

Myocardial Strain Abnormalities in Patients with Long COVID After Mild to Moderate Acute COVID-19 Disease

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To cite this article:

Atul Kapoor, Aprajita Kapur. Myocardial Strain Abnormalities in Patients with Long COVID After Mild to Moderate Acute COVID-19 Disease. *Cardiology and Cardiovascular Research*. Vol. 6, No. 4, 2022, pp. 109-117. doi: 10.11648/j.ccr.20220604.14

Received: November 10, 2022; **Accepted:** November 28, 2022; **Published:** December 8, 2022

Abstract: Background: Global pandemic of COVID-19 disease has left many recovered patients with variety of sequelae out of which involvement of heart in the form of myocarditis has been an important and a challenging problem from not only diagnosis but also treatment point of view. Aim: The aim of this study was to evaluate the changes in the heart of recently recovered patients of COVID 19 disease with mild to moderate severity of disease using cardiac magnetic resonance imaging along with strain imaging for both left and right ventricles. Methods: A prospective observational study of 52 symptomatic patients post recovery from recent mild to moderately severe COVID 19 disease was taken. Exclusion criteria included any prior cardiovascular risk, diabetes and smoking. CMR was done and ventricular functions were calculated and recorded along with T1 MOLLI mapping with T2 parametric maps in short axis followed by strain imaging using feature tracking for global circumferential shortening (GCS) and global circumferential early strain rate (GCSe'r) for left and right ventricle. Results: All 52 patients evaluated had normal ejection fraction of both ventricles. T2 maps showed diffuse pattern of involvement of free right ventricle wall while mixed pattern of edema involving mid and basal septum, inferolateral or mid lateral walls was seen along with subendocardial involvement. Right ventricle showed a diffuse pattern of involvement by edema. Strain abnormalities were seen in all patients with a median reduction of GCS and GCSe'r of 9.9%, 61.8% and 6.2% and 46.5% for left and right ventricle respectively. Conclusion: The study highlights the presence of myocarditis in post recovered patients of COVID-19 disease with mild to moderate severity and its detection with the use of CMR and also shows the predominant involvement of right ventricle. Marked reduction of GCS and GCSe'r of both the ventricles were seen with preserved ejection fraction and absent wall motion abnormalities and high lights the need for long term follow up of these patients.

Keywords: COVID-19, Myocarditis, Cardiac MRI

1. Introduction

Post pandemic of the two global COVID-19 waves increasing concern has been emphasized on the involvement of the heart in patients recovered from acute COVID-19 illness. PASC (post-acute sequelae COVID-19) is a term used to describe a constellation of new, returning, or persistent health problems experienced by individuals for more than four weeks after SARS-CoV-2 infection [1]. Studies have demonstrated the involvement of the myocardium in both acute and in the PASC (post-acute sequelae COVID-19) phase [2-4]. Persistent heart inflammation has also been shown in cases with only mild acute illness which may signal increased burden of heart

failure [3]. Gluckman et al [5] in ACC expert consensus statement on cardiovascular sequelae of COVID-19 highlighted the algorithm of evaluation and management of suspected cardiac involvement. However seeing the magnitude of the problem its global prevalence and the risk of development of future cardiac complications we designed this study with the aim to evaluate PASC patients with mild to moderate COVID-19 disease 8-16 weeks after the acute illness to assess for ongoing cardiac involvement using cardiac magnetic resonance imaging (CMR) for structural and functional evaluation of both the ventricles with emphasis on strain imaging using feature tracking. To our knowledge there has been only one recent study published by Wassenaar et al

[6]. So far to assess circumferential strain in athletes post COVID-19 where only left ventricular strain was assessed.

2. Methods

75 consecutive patients with recent history of COVID-19 disease who presented with symptoms of fatigue, palpitations and breathlessness were enrolled in the study. Informed consent was obtained along with approval from local ethics board (Adv/IRB/06/22). 23 patients with history of any of the following: diabetes, hypertension, known coronary artery disease and obesity with BMI more than 32 Kg/m² were excluded. Demographic data was recorded for all 52 patients. All patients under went echocardiography examination followed by cardiac MRI on 1.5 tesla (Siemens Amira System) using standard cardiac protocol which comprised of short axis and four chamber cine balanced-state free processed images for wall motion, ejection fraction and left and right ventricle volumes. Tissue mapping was done in short axis views using T1 MOLLI sequence followed by T2 parametric maps at basal, mid and apical short axis views. Post contrast Gadolinium was not performed to keep the study as non-invasive. Diagnosis of myocarditis was done using updated Lake Louis criteria 2018 (7) using increased signal on T2 and T1 maps as major criteria.

2.1. Post Processing

Post processing was done with feature tracking on Siemens TruFi strain software using Short axis views separately for left and right ventricle. Global circumferential shortening (GCS) was measured for left and right ventricle as systolic strain measure while global circumferential shortening early strain rate (GCSe'r) was calculated as a measure for diastolic strain rate.

2.2. Statistical Analysis

It was done using Analyse-It Software (Leeds UK).

Mean, Median values were calculated along with confidence intervals with parametric distribution box plots using Shapiro Wilk test for normality. Correlation between T2 signal abnormalities and Strain abnormalities was done using Pearson correlation test.

3. Results

The study comprised of 52 symptomatic patients of PASC, demographics of which are enlisted in (Table1).

Table 1. DEMOGRAPHICS OF PASC PATIENTS.

SNO	PARAMETER	MEAN	95% CI
1	AGE	49.6	46-53.3
2	SEX		
	MALE	34	
	FEMALE	18	
3	MILD COVID-19	40	
4	MODERATE COVID-19	12	
5	SYMPTOMS		
	PALPITATIONS	18 (34%)	
	FATIGUE	38 (73%)	
	BREATHLESSNESS	11 (21%)	
6	hs-cTNT	1.1 ng/l	0.8-1.8
7	C-reactive protein	1.8mg/ml	1.3-2.1
8	LVEDV (ML)	73.5	69.5-78.5
9	RVEDV (ML)	61.4	57.2-65.3
10	LV EJECTION FRACTION %	57.5	51-63
11	RV EJECTION FRACTION %	46.6	43.8-49.5
12	T2 signal of affectedLV	51.5	48-5-56.5
13	T2 signal of affectedRV	63	59.4-68.5
14	T1 signal of affected LV	1031	1011-1041

The mean age group was 49.6 years (44-53.3: 95.1% CI), there were 34 males and 18 females. Commonest symptoms were fatigue (73%) and palpitations (34%). On CMR segmental involvement of left ventricle was seen in all symptomatic patients with mixed, focal mural and subendocardial patterns of demaonT2 maps (Table 2) (Figure 1-3).

Table 2. Distribution of strain and T2 signal abnormalities.

S No.	Parameter	Left ventricle	Right ventricle
1	GCS	20	1
2	GCSe'r	7	0
3	Both	24	51
4	T2 signal abnormality		
	Subendocardial	17	0
5	Mural	9	0
6	Mixed	26	52

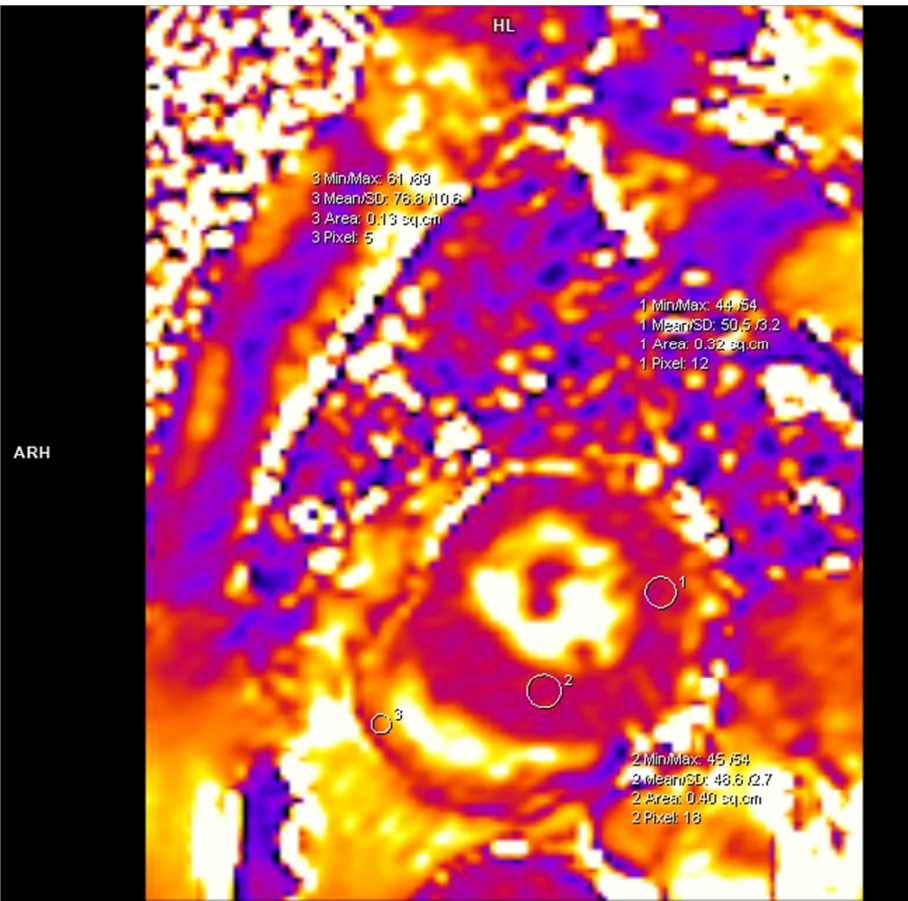


Figure 1. Short axis T2 map at mid left ventricle level showing increased mixed pattern of left ventricle involvement (T2=48-51ms) with diffuse pattern of free Right ventricle wall with T2 of 76.8ms.

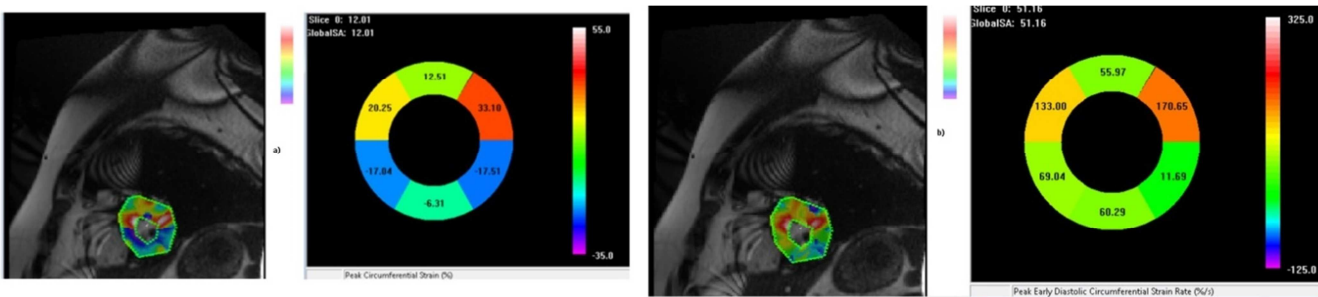


Figure 2. Strain analysis of left ventricle with GCS of 12.0% and GCSe'r of 51.1%.

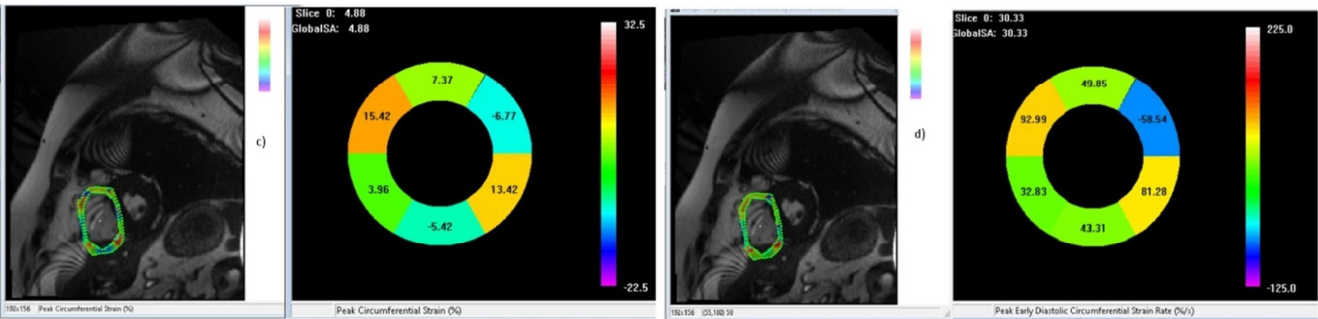


Figure 3. Strain analysis of same patient with c) Reduced right ventricle GCS 4.8% d) Reduced GCSe'r of 30.3%.

The most common segments were basal and mid ventricular septum, inferolateral and mid lateral walls. 26 (50%) cases had a mixed pattern of mural and subendocardial

region involvement while 17 (32%) had subendocardial involvement 9 (17%) had only mural involvement. Right ventricle involvement was seen in all patients and unlike left

ventricle there was diffuse involvement of free wall in all the cases (figure4).

Pattern of distribution of strain and T2 signal abnormalities of Left and right ventricle.

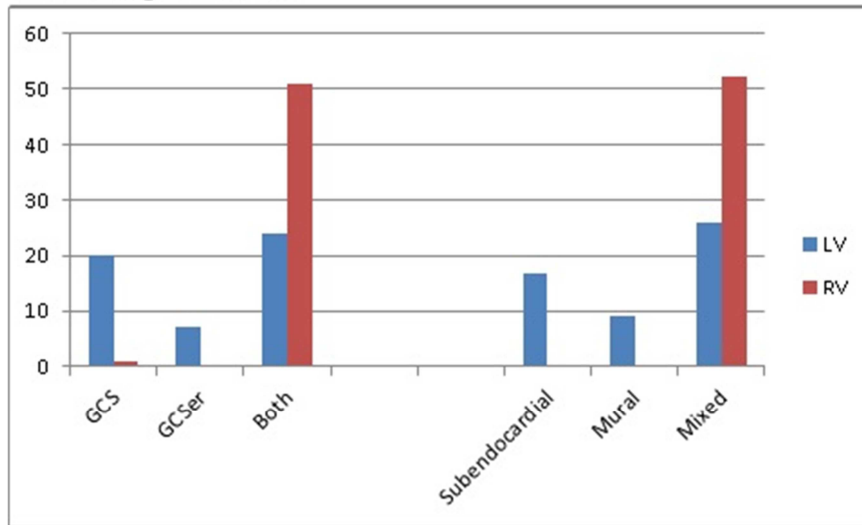


Figure 4. Pattern of distribution of strain and T2 signal abnormalities of left and right ventricle.

Cine images showed no regional wall motion abnormalities with normal mean ejection fraction of 57.5% and 46.6% of left and right ventricles respectively. Strain imaging of the left and right ventricle revealed reduced global circumferential shortening (GCS) of both the ventricles with median GCS of 9.9% and 6.2% for left and

right ventricle respectively and an reduced global circumferential early strain rate (GCSe'r) of 61.8% and 46.5% for left and right ventricle of respectively (figure 5). T1 maps showed mild increased signal of left ventricle in cases with mean of 1031 (1011-1041: 95.1%CI) milliseconds (figure 6).

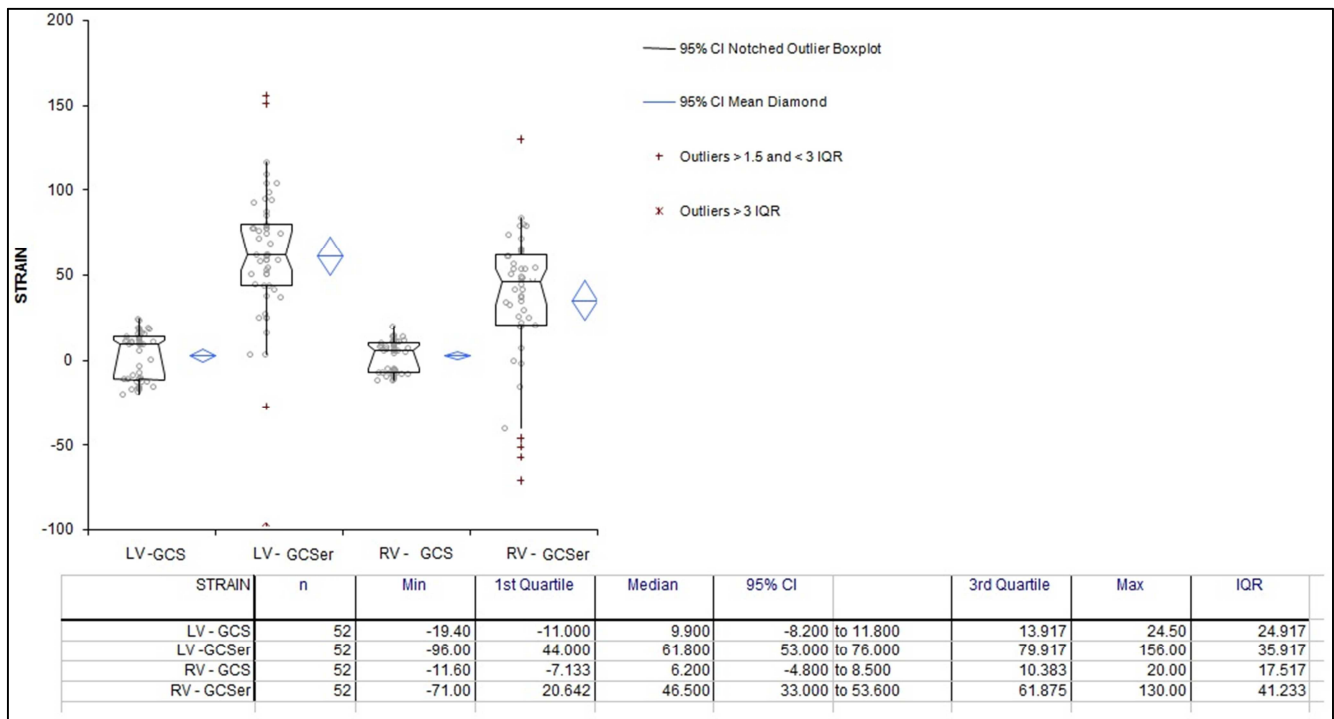


Figure 5. Box plot of changes of strain of both left and right ventricle.

Further analysis showed that left ventricle had reduced systolic GCS alone in 20 patients, reduced GCSe'r alone in 8 and both systolic and diastolic strain were reduced in 24 patients while right ventricle showed reduced GCS and GCSe'r in all 52 patients. (Table 2) (figures 7-12).

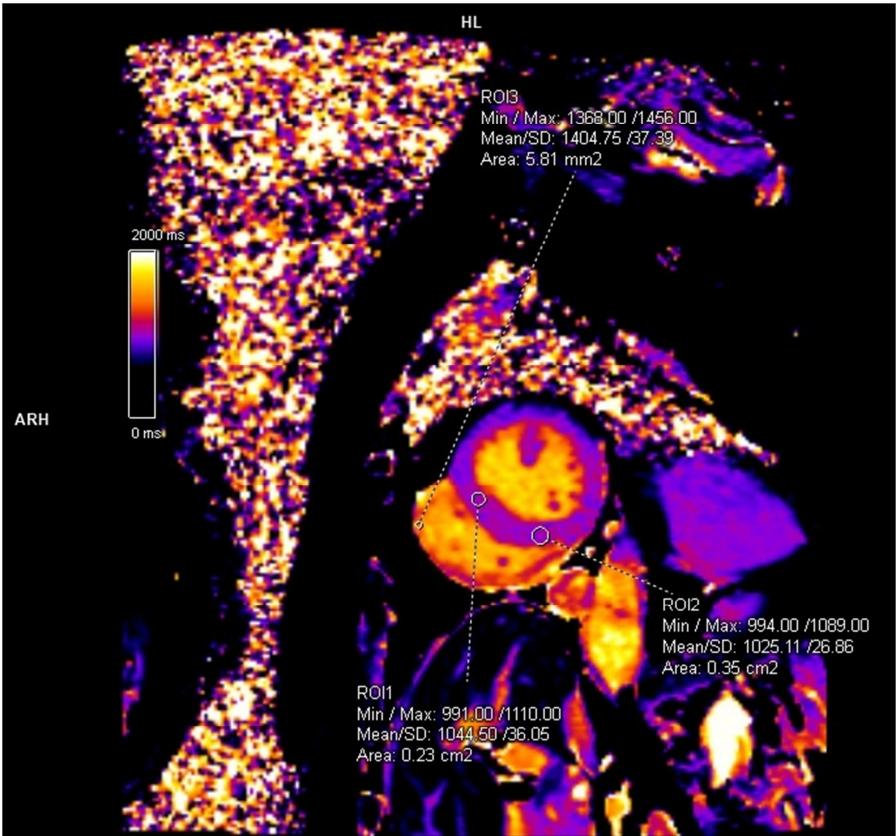


Figure 6. T1 map of left ventricle eat mid cavity level showing increased T1signalinal segments.

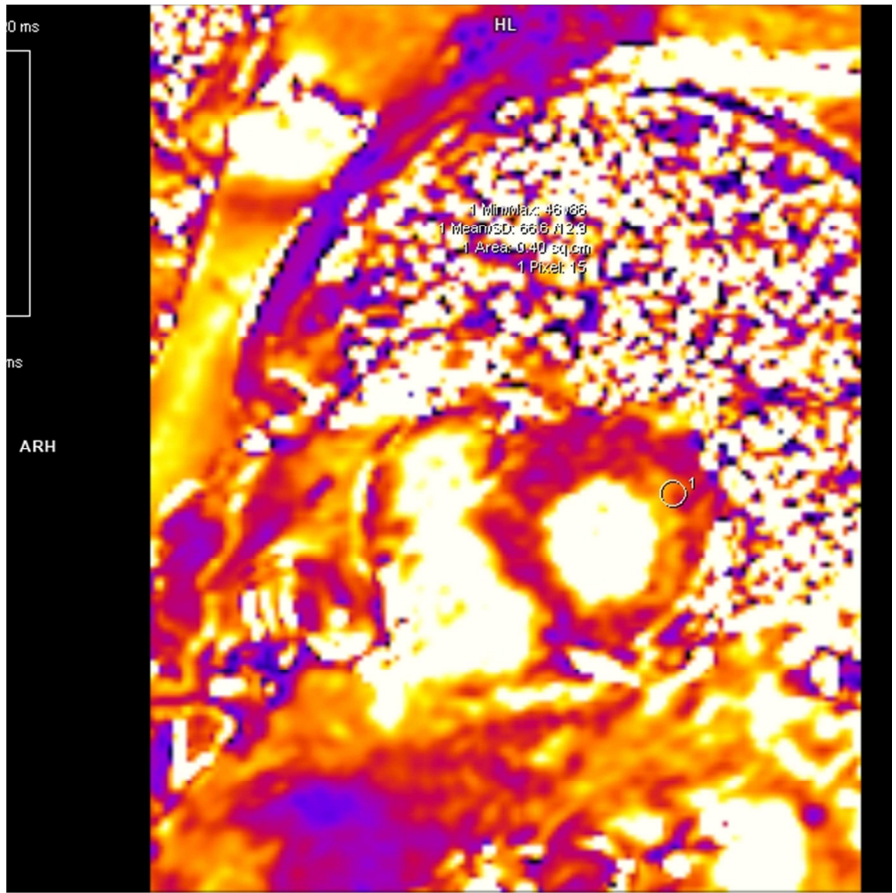


Figure 7. T2 map showing predominant areas of subendocardial involvement in the lateral wall.

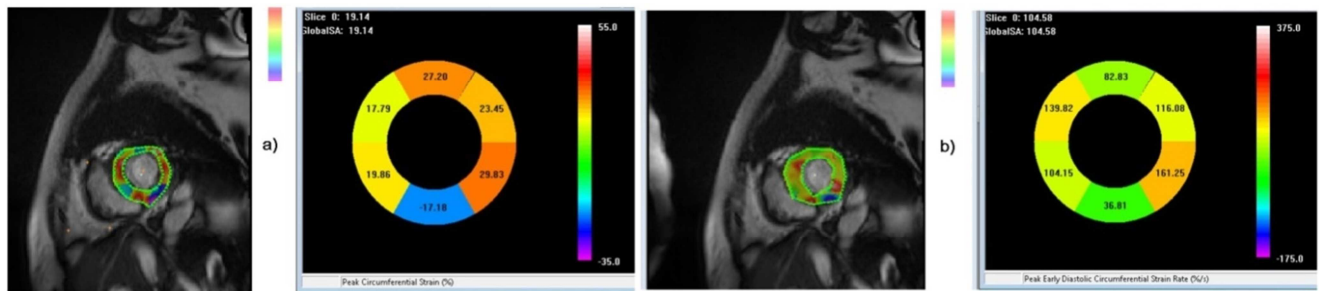


Figure 8. Strain analysis of left ventricle showing a) markedly reduced GCS of 19.14% b) Normal GCSe'r of 104.5%.

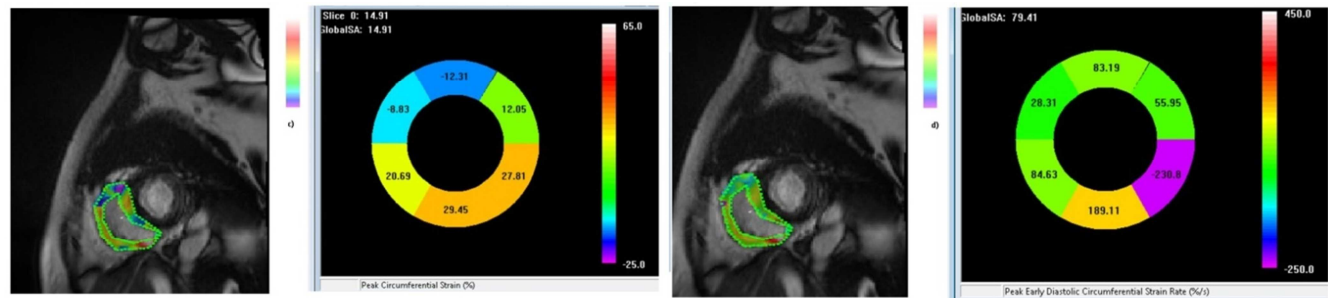


Figure 9. Strain analysis of right ventricle of same patient c) Reduced GCS of 14.9% with d) normal GCSe'r of 78.4%.

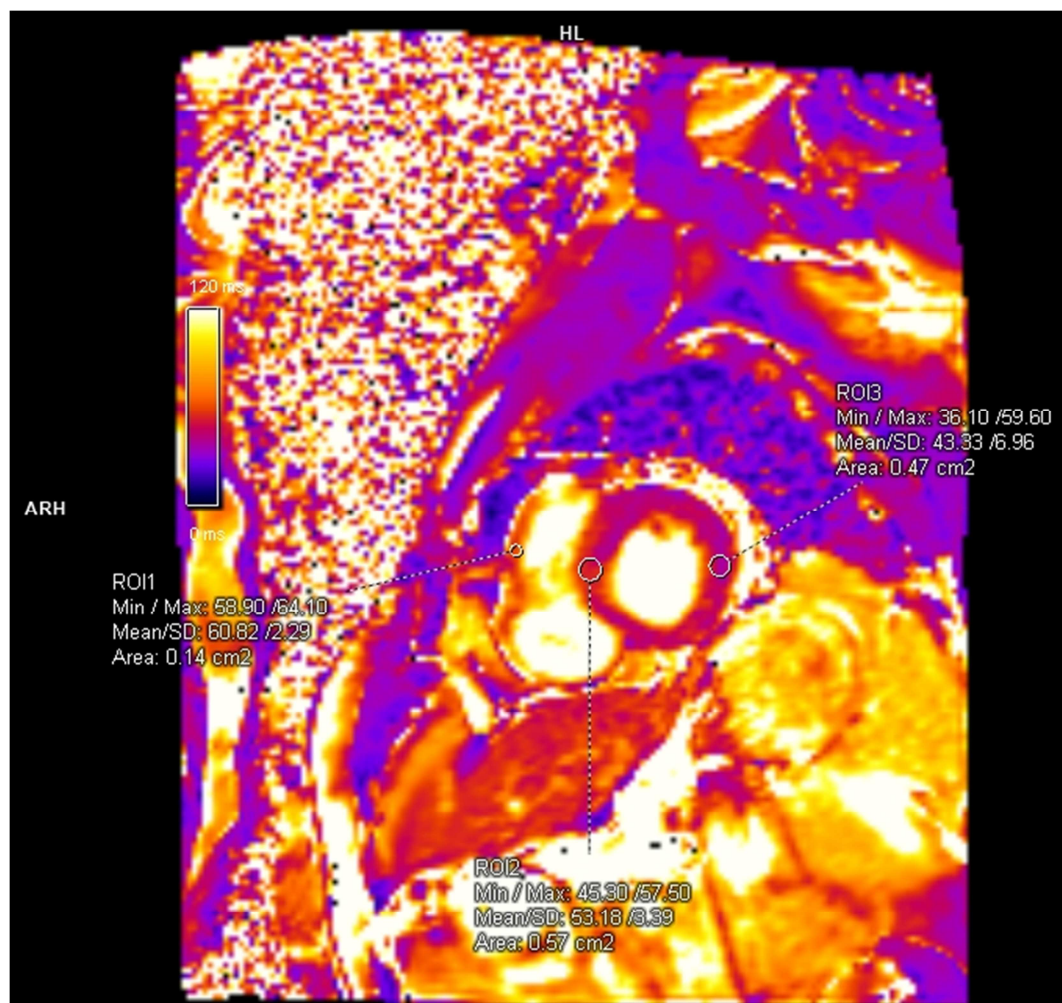


Figure 10. T2 map of short axis view of basal left ventricle showing mural pattern of increased signal in the septal wall with T2 of 53ms with diffuse increased T2 of right ventricle free wall of 60.8ms.

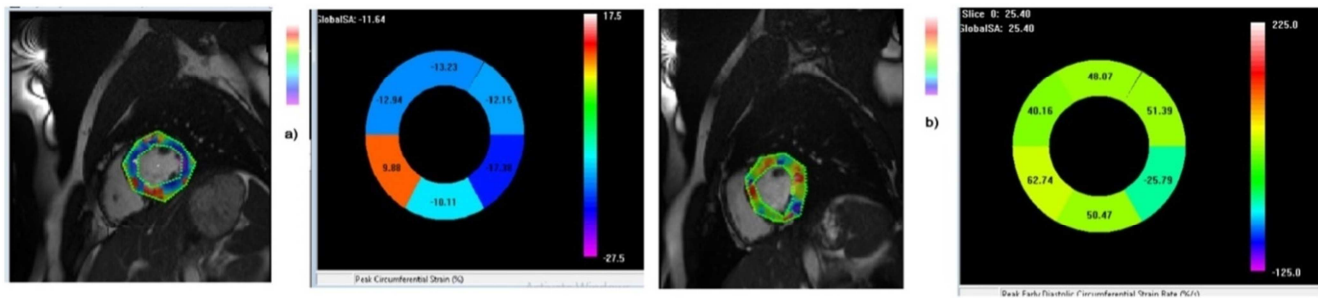


Figure 11. Strain analysis of same patient with left ventricle a) showing GCS of -11.64% b) markedly reduced GCSe'r of 25.4%.

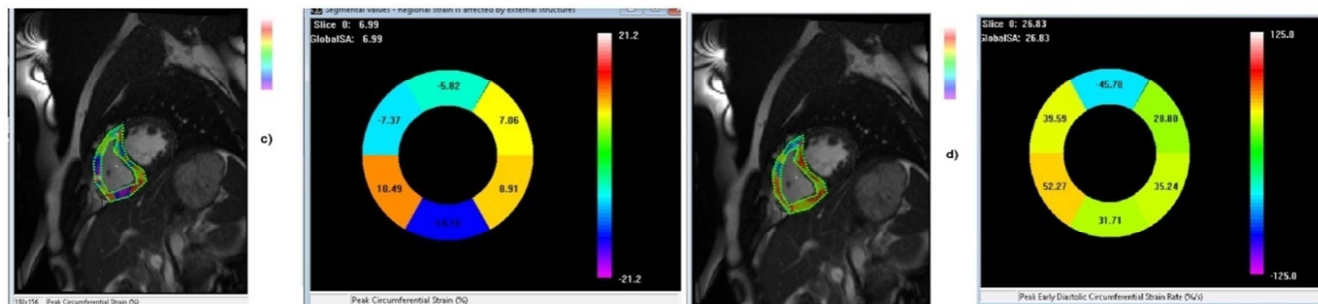


Figure 12. Strain analysis of right ventricle c) reduced GCS of 6.99% d) markedly reduced GCSe'r of 26.83%.

Correlation of pattern of T2 signal abnormalities was done with strain abnormalities and showed high correlation of mixed pattern of T2 signal changes with reduced systole strain and diastolic strain rate ($p < 0.001$) while patients with mural abnormalities of left ventricle showed moderate correlation with reduced GCSe'r only ($p < 0.01$).

4. Discussion

Our study shows that PASC patients following mild to moderate acute COVID-19 having symptoms of fatigue, palpitations, breathlessness have persistent findings of COVID-19 myocarditis demonstrated on CMR using tissue mapping even when all other routine investigations are normal making it difficult to explain the cause of symptoms. All 52 patients evaluated showed involvement of both left and right ventricles along with ventricular strain abnormalities i.e. reduced GCS and GCSe'r which have not been studied so far. A good correlation was also seen with patterns of involvement of ventricles and the systolic and diastolic strain rate abnormalities in the present study. The site of left ventricle involvement was the basal and septum, mid lateral and inferolateral walls as was observed by Wassenaar et al [6]. Mixed pattern of edema on T2 maps in the left ventricle was the commonest pattern which caused reduction of both GCS and GCSe'r of left ventricle. The subendocardial involvement was the second commonest pattern and showed reduced GCS only. The mechanism of mixed pattern was explained by involvement of vascular and micro endothelium of the myocardium coupled with the release of cytokines due to immune dysregulation thus causing reduced systolic strain along with myocardial stiffening resulting in diastolic impairment [7]. In the present

study right ventricle involvement was a dominant feature and a diffuse pattern was seen which was not observed in the left ventricle. The likely mechanism of right ventricle damage has been attributed to increased after load caused by combination of pulmonary thrombosis, hypoxia, direct viral injury and inflammatory dysregulation. Repesse et al [8] explained in their study that right ventricle free wall is thin with larger surface area as compared to left ventricle hence any increase in after load in pulmonary circulation leads to overload injury resulting in wall edema which may lead to dilatation of chamber further damage and fibrosis reduced strain and strain rates and dysfunction.

Selezsky et al [9] and Mahmoud et al [10] also showed that right ventricle involvement in COVID-19 was 40% higher than left ventricle. They suggested that right ventricle wall damage could cause right ventricle dysfunction and adversely affect the clinical outcome. All these studies have been done on patients with severe COVID-19 disease and hospitalized patients unlike our study which was PASC patients with history of mild to moderate acute COVID-19 disease. Since right ventricular dysfunction was more than the left ventricular dysfunction in our study in all the patients it could be an important prognostic factor in long term follow up of these patients. Li et al [11], Pagnesi et al [12] and Agnesia et al [13] also suggested in their studies that right ventricle dysfunction with chamber dilatation or pulmonary hypertension were independent risk factors for poor prognosis in COVID-19 disease. Even though Khan et al [14] in their study suggested that the myocarditis of COVID-19 is potentially reversible due to relative sparing of myocardial cells and lesser necrosis with predominant interstitial macrophage lymphohistiocytosis; the findings of our study suggest that it would be more prudent to follow up these symptomatic patients with CMR for resolution of tissue edema and ventricular dysfunction. Findings of our

study are in agreement with those of Fisher et al [15], Lee et al [16] which suggested that strain quantified by feature tracking by CMR should be an independent prognosticator of long-term major adverse cardiac events. Demonstration of complete functional recovery after myocarditis in both preserved and reduced ejection fraction cases is therefore important. Similar findings have also been suggested by many other studies [17-20]. Puntmann et al [21] also demonstrated in a cohort of PASC with mild initial COVID-19 disease the myocardial inflammation in left ventricle along with a mean global longitudinal strain reduction of 5% of the left ventricle. This reduction was quite less as compared to that seen in our study likely reason of difference being that the GCS may be affected more in COVID-19 due to nature of involvement of fibres. Further Puntmann et al [21] also did not comment about the status of right ventricle strain which the present study showing gross reduction of both GCS and GCSe'r in both right and left ventricles with normal ejection fraction which not only explains the patient symptoms but may have long term prognostic value. Would it not be prudent to add this feature in the recently updated Lake Louise criteria for diagnosis along with T2 maps needs further discussion? Potential limitations of study have been that the number of patients evaluated is small b) we did not use intravenous contrast to look for any myocardial scarring or pericarditis c) long term follow up was not done.

5. Conclusion

To conclude the study demonstrates a) the presence of ongoing COVID-19 myocarditis with subclinical biventricular dysfunction in PASC patients after mild to moderate acute COVID-19 patients and shows b) dominant involvement of right ventricle c) differences in the patterns of involvement and tissue edema changes on T2 maps in left and right ventricle and their correlation with the strain abnormalities d) highlights the usefulness of feature tracking with CMR especially when the LVEF is preserved. The findings of the current study suggest the need to follow up these patients on long term basis for resolution of disease.

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