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Left ventricular global longitudinal strain imaging in identifying subclinical myocardial dysfunction among covid-19 survivors

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ABSTRACT

Background: Covid-19 is multi-system viral infection caused by SARS-CoV-2 virus. Apart from having acute severe respiratory illness causing high mortality, the disease also has a variety of cardiovascular manifestations contributing to morbidity as well as mortality. Cardiac dysfunction and myocarditis are well established complications of Covid-19 as evident in multiple studies after the Covid-19 pandemic. However it is not sufficiently studied in Indian patients either by Echocardiography or by any other imaging modalities like cardiac magnetic resonance imaging (MRI).

Methodology: In this study, we analysed the severity of Left ventricular(LV) dysfunction in Covid-19 survivors. A total of 100 consecutive patients of Covid-19 after one month of discharge who had no underlying cardiovascular diseases underwent echocardiography and global longitudinal strain (GLS) imaging. This study cohort included patients with mild 42 (42%),moderate 46(46%) and severe 12(12%) Covid-19 disease as defined by computerised tomography (CT) severity score.

Result: We observed that total 36(36%) patients had reduced ejection fraction(EF) which included 11 patients having EF <40% and remaining 25(25%) having EF 40–50% ($p<0.002$). Also 22 (22%) patients had abnormal global longitudinal strain (GLS) values with normal ejection fraction which is suggestive of subclinical myocarditis. We observed LV dysfunction in 7(19.5%) patients who had severe Covid-19 while mild to moderate LV dysfunction observed in 29(80.5%) non critical patients.

Conclusion: In conclusion our study demonstrates that myocardial dysfunction is common in covid-19 regardless of disease severity. 2D-echocardiography with GLS is likely to detect early LV dysfunction among these patients.

1. Introduction

Since its inception in December 2019, Corona virus disease (Covid- 19) has caused significant morbidity and mortality. The global mortality rate of Covid 19 disease is 16.9% in hospitalised patients which is higher than the other seasonal flu i.e 5.8%.[1] Based on earlier analyses, cardiovascular diseases(CVD) were statistically more prevalent in patients who die from the infection.[2] Till now India has recorded more than 23 million patients with mortality rate of 1.11%[3]

Cardiotropism of the virus is thought to cause cardiovascular manifestations of Covid-19 disease. Patients with pre-existing cardiovascular diseases are prone for the complications arising due to Covid-19 infection. Common cardiovascular complications that occur due to the Covid-19 disease range from subclinical myocarditis, new onset heart failure (HF), exacerbation of the pre-existing heart failure, arrhythmia, pulmonary thromboembolism, acute coronary syndromes to sudden cardiac death. New-onset myocarditis, Left Ventricular (LV) dysfunction and HF was observed in as many as a quarter of hospitalized Covid-19 patients; and in as many as one-third of those admitted to the intensive care unit (ICU).[4,5]

Few studies showing cardiovascular involvement in Covid-19 have been done world-wide. However, most of the studies were done on critically ill, in-hospital patients. According to a recent

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study by Arentz et al, nearly 33% of patients with Severe Covid-19 have cardiovascular manifestations.[5] However, the majority of the Covid-19 survivors are treated cases of mild to moderate disease. There has been very limited data on cardiovascular manifestations in these Covid 19 survivors. Also, most studies used Cardiac MRI as the modality to detect left ventricular (LV) dysfunction.Chen et al conducted a retrospective study in 274 patients and found that 89 patients (44%) had acute cardiac injury and 43(24%) had heart failure.[6] Similarly, a study conducted by Valentina et al in Germany where 100 post-covid patients underwent cardiac MRI revealed cardiac involvement in 78 (78%) and ongoing myocardial inflammation in 60(60%) of patients. This was independent of pre-existing conditions, severity and course of the acute illness.[7] To the best of our knowledge, there have been no Indian studies done to ascertain the cardiovascular disease burden amongst both critical and non-critical Covid-19 survivors. Global longitudinal strain (GLS) imaging is a convenient & cost effective alternative to Cardiac MRI for detecting subtle left ventricular systolic dysfunction[8,9,10,11] .

We assessed cardiac function by conventional 2D- Echocardiography and GLS imaging among Covid-19 survivors between 1 and 3 months of discharge and correlated these findings with the disease severity as per CT severity score.[12]

2. Materials and methods

2.1. Study design and population

This study was an cross-sectional, single-centre study carried out in a tertiary care hospital. A 2D echocardiography was performed in 100 randomly recruited patients from September 2020 to March 2021**.** The patients were recruited from the Post Covid Care Out Patient Department specially initiated for the same. Patients included in study were Covid-19 survivors above age of 18 years also including pregnant and lactating mothers. Those who recovered from Covid-19 were recruited between 1 and 3 months of recovery. Patients excluded from the study were 1) immunocompromised patients or patients on any immunomodulator therapy 2) patients with prior documented LV dysfunction, pre-existing or current acute coronary syndrome (ACS) or stroke, pre-existing ischemic or non-ischemic cardiomyopathy, severe valvular heart disease.

2.2. Data collection

We collected all the basic clinical parameters including oxygen-saturation,mode of oxygen therapy, laboratory findings (CBC, CRP, ferritin, D-dimer) during hospitalisation and ECG data from the discharge records. All patients giving consent for enrolment were included in the study. The demographics and baseline characteristics of all the enrolled patients including age, sex, BMI and any chronic medical illness were recorded. Assessment of functional status using 6-min Hall walk test was performed by an operator who was blinded.

The severity of Covid-19 disease was defined based on the Guidance document released by Government of India for diagnosis & management of Covid 19[13]. According to these, mild cases were defined as patients with uncomplicated upper respiratory tract infection without any breathlessness/hypoxia. Radiologically they were placed with CT severity score of 1–8 out of 25. Moderate cases were classified as patients with pneumonia with features of dyspnea and oxygen saturation of 90–94%. CT severity score in such patients was 9–15. Severe cases were defined as patients with severe pneumonia with oxygen saturation of less than 90%, CT score in such patients was 16–25.[12]

For our study purpose, patients with mild to moderate CT severity score were grouped into non-critical patients and those with severe CT severity score into critical group.

2.3. 2D-echocardiography and GLS

Detailed 2D-Echocardiography was performed by an independent operator who was blinded from the severity of the patient's disease.

Transthoracic echo was performed using Philips EPIQ 7C machine. LV end-systolic and LV end-diastolic dimensions were noted in para-sternal long axis view. LV systolic function was recorded using Simpson's biplane method.

For the measurement of GLS imaging, the Q-lab application was used. Three apical views were required for GLS, namely apical 2 -chamber, 3 -chamber and 4- chamber. Two endocardial points were applied on each side of the mitral annulus and one on the apex. The machine automatically provided delineation of the endocardial border which could be adjusted accordingly.Once the appropriate views were approved by the user, average GLS values were obtained by an automated algorithm. An 18-segment polar plot (Bull's eye) provided quantitative representation of LV myocardial strain. In this study, we defined EF >50% as preserved ejection fraction, EF between 40 and 50% as mild to moderate (mid-range) LV dysfunction and EF below 40% as severe LV dysfunction as per the European society of cardiology (ESC) 2016 update. Every patient also underwent Global longitudinal strain(GLS) imaging and value below −18% was considered as abnormal.

Patients with evidence of LV dysfunction were kept on regular follow-up in heart-failure OPD and managed as per guideline-directed medical therapy.

2.3.1. Statistical analysis

After data collection, data entry was done in Microsoft Excel. Data analysis was done withthe help of SPSS Software version 23. Quantitative data like age, ejection fraction (EF), GLS, CT score were presented with the help of Mean, Standard Deviation, Median and Interquartile range (IQR). Qualitative risk factors like gender, age group, type of O 2 support, radiological findings, symptoms, etc were presented with the help of Frequency and Percentage table. Association among two or more risk factors and categories of CT Severity (mild, moderate and severe) were assessed with the help of Chi-Square or Fishers Exact Test. The comparison between the age, BMI and laboratory parameters was assessed by using the Mann Whitney U Test. The normality of the data was assessed by Shapiro–Wilk test. The backward elimination method of binary logistic regression analysis was used to reach the current models. At every step, variables with p value <0.1 were omitted. It was a statistically significant model by Hosmer–Lemeshow goodness of fit test. 95% confidence interval level was taken as significant. ($p<0.05$).

3. Results

3.1. Clinical characteristics

Total 100 patients were enrolled in the study of which 57 (57%) were males and 43(43%) were females. The demographic and clinical characteristics of the patient cohort stratified by disease severity are described in Table 1. Patients enrolled in the study were classified as per disease severity by CT severity score. Of the 100 included patients, 42 (42%) had mild disease, 46 (46%) had moderate disease and 12 (12%) had severe disease.

Of the 57 male patients,22(38.6%)had mild disease and among the 43 female patients, 20 (46.5%) had mild disease. Thus, mild

Table 1
The demographic and clinical characteristics of the patient cohort stratified by disease severity.

Variables		Computed Tomography Grades			Total	*p* value
		Mild (0–8)	Moderate (9–15)	Severe (16–25)		
Gender	Male	22 (38.6%)	28 (49.1%)	7 (12.3%)	57	**0.721**
	Female	20 (46.5%)	18 (41.9%)	5 (11.6%)	43	
Age Groups	18–35 years	8 (57.1%)	6 (42.9%)	0 (0.0%)	14	**0.362**
	36–55 years	24 (42.1%)	24 (42.1%)	9 (15.8%)	57	
	>55 years	10 (34.5%)	16 (55.2%)	3 (10.3%)	29	
Hypertension		7 (25.9%)	15 (55.6%)	5 (18.5%)	27	**0.115**
Diabetes Mellitus		7 (29.2%)	13 (54.2%)	4 (16.7%)	24	**0.322**
Obesity		4 (14.8%)	17 (63.0%)	6 (22.2%)	27	**0.002**
Chronic Kidney Disease		0 (0.0%)	3 (75.0%)	1 (25.0%)	4	**0.212**
Any 1 Comorbidity		14 (26.9%)	28 (53.8%)	10 (19.2%)	52	**0.002**
>2 Co morbidities		6 (20.0%)	19 (63.3%)	5 (16.7%)	30	**0.014**
ECG Changes	Tachycardia	6 (28.6%)	11 (52.4%)	4 (19.0%)	21	**0.166**
	ST Depression	0 (0.0%)	3 (100.0%)	0 (0.0%)	3	
	T Wave Inversion	1 (50.0%)	0 (0.0%)	1 (50.0%)	2	

disease was more common in female patients. However, moderate and severe disease was similarly represented in both male and female groups. The mean age of the patients in the study was 50 years.Most of the younger patients had mild Covid-19.Obesity was found to have a positive correlation with disease severity n = 27(p<0.002).

At the time of echocardiography, 55(55%) patients were asymptomatic while 42 (42%) patients were in NYHA class II. Two patients were in NYHA class III. Twenty one (21%) patients had palpitations.

Elevated Serum CRP levels (p< 0.003), serum ferritin levels (P<0.017) and D Dimer levels (p<0.001) were progressively higher with a statistically insignificant trend from Mild to Severe cases diagnosed with CT Score values.

3.2. ECG

Majority of the patients had sinus rhythm on ECG. Sinus tachycardia was noted in 21 patients. 3 patients had T-wave inversion on ECG and 3 patients had non-significant ST segment depression.

3.3. 2D-echocardiography and GLS

Amongst the patients who came for follow-up (n = 100) it was observed that the odds of reduced LVEF are 1.316 times higher with every 1 unit increase in CT severity score (p<0.000,C.I 1.130–1.538).

Echocardiographic parameters and GLS are separately shown in Tables 2 and 3.

2D- Echocardiographic indices of mean Left Ventricular sizes were 33 ± 4 mm in systole and 44 ± 5 mm in diastole. Three patients had LV dilatation. Out of 100 patients, 36(36%) had reduced LVEF <50% of which 11(11%) had LVEF<40% and the remaining 25(25%) patients had ejection fraction of 40–50% (p<0.007).

The CT severity was correlated with the GLS in those patients with a LVEF>50%. Twenty-two patients had an abnormal GLS (global longitudinal strain) with ejection fraction >50%(P< 0.027). 22 patients had normal EF with abnormal GLS of which 45.5%(n = 10) had mild disease and 40.9%(n = 9) had moderate disease severity. The GLS of only those patients with LVEF >50% were considered for discussion.

Table 4 shows the Binary Logistic Regression by backward elimination analyses to predict the factors for reduced GLS. The factors which yielded statistically significant at (p < 0.1) were further considered for logistic regression, The predictors were CT Severity, age group, gender, comorbidity, BMI, oxygen requirement. The CT Severity and other parameters showed significant association with abnormal GLS individually but none of the predictors were significantly associated with abnormal GLS(p>0.05) when analysed in the Binary Regression model as a whole.

4. Discussion

Cardiotropism of the virus is the basic tenet of the pathophysiology of myocardial injury. In a recent study, Esfandiarei and McManus[14] proposed that the pathophysiology of viral myocarditis is a combination of direct cell injury and T-lymphocyte–mediated cytotoxicity, which can be augmented by cytokine-storm syndrome. The virus enters cells via ACE2 receptor which is found in many other tissues.

Rocio[15] et al conducted a study in Spain on 139 covid patients and found cardiac involvement in 75% (104) cases by (11) and another study conducted by Valentina[7] et al in Germany showed cardiac involvement in 78% patients and 60% with ongoing

Table 2
Comparison of all descriptive data between Grades of CT score by using One way ANOVA test and Post HOC analysis by Bonferroni Correction.

	Mild (0–8)		Moderate (9–15)		Severe (16–25)		p value	P value Mild and Moderate	P value Mild and Severe	p value Moderate and Severe
	Mean	SD	Mean	SD	Mean	SD				
LVID(s)	31.2	4.9	32.4	5.0	32.4	4.1	0.467	0.728	1.000	1.000
LVID(d)	41.3	5.2	42.8	5.0	43.4	4.7	0.274	0.526	0.605	1.000
LVEF %	0.6	0.1	0.5	0.1	0.5	0.1	0.002*	0.010*	0.011*	0.932
GLS (Mean)	−16.3	9.7	−14.9	8.2	−13.3	8.6	0.533	1.000	0.896	1.000

•Significant at 0.05 level.
CT: Computed tomography, LVID: Left Ventricular Internal Diameter, s: systole, d: diastole, LVEF: Left Ventricular Ejection Fraction, GLS: Global Longitudinal Strain.

Table 3
Relationship of CT severity score with LVEF and GLS.

CT Severity Score		MILD (0–8)	MODERATE 9–15	SEVERE 16–25	Total	*p* value
LVEF	<40%	2 (18.2%)	8 (72.7%)	1 (9.1%)	11	**0.007**
	41–50%	5 (20.0%)	14 (56.0%)	6 (24.0%)	25	
	>50%	35 (54.7%)	24 (37.5%)	5 (7.8%)	64	
Abnormal GLS with Normal LVEF		10 (45.5%)	9 (40.9%)	3 (13.6%)	22	**0.027**

LVEF: Left Ventricular Ejection Fraction, GLS: Global Longitudinal Strain.

Table 4
Binary Logistic Regression to predict GLS among all the patients.

	Adjusted Odd Ratio	p value	OR (95% CI)
ICU Admission (Yes)	1.542	0.021	4.673 (1.260–17.338)
Hypertension	1.659	0.067	5.253 (0.892–30.936)
At least one Comorbidity	−1.648	0.064	0.192 (0.034–1.104)
Age Group		0.113	
18-35 Yrs	−2.081	0.049	0.125 (0.016–0.987)
36-55 Yrs	−1.155	0.099	0.315 (0.08–1.244)
Constant	1.703	0.133	5.488

myocardial inflammation. In both the studies, MRI was used for LV function assessment.

Many studies conducted worldwide have established Cardiac MRI as the gold standard modality to look for myocardial injury. Cardiac MRI in Indian scenario is costly, not widely available and requires specialist manpower which is often lacking in many cardiac centres. Moreover, it involves use of gadolinium contrast which is nephrotoxic. Echocardiography along with GLS imaging is a handy and effective tool to ascertain subtle left ventricular dysfunction which is often seen in myocardial injury and resolving myocarditis. In addition, it can be used to document improvement in left ventricular function on follow up. Till date only two studies have been done worldwide to establish myocarditis in covid survivors[7,15]

In our study, it was observed that a significant proportion of patients with mild to moderate disease also have LV dysfunction. To the best of our knowledge, ours is the first Indian study which has been done to look for cardiac involvement in the patients using echocardiography as the screening tool.

We used Echocardiography with Global longitudinal strain Imaging and colour doppler to evaluate myocardial function. Global longitudinal strain imaging is more sensitive to diagnose subtle LV dysfunction and also provides prognostic implications as compared conventional echocardiography[8,9,10,11] . Studies conducted previously have established that patients with subclinical LV dysfunction have a normal ejection fraction but reduced global longitudinal strain[16,17,18,19] .

Shmueli[20] et al conducted a study in 589 in-hospital patients over the period of 5 month and 60 patients were evaluated with echocardiography. It was observed that only 23% of them had reduced ejection fraction. However, 80% of patients had evidence of subclinical myocarditis in the form of reduced global longitudinal strain. Similarly, in a study conducted by Rui Li[21] et al, 218 patients were studied of which 52 (23.8%) patients were critically ill and 166(76.2%) patients were non critical. 2D-Echocardiography was done along with layer specific longitudinal strain and it showed that 83% had reduced GLS (<21%). The reduction in GLS values has correlation with the severity of the illness. **Another study conducted by Marc R Dweck[22] et al in 1216 patients found that 479(39%) patients had left ventricular abnormalities.**

In our study including 100 post-discharge patients 42(42%)had mild disease, 46 (46%) had moderate disease and 12 (12%) had severe disease as per CT severity score. Similarly in study conducted by the Rui[21] et al 218 in-hospital patients underwent echocardiography with 68% male patients, nearly 23.8% (n = 52) were critically ill and 67.2%(n = 166) were non critical.

ECG data showed that majority of the patients in the study were in sinus rhythm. Sinus tachycardia was the most common abnormality noted in 21(21%) who had reduced ejection fraction or reduced GLS. According to study by Rui[21] et al there was evidence of tachycardia among the critically ill patients.

We observed that total 36 (36%) had reduced ejection fraction, among which 25 patients had reduced ejection fraction with EF 40–50% and remaining 11 patients had ejection fraction of less than 40%. Twenty two (34.37%) patients out of 64 patients having normal EF had reduced LV GLS values of < −18%. Thus, 58 (58%) of the patients in our study had LV dysfunction.

Majority of the patients (n = 29) with LV dysfunction and reduced GLS had moderate to severe disease severity (80% vs 20%).It is our opinion that myocardial deformation imaging has superior predictive value for detecting LV dysfunction and subclinical myocarditis compared to conventional 2D Echocardiography alone. In comparison with the study conducted by the Rui et al where 166 (67.2%) out of 218 patients had reduced GLS i.e <-21%, our study considered reduced GLS <-18% as abnormal which is a standardised reference value.[23] That could be one of the reasons for a lower incidence of LV dysfunction in our patients(58% vs 80%). Another reason could be that all of the included patients were assessed 1 month after the Covid-19 illness. Both these studies done by Shmueli[20] et al and Rui[21] et al were carried out on in-hospital patients during their covid illness. The evidence of subclinical myocarditis and reduction in ejection fraction in these patients could be attributed to acute nature of the illness and a variety of reasons like stress-induced,viral cum cytokine induced cardiomyopathy, acute respiratory failure etc.

On regression analysis of the data, it was found that myocardial strain imaging or GLS is more likely to detect subclinical myocarditis than the standard Simpsons biplane method which can readily detect left ventricular dysfunction in patients with EF below 50%. Our study also shows that there are no single most important

predictors for reduced GLS. Hence, it can be said that patients with Covid-19 illness can have reduced GLS irrespective of the disease severity. It also shows that patients with mild disease are more likely to have subclinical myocarditis as compared to the patients with moderate to severe illness who are more likely to develop overt left ventricular dysfunction. It is our view that patients can have subclinical myocarditis irrespective of comorbid conditions which is also supported by the study conducted by Valentina et al.[7]

It has been very well established that patients with severe Covid-19 infection have documented evidence of heart failure and cardiac injury.[6]However our study shows that patients after 1 month of discharge can have subclinical myocarditis with or without reduction in the ejection fraction regardless of the severity of illness. We feel that onset of myocardial damage occurs during the acute Covid-19 infection. Hence all the covid patients should be monitored for signs and symptoms of heart failure and undergo echocardiographic screening with myocardial strain imaging.

Previous studies have reported the occurrence of de-novo LV dysfunction as well as deterioration of LV function in patients with pre-existing heart failure due to Covid-19 related myocarditis. The latter subset was excluded from our study. However, it would be prudent to monitor such patients with echocardiography post Covid-19 related illness, considering the high incidence of de-novo heart failure found in our study. In keeping with above, we might see a surge in the incidence of heart failure cases after the covid-19 pandemic.

As the follow-up of the study population was short, it is difficult to comment whether this left ventricular dysfunction in Covid- 19 survivors is transient as part of cytokine storm or it is long-standing and progressive culminating in non-ischemic cardiomyopathy. However we strongly feel that such patients should be followed-up to determine their recovery pattern. The ideal management strategy is to classify these patients as per the existing heart failure guidelines & to manage them accordingly.

It remains to be seen whether patients with LV dysfunction will recover with modifying therapy in the form of ACE inhibitors & Beta Blockers or novel anti-HF therapy (ARNI, SGLT2 inhibitors).

5. Study limitation

Though the study has resulted in significant insight into the burden of left ventricular dysfunction amongst covid-19 survivors in India, the study has a few limitations to note.

Being a single centre study with a small number of patients, the results may not be extrapolated to the general population.As the follow up period is relatively short it is difficult to ascertain whether the left ventricular dysfunction is reversible(resolving myocarditis)or due to irreversible myocardial injury. Another limitation of the study was lack of control group. As the study is retrospective in nature, selection bias is not completely ruled out.

6. Conclusion

In conclusion our study demonstrates that myocardial dysfunction is common in covid-19 regardless of disease severity. 2D-echocardiography with GLS is likely to detect early LV dysfunction among these patients.

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