

Diffused Myocardial Inflammation in COVID-19 Associated Myocarditis Detected by Cardiac Magnetic Resonance Imaging in Post-COVID Patients

Abdul Rehman Jokhio, Muhammad Nadir Khan, Nazish Saeed, Mehtab Jokhio, Jahanzab Ali, Sobia Mehreen, Abdul Hameed Siddiqui, Ghulam Rasool Maken, Mohsin Saif, Syed Khurram Shahzad

Armed Forces Institute of Cardiology/National Institute of Heart Diseases (AFIC/NIHD)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the frequency of myocarditis in patients recovered from COVID-19 infection.

Study Design: Analytical Cross-sectional study.

Place and Duration of Study: Cardiac Magnetic Resonance Imaging Department, Armed Forces Institute of Cardiology/National Institute of Heart Disease (AFIC/NIHD), Rawalpindi Pakistan, from Jul 2020 till Apr 2022.

Methodology: All patients who underwent Cardiac Magnetic Resonance Imaging after recovery from COVID-19 were enrolled. Non-probability consecutive sampling technique was used for sample selection and was calculated on the basis of G-power. Data of patients fulfilling the inclusion criteria was selected. All PCR positive cases of COVID-19 who recovered from COVID-19 and completed their 12 days of isolation not exceeding 60 days of 1st Polymerase chain reaction positive, and who have any symptoms of shortness of breath, fatigue and chest pain with reduced left ventricular ejection fraction (LVEF) on 2D-echocardiogram were included in the study. Data was recorded, stored, and analyzed by using SPSS version-21. Quantitative data was reported as Mean±SD. Categorical variables were reported as frequency and percentage. To determine the association between different variables Chi square test was used.

Results: A total 83 patients were included in this study who recovered from COVID-19 and underwent Cardiovascular magnetic resonance. Mean age of the patients was 39.17±12.9 years. 67(80.72%) were male while 16(19.28%) were females. 50(60%) had myocarditis after recovery from COVID-19. This study showed statistically significant association of all the Cardiovascular magnetic resonance imaging findings with Myocarditis ($p<0.05$) at 95% confidence interval and 5% margin of error.

Conclusion: Early detection of COVID-19 related myocarditis will help in better management of patient. In such patients, cardiac Magnetic Resonance Imaging is the modality of choice, since it allows for noninvasive assessment of myocardial edema and fibrosis, as well as therapeutic guidance and improved patient outcomes.

Keywords: Cardiac Magnetic Resonance Imaging, COVID-19, Myocarditis.

How to Cite This Article: Jokhio AR, Khan MN, Saeed N, Jokhio M, Ali J, Mehreen S, Siddiqui AH, Maken GR, Saif M, Shahzad SK. Diffused Myocardial Inflammation in COVID-19 Associated Myocarditis Detected by Cardiac Magnetic Resonance Imaging in Post-COVID Patients. *Pak Armed Forces Med J* 2022; 72(Suppl-3): S418-422. DOI: <https://doi.org/10.51253/pafmj.v72iSUPPL-3.9524>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

SARS-CoV-2 causes Coronavirus Disease 2019 (COVID-19), an infectious disease. In December, 2020 the first known case was reported in Wuhan city of China.¹ Since then, the disease spread worldwide and became a pandemic. Fever, headache, cough, breathing difficulty, exhaustion, and loss of taste and smell were common symptoms of COVID-19.² 81% of symptomatic patients developed only mild to moderate symptoms (up to mild pneumonia), while 14% developed severe symptoms (dyspnea, hypoxia or more than 50% involvement of lungs on imaging) and 5% of patients suffered critical symptoms (shock, respiratory failure, or multi organ dysfunction). Despite being a minor cause of all viral myocarditis cases, human

coronaviruses have been linked to myocarditis in patients of all age groups.³ Reports show an association of multiple organs including heart.⁴ The viral RNAs of Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, which are close relatives of SARS-CoV-2, were found in the heart tissues of infected animals, suggesting that these coronaviruses possess cardio tropism. Raised serum troponin levels are often allied with acute respiratory infections and sepsis, which is a reason of mortality even after recovery.⁵ Similarly, in hospitalized COVID-19 patients, serum troponin levels are elevated, and 30% cases reported cardiac injury which is associated with adverse outcomes.⁶ 40% deaths were caused due to this.⁷ Troponin rise have been reported in multiple disease mechanisms like acute coronary syndrome, arrhythmias, myocarditis, underlying cardiovascular disease and systemic inflammatory syndrome.

Correspondence: Dr Abdul Rehman Jokhio, Resident Cardiologist, Armed Forces Institute of Cardiology, National Institute of Heart Diseases (AFIC/NIHD), Rawalpindi, Pakistan

Myocardial injury related to COVID-19 is a common complication and has dire implications on prognosis of disease. The advanced stage of COVID-19 associated with systemic hyper inflammation likely contributes to myocardial injury. The non-invasive imaging modality includes echocardiogram being less sensitive so, Cardiac magnetic resonance imaging (CMR) can be used preferably for the diagnosis of increased troponin from unclear etiology,⁸ and evaluation of acute myocarditis, enabling risk stratification and prognostication. COVID-19 related myocarditis is one of important complication and early detection will help in better management of patient.

The COVID patients have been reported to have myocarditis as a possible clinical presentation or complication. Significant proportion of recovered patients has evidence of ongoing myocardial inflammation. Although the long-term consequences of this finding are uncertain, COVID-19 individuals are likely to have persistent residual cardiac damage and possibly heart failure in the long run. The diagnostic tests include; echocardiography and CMR.

During the recent decade, CMR (where available) has become gold standard non-invasive diagnostic imaging tool in cardiovascular medicine but only in tertiary care centers of patients with evidence for acute non ischemic myocardial injury. Suspected myocarditis is one of the most frequent indications for CMR scans and, in Europe, represents about one third of CMR referrals.⁹

In patients with suspected myocarditis, CMR is the most complete and accurate diagnostic tool available, with no deterministic and minor stochastic effects. It allows for the verification or exclusion of myocardial inflammation and reversible/irreversible injury, as well as the assessment of myocarditis activity and severity. The high specificity and positive predictive value of CMR, especially when employing the Lake Louise Criteria, are its key advantages. As a result, it's particularly well-suited to verifying suspected myocarditis in patients with a high pre-test score.

The prognostic significance of these findings needs more information, and for the follow up and monitoring of residual abnormalities CMR (Cardiac magnetic resonance) mapping techniques should be considered as first line investigation to assess post COVID myocardial injury. Parametric T1 and T2 maps are the quantitative evaluation of infarction and edema respectively. This study will be helpful for medical practitioners. Regardless of knowing this possibility

among physicians, there is lack of information about prevalence, mechanism, diagnosis, prognosis and treatment of myocarditis in the context of COVID-19. A contemporary study from Wuhan has stated that more than half of recovered COVID-19 patients with stand cardiac edema and fibrosis.¹⁰ No literature has been found on role of CMR for screening of myocarditis in recovered patients of COVID-19 in context of Pakistan therefore, the purpose of present research is early identification or screening of myocarditis by using CMR in post COVID-19 patients in Pakistan. Aim of current study was to determine the frequency of myocarditis in patients recovered from COVID-19 infection.

METHODOLOGY

This was a single center cross-sectional study.

Sample Size: We recruited all COVID-19 patients who underwent CMR with a suspicion of myocarditis from July 2020 till April 2022. Non-probability consecutive sampling technique was used for sample selection.

The study was carried out after approval by Institutional Review Board and Hospital Ethical and Research Committee (IERB letter # 9/2/R&D/2022/152).

Inclusion Criteria: Used was: (1) All PCR positive cases of COVID 19 who recovered from COVID 19 and completed their 12 days of isolation not exceeding 60 days of 1st PCR positive, (2) who have any symptoms of shortness of breath, fatigue and chest pain with reduced left ventricular ejection fraction (LVEF) on 2D echocardiogram.

Exclusion Criteria: Included patients with: (1) Previous history of coronary artery disease (CAD), (2) pacemaker placement, (3) previous myocardial infarction, (4) uncontrolled hypertension, (5) valvular dysfunction, (6) previous atrial fibrillation, (7) known cardiomyopathy, (8) previous myocarditis, (9) previous heart failure, (10) absolute contraindication for contrast enhanced magnetic resonance study, (11) unable to cooperate with breath holding, (12) cannot undergo CMR examination (claustrophobic).

Cardiovascular magnetic resonance scanning protocol; Siemens 3.0 Tesla Magnetom Skyra scanner was used to scan the patients. Scanning protocol consists of functional images, morphological assessment images, parametric mapping and delayed enhancement images. Standard long axis images are of single slice while, multiple almost 9 slices were obtained in short axis view covering the whole heart from base to apex. Native T1 and T2 mapping was performed in

short axis view with 3 slices at base, mid and apex. Early and late gadolinium enhancement (EGE & LGE) images were taken in both short and long axis view. Short axis view of EGE and LGE is similar to cine short axis while in long axis we acquired 4 slices of each 2, 3 and 4 chamber view.

All images were obtained in breath hold with ECG gating, some sequences with retrospective gating and some with prospective gating. Intravenous contrast (Gadovist 1.0 mmol/ml, Bayer Healthcare, Berlin, Germany) was given with a dose of 0.15 mmol/kg and images were acquired after 10 mins of contrast administration.

- SSFP cine images: Voxel size was 1.5x1.5x6.0mm³, TR was 37.18 while TE was 1.16ms with a flip angle of 80°, slice thickness was 6.0mm and 25 calculated phases.
- Native T1 maps: voxel size was 1.4x1.4x6.0mm³, TR and TE was set to be at 279.12ms and 1.1ms respectively, flip angle of 35°, TI of 180ms, and 1 trigger pulse with a delay of 497ms.
- Parametric T2 map: voxel size was 2.1x2.1x6.0 mm³, TR and TE was set at 203.95ms and 1.29ms respectively, flip angle of 12°, 3 T2 preps at 0,30,-55ms, and a trigger pulse with trigger delay of 596ms.
- High resolution LGE: voxel size was 1.4x1.4x6.00 mm³ with TR, TE and flip angle of 800ms, 2.75ms and 25° respectively. Time to invert (TI) depends upon scout image usually ranging from 230-330ms. 2 trigger pulses were applied with trigger delay of 0ms.
- Overview LGE: 1.8x1.8x6.0mm³ was the voxel size with TR of 700ms, TE of 1.09ms and a flip angle of 55°. Trigger pulses were two with a delay of 0ms.

CMR post processing; Images were analyzed on syngovia software. LV function and volumes were calculated on SSFP cine images. Native T1 and T2 times were estimated by drawing an ROI (region of interest) on the myocardium. Enhancement pattern either subendocardial, mid myocardial and subepicardial or transmural were assessed by the consultant Cardiologists on phase sensitive inversion recovery (PSIR) late gadolinium enhancement images.

Data analysis procedure; Descriptive statistics were applied with the help of SPSS ver 21. Continuous variables were reported as Mean±SD. Categorical variables were reported as frequency and percentage. Association between the variables was find out by

using Chi Square/Fischer Exact test by taking *p*-value <0.05 as significant.

RESULTS

Total 83 patients were included in this study who recovered from COVID-19 and underwent CMR. Mean age of the patients was 39.17±12.9 years. Mean height and weight was 170.37±8.2cm and 75.42±15.7 kg respectively in Table-I. Sixty seven (80.7%) were male while 16(19.3%) were females as shown in Figure-1.

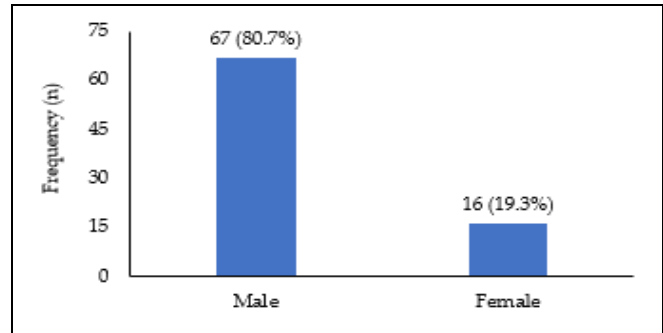


Figure-1: Gender based frequency of study population

Table-I shows the frequency of myocarditis and ST changes. Total of 50(60%) patients had myocarditis after COVID-19 recovery.

Table-I: Statistics of Demographics, Myocarditis and ST-Changes

Variable	Mean±SD
Age (years)	39.17±12.99
Height (cm)	170.37±8.23
Weight (kg)	75.42±15.73
BMI (kgm-2)	26.08±5.76
LV EDV (ml)	158.4±60.63
ST changes	41±49.4
Myocarditis	50(60%)

Forty two (50.6%) cases of myocarditis were males while only 8 (9.6%) were females that showed male population was more effected by post COVID-19 myocarditis, as shown in Figure-2.

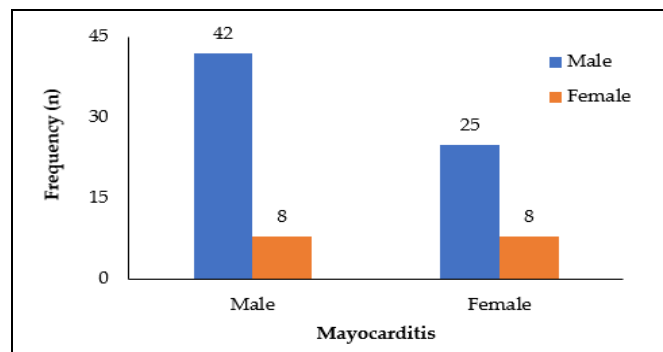


Figure-2: Gender distribution with Myocarditis

The Pearson’s Chi Square test results presented in given Table-II is showing statistically significant association of all the findings (CMR-EF, T1 MAP, T2 MAP and LGE) with Myocarditis ($p < 0.05$) except ST-changes ($p > 0.05$) at 95% confidence interval and 5% margin of error.

Table-II: Association of multiple CMR Variables and ECG changes with Myocarditis

Variables	Myocarditis		p-value
	Yes	No	
CMR (EF%)			
<40	13	5	<0.0001
41-50	14	5	
51-60	9	20	
>60	0	17	
T1 MAP (EF%)			
<1100	0	1	0.005
1100-1300	24	43	
>1300	12	3	
T2 MAP (EF%)			
30-45	24	45	0.001
>45	12	2	
LGE			
Yes	33	7	<0.0001
No	3	40	
ST Changes			
Yes	22	19	0.62
No	14	28	

DISCUSSION

Current study showed statistically significant association of all the findings (CMR-EF, T1 MAP, T2 MAP and LGE) with Myocarditis (p -value < 0.05). Many studies supporting the given result have been discussed in following sections.

The COVID patients have been reported to have myocarditis as a possible clinical presentation or complication. Significant proportion of recovered patients has evidence of ongoing myocardial inflammation. Although the long-term consequences of this finding are uncertain, COVID-19 individuals are likely to have persistent residual cardiac damage and possibly heart failure in the long run.

A study has been carried out in China on patients recovered from COVID-19 who had presented with cardiac symptoms showed that there was evidence of myocarditis on cardiac MRI in 58% of the patients, revealing that there is high incidence of involvement of myocardium with COVID-19 disease. A cohort study of German patients recovered recently from COVID-19 infection, reveals that there was involvement in 78 patients (78%) and ongoing myocardial inflammation

in 60 patients (60%) on CMR, independent of severity, preexisting conditions, time from original diagnosis and overall acute illness course. This study resembles with them showing 50 patients (60%) having cardiac involvement of myocarditis after recovered from COVID-19.⁵

Myocarditis has a strong association with variety of viral diseases but the true incidence of myocarditis among them is unknown.¹⁶ Autopsy reveals inflammatory myocardial infiltrates in COVID-19 patients but the real prevalence was unknown.^{17,18} Kotecha *et al.* stated 27% patients with LGE pattern of myocarditis and present study shows myocarditis in 60% patients.¹⁹ Recent studies reported elevated T1 and T2 times in septum suggesting fibrosis and edema respectively.

According to the scale of COVID-19, long term follow-up with cardiac MRI is not feasible. However, a small group should be targeted and evaluated with CMR as LGE had a crucial role in pathophysiology of dilated cardiomyopathy.²⁰ Long term presence of scar is associated with cardiac involvement of myocarditis. For such evaluations, follow-up studies are recommended.

LIMITATIONS OF STUDY

It was a single centre study with limited number of COVID-19 patients enrolled for research as the institute in which study was conducted was cardiac rather than medical facility where COVID-19 patient inflow comparatively less.

CONCLUSION

The Coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 is a highly contagious Viral disease. Myocardial injury related to COVID-19 is a common complication and has dive implications on prognosis of disease, early detection of COVID-19 related myocarditis will help in better management of patient.

The non-invasive imaging modality includes echocardiogram being less sensitive so, Cardiac magnetic resonance imaging (CMR) can be used preferably for the diagnosis of Post COVID myocarditis and evaluation of acute myocarditis, enabling risk stratification and prognostication. MRI is an important imaging technique which permits non-invasive assessment of myocardial injury and edema as well as identification of potentially treatable underlying causes of inflammation in suspected patients of myocarditis and myocardial inflammation, to guide management and improve patient outcomes. It can also be helpful in asymptomatic patients of myocarditis after getting infected with COVID-19.

ACKNOWLEDGMENT

I am deeply grateful to my supervisor for his guidance, patience and support who provided insight and expertise that greatly assisted my research project. I also want to share my gratitude for Comdt Exec Dir AFIC/NIHD & HoD R&D

for their support and contribution in completion of the research paper.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

ARJ: Manuscript writing, concept & manuscript drafting

MNK: Intellectual contribution, concept and final approval

NS: Analysis, manuscript writing and proof reading

MJ: Formatting, critical review and data collection/entry

JA: Review of article, formatting and critical review

SM: Data collection, data entry and review of article

AHS: Study design, concept and critical review

GRM: Intellectual contribution, concept & final approval

MS: Proof reading, Intellectual contribution, final approval

SKS: Intellectual contribution, study design and conception

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Page J, Hinshaw D, McKay B. In Hunt for COVID-19 Origin, Patient Zero Points to Second Wuhan Market-The man with the first confirmed infection of the new coronavirus told the WHO team that his parents had shopped there. *The Wall Street Journal*. 2021 Feb. [Internet] available at: <https://www.wsj.com/articles/in-hunt-for-covid-19-origin-patient-zero-points-to-second-wuhan-market-11614335404>
2. Zimmer C. The Secret Life of a Coronavirus - An oily, 100-nano meter-wide bubble of genes has killed more than two million people and reshaped the world. Scientists don't quite know what to make of it. Scientists don't quite know what to make of it. Retrieved. 2021 Feb; 28, [Internet] available at: <https://www.nytimes.com/2021/02/26/opinion/sunday/coronavirus-alive-dead.html>
3. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis. *In Mayo Clinic Proceedings* 2020; 95(8): 1621-1631. Elsevier.
4. Riski H, Hovi T, Frick MH. Carditis associated with coronavirus infection. *Lancet (London, England)* 1980; 316(8185): 100-101.
5. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020; 142(1): 68-78.
6. Long B, Long DA, Tannenbaum L. An emergency medicine approach to troponin elevation due to causes other than occlusion myocardial infarction. *Am J Emerg Med* 2020; 38(5): 998-1006.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395(10223): 497-506.
8. Wei JF, Huang FY, Xiong TY, Liu Q, Chen H, Wang H, et al. Acute myocardial injury is common in patients with COVID-19 and impairs their prognosis. *Heart* 2020; 106(15): 1154-1159.
9. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intens Care Med* 2020; 46(6): 1294-1297.
10. Bhatia S, Anstine C, Jaffe AS, Gersh BJ. Cardiac magnetic resonance in patients with elevated troponin and normal coronary angiography. *Heart* 2019; 105(16): 1231-1236.
11. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance-2020 update. *J Cardiovasc Magn Reson* 2021; 22(1): 1-22.
12. Bruder O, Wagner A, Lombardi M, Schwitler J, van Rossum A, Pilz G, et al. European cardiovascular magnetic resonance (Euro CMR) registry-multi national results from 57 centers in 15 countries. *J Cardiovasc Magn Reson* 2013; 15(1): 1-9.
13. Sanghvi SK, Schwarzman LS, Nazir NT. Cardiac MRI and myocardial injury in COVID-19: diagnosis, risk stratification and prognosis. *Diagnostics* 2021; 11(1): 130.
14. Hopkins J. COVID-19 Map-Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Resource Center 2020; 1. [Internet] Available at: <https://coronavirus.jhu.edu/map.html>
15. Huang L, Zhao P, Tang D, Zhu T, Han R. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *Cardiovasc Imag* 2020; 13(11): 2330-2339.
16. Heymans S, Eriksson U, Lehtonen J, Cooper LT. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. *J Am Coll Cardiol* 2016; 68(21): 2348-2364.
17. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol* 2020; 75(18): 2352-2371.
18. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol* 2021; 50(1): 107300.
19. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalasvaran K, Thornton G et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J* 2021; 42(19): 1866-1878.
20. Becker MA, Cornel JH, Van de Ven PM. The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. *Cardiovasc Imag* 2018; 11(9): 1274-1284.