalgia, Hb value, TAPSE, septal e, lateral e, E/A ratio, and RSWMA, these parameters had a significant inverse association ($p < 0.001$) with a reduced likelihood (0.114) of myocarditis. While chest pain, palpitations, steroids, ferritin, LAVI, and A velocity showed a significant positive association with increase in the likelihood of myocarditis.

Implementing the univariate analysis significant predictors in a multivariate analysis showed that the parameters that still significant were chest pain, higher ferritin level, and high LAVI. They showed a strong positive association with an extraordinarily high likelihood of myocarditis **(Table 4).**

Table 4: Univariate and multivariate binary logistic regression analysis for the predictors of COVID-19 related myocarditis

	B	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)	
					Lower	Upper
Univariable analysis						
Myalgia	-2.172	0.588	<0.001	0.114	0.036	0.361
Chest pain	1.54	0.659	0.019	4.667	1.283	16.98
Palpitations	1.224	0.515	0.018	3.399	1.239	9.327
Steroids	1.338	0.663	0.044	3.81	1.039	13.968
Hb	-0.602	0.212	0.005	0.548	0.361	0.831
Ferritin	0.001	0	0.04	1.001	1	1.002
LAVI	0.129	0.04	0.001	1.879	0.813	1.95
TAPSE	-0.146	0.073	0.045	0.864	0.749	0.997
A velocity	0.046	0.016	0.003	1.047	1.015	1.08
Septal e	-0.414	0.136	0.002	0.661	0.506	0.863
Lateral e	-0.167	0.068	0.015	0.847	0.741	0.968
E/A	-1.277	0.621	0.04	0.279	0.083	0.942
RSWMA	-0.953	0.444	0.032	0.385	0.162	0.92
Multivariate analysis						
Chest pain	8.08	3.369	0.016	3227.854	4.379	2379061.41
Ferritin	0.008	0.002	<0.001	1.008	1.004	1.012
LAVI	0.384	0.112	<0.001	0.681	0.547	0.849
Constant	-6.881	6.423	0.284	0.001		

Hb: Hemoglobin, LAVI: Left atrial volume index, TAPSE: Tricuspid annular plane systolic excursion, RSWMA: regional wall motion abnormality.

DISCUSSION

Early in the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, individual case reports and smaller case series suggested that coronavirus-induced disease 2019 (COVID-19) can lead to deterioration of cardiac function in patients with previous cardiovascular diseases [2]. Previous study used cardiovascular magnetic resonance (CMR) imaging, which is considered the gold standard for non-invasive myocarditis diagnosis [9].

In clinical practice we are often confronted with post-COVID patients without previous cardiac diseases who suffer from persistent thoracic complaints, exertional dyspnea and/or exercise intolerance, even months after their SARS-CoV-2 infection. Data specifically for this increasing group of patients is scarce.

In this study, we used strict criteria, requiring fulfillment of the 2018 Lake Louise criteria to diagnose myocarditis [10], implied that a significant majority of the patients exhibited CMR findings suggestive of myocardial involvement, although the diagnosis had not been conclusively confirmed.

On the other hand, our study showed that a considerable portion of the study population, comprising 31%, fell into the category of "Proved myocarditis." This classification indicates that these patients exhibited CMR findings that not only raised suspicion but also met the criteria for a definitive diagnosis of myocarditis, in accordance with the 2018 Lake Louis criteria. This subgroup represents a significant proportion of the study cohort where myocarditis was confirmed based on CMR evaluation.

When we compare our findings with those of other studies, such as the one conducted by **Sawyer *et al.*** [11] who reviewed cardiac MRIs for 11 patients vaccinated for COVID-19, we observe some variations in the rates of confirmed myocarditis. They reported patients with suspected myocarditis following COVID-19 vaccination. This suggests that myocarditis in this specific context may have a higher confirmation rate, possibly due to the unique circumstances of post-vaccination myocarditis.

In contrast, another study by **Breitbart *et al.*** [12] reported a lower confirmation rate, with only one confirmed case of myocarditis out of 56 suspected cases after COVID-19 infection. The study of **Magdalena *et al.*** [13] explained that they included all patients discharged after COVID-19 pneumonia regardless the presence of signs suggesting myocarditis.

In the present study, regarding the time of presentation, there was statistically significant difference between groups regarding time of presentation as patients with proved myocarditis exhibited the shortest mean time of presentation ($p < 0.001$).

In this context, it was described that COVID-19-related myocarditis can present at different time intervals after COVID-19 infection or vaccination. One study conducted by **Samimisedeh *et al.*** [14] performed a systematic review and meta-analysis aimed to summarize cardiac MRI findings in COVID-19 vaccine-related myocarditis. Based on meta-analysis of

102 studies (n = 468 patients), they found that myocarditis occurred within 1 month after infection, while another study by **Janga *et al.*** [15] reported a rare case of delayed eosinophilic myocarditis following COVID-19 mRNA vaccination.

In our study, when examining the clinical presentation, notable differences emerged across the groups. For symptoms such as "Cough," "Myalgia," and "Palpitations," the proportions of patients experiencing these symptoms were high in all groups. However, significant differences were observed in the presence of "Dyspnea". Patients with "Proved myocarditis" had a significantly higher percentage of dyspnea prevalence.

The association between COVID-19-related myocarditis and dyspnea is likely attributed to the inflammatory impact of the SARS-CoV-2 virus on the heart muscle. Myocarditis, characterized by heart muscle inflammation, can impair cardiac function, leading to symptoms like dyspnea, as the heart struggles to meet the body's oxygen demands. Extensive clinical evidence, coupled with reports of COVID-19 patients presenting with these symptoms and later being diagnosed with myocarditis [1, 16], supports the link between COVID-19 infection, myocarditis, and dyspnea.

In the present study, the use of medications also displayed significant differences. Notably, the administration of "Steroids" was significantly higher among patients with "Suspected myocarditis" (31.7%) and "Proved myocarditis" (9.7%). Our finding is close to the study of **Ammirati *et al.*** [17], which found significantly higher treatment with steroids in patients with suspected and proved myocarditis.

In the current study, concerning the laboratory parameters, hemoglobin levels showed a significant difference, with patients in the "Proved myocarditis" group had a significantly lower mean Hb levels. This can be attributed to the inflammatory response associated with myocarditis since inflammation can disrupt the production and lifespan of red blood cells [18].

In our study, C-reactive protein (CRP) and ferritin levels also exhibited substantial variance, where the "Proved myocarditis" group had a notably higher median value. In line with our findings, the study of **Urban *et al.*** [19] endorsed that CRP and ferritin were significantly associated with COVID-19 myocarditis. The association between elevated C-reactive protein (CRP) and ferritin levels and myocarditis are particularly in the context of COVID-19.

Among the significant findings in this study, it's worth noting that patients with "Proved myocarditis" exhibited a notably higher prevalence of prolonged QRS duration (9.7%) compared to those without myocarditis or with "Suspected myocarditis". This suggests that prolonged QRS duration may be a distinctive ECG characteristic associated with confirmed myocarditis. Additionally, "Proved myocarditis" patients showed a higher prevalence of abnormal ST segments. These ECG abnormalities may serve as important diagnostic indicators for myocarditis. The plausible explanation for these findings is that inflammation can disrupt the normal conduction of electrical impulses in the heart, leading to delays in the QRS complex on the ECG. Secondly, abnormal ST segments are often observed in myocarditis because inflammation can cause injury to the myocardium. ST segment elevation or depression can occur, indicating myocardial damage.

Kaliyaperumal *et al.* [20] in their cross-sectional study **"**reported that ST-T abnormalities are commonly observed in patients with COVID-19, although their association with myocardial injuries is still under dispute.

In the context of echocardiography findings, our study revealed several significant associations when comparing participants based on the presence of myocarditis. Notably, individuals in the "Proved myocarditis" group exhibited distinctive alterations in cardiac parameters. Left ventricular end-systolic volume (LVESV) was significantly higher in this group, signifying possible impairment in systolic function or increased cardiac afterload. Furthermore, the "Proved myocarditis" group demonstrated a lower left atrial volume index (LAVI), indicating potential left atrial dysfunction or remodeling resulting from myocarditis. Tricuspid annular plane systolic excursion, a measure of right ventricular function, was notably reduced in individuals with "Proved myocarditis". The "Proved myocarditis" group displayed a higher A velocity, which suggests increased atrial contribution to ventricular filling, potentially indicating diastolic dysfunction. Our study also revealed significantly lower values for septal e and lateral e, which are indicative of myocardial relaxation, in the "Proved myocarditis" group. Consistently, the E/A ratio, another parameter associated with diastolic function, was notably lower in the "Proved myocarditis" group. Lastly, the presence of RSWMA was significantly higher among those with "Proved myocarditis". These regional abnormalities are consistent with localized myocardial damage or dysfunction often observed in myocarditis cases.

Overall, these findings align with the notion that myocarditis can lead to compromised cardiac contractility or increased workload on the heart.

In alignment with our results, **Mahmoud-Elsayed *et al.*** [21] performed a research to characterize the echocardiographic phenotype of patients with COVID-19 pneumonia. They included 74 patients admitted with COVID-19, the chief abnormalities were right ventricle (RV) dilatation (41%) and RV dysfunction (27%).

In discrepancy with our findings, **Yar *et al.*** [22] study found that only two COVID-19 patients (7%) had myocarditis scar combined with left ventricular dysfunction and myocardial edema was not detected in any participant.

In the present study, we examined cardiac MRI findings to assess the impact of myocarditis on various cardiac parameters. Our findings revealed several

significant associations between myocarditis presence and cardiac MRI parameters.

Specifically, this study showed that the "Proved myocarditis" group exhibited significantly lower left ventricular EF (LVEF)". This reduction in LVEF suggests impaired systolic function in individuals with confirmed myocarditis, indicating a compromised ability of the heart to pump blood efficiently. Furthermore, left ventricular end-diastolic volume (LVEDV) was significantly higher in the "Proved myocarditis" group, indicating increased volume within the left ventricle during diastole. This finding suggests that myocarditis may lead to ventricular dilation, potentially as a result of inflammation and myocardial damage. LVESD was also significantly higher in individuals with "Proved myocarditis". Elevated LVESD can indicate impaired systolic function and further supports the notion of compromised cardiac performance in these patients.

In terms of affected cardiac segments, the present study showed that the "Proved myocarditis" group exhibited a significantly higher prevalence of involvement in the apical and mid-ventricular segments compared to other groups. This regional distribution of myocardial involvement may have clinical implications for patient management and prognosis.

These findings were also reported in the study of **Urban *et al.* [19]**, which included regression analysis to identify the clinical, laboratory, and echocardiographic parameters that predict the occurrence of myocarditis.

We recommended that cardiac imaging, utilizing a combination of ECG, echocardiography, and cardiac MRI, is crucial for a comprehensive evaluation of myocardial involvement. Specific attention should be given to parameters such as LAVI, which emerged as a significant predictor of myocarditis. Multidisciplinary approach: Collaborative efforts between cardiologists, infectious disease specialists, and other relevant healthcare professionals are essential for the holistic management of post-COVID patients. This approach ensures a comprehensive understanding of the diverse clinical manifestations and facilitates tailored interventions. Long-term follow-up: Longitudinal studies with extended follow-up periods are needed to monitor the evolution of cardiac sequelae in post-COVID patients. Understanding the long-term implications on cardiac health will contribute to the development of appropriate guidelines for ongoing care. Patient education: Providing education to patients and healthcare providers about the potential cardiac implications of COVID-19 is crucial. This includes raising awareness about symptoms indicative of myocarditis and the importance of seeking timely medical attention. Further research: Continuous research efforts are necessary to expand our knowledge of the pathophysiology and optimal management of COVID-19-associated myocarditis. Large-scale studies and international collaborations can enhance our understanding and contribute to evidence-based guidelines.

CONCLUSIONS

Active COVID-19 infection within three months was associated with distinct cardiac MRI findings suggestive of high prevalence of suspected and proved myocarditis. The findings underscore the complexity of cardiac involvement in post-COVID patients.

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