



Clinical profile and the extent of residual myocardial dysfunction among patients with previous coronavirus disease 2019

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Abstract

Background Many patients who have recovered from their coronavirus disease 2019 (COVID-19) episode continue to remain symptomatic and seek medical opinion. The clinical characteristics and echocardiography findings of such subjects have not been adequately studied.

Methods The study included 472 subjects (age 54.0 ± 13.4 years, 57% men) with previous COVID-19 (median duration since COVID-19 12.0 weeks, interquartile range 9.0–26.0 weeks) and 100 controls (age 53.9 ± 13.6 years, 53% men). All subjects underwent detailed clinical assessment and echocardiography, including measurement of left ventricular (LV) ejection fraction (EF) and global longitudinal strain (GLS).

Results Less than third (29.2%) of the post-COVID subjects had needed hospitalization for their initial infection. Exertional dyspnea or breathing difficulty at rest were the commonest reasons for post-COVID presentation. As compared to controls, the post-COVID subjects had impaired LV systolic (LVEF 63.2 ± 2.2 vs. 61.9 ± 4.6 , $P=0.007$; GLS $-19.9 \pm 2.6\%$ vs. $-17.6 \pm 3.4\%$, $P<0.001$) and diastolic function. Majority of those with reduced LV GLS had preserved LVEF. The patients presenting before 12 weeks were more likely to be symptomatic, but LV GLS did not differ. The patients needing hospitalization had higher burden of co-morbidities and significantly reduced LV GLS as compared to those who had received domiciliary treatment. The patients in the lowest GLS tertile were older, had higher burden of co-morbidities, and had had more severe initial infection with greater need for hospitalization, oxygen therapy and steroids. The need for hospitalization was independently associated with lower GLS at the time of current presentation.

Conclusion This study shows that impairment of LV systolic and diastolic function is common among subjects recovering from previous COVID-19 episode. The patients with more severe initial infection have more marked impairment of LV function and this impairment persists even after several months of recovery from the initial infection. Routine measurement of GLS may be helpful since LV systolic dysfunction in these patients is mostly subclinical.

Keywords Severe acute respiratory syndrome coronavirus 2 · Myocardial injury · Pandemic · Speckle tracking echocardiography

Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2), has exhibited a wide spectrum of acute presentations ranging from asymptomatic form to severe respiratory distress, myocardial injury, and even death. Approximately 20–30% of the patients developing COVID-19 have some evidence of myocardial involvement [1–4]. There are several mechanisms responsible for myocardial injury, including direct viral myocardial invasion, inflammation, thrombosis, vasculitis, myocardial infarction, or secondary effects of hypoxia, tachycardia and systemic stress [1, 2, 5–7].

Myocardial injury in COVID-19 may result in long-term sequelae. Healing of the initial injury may lead to myocardial fibrosis whereas in some patients, the myocardial

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inflammation may itself persist for long. The extent of such residual myocardial abnormalities depends on the severity and the nature of the initial myocardial injury. These residual myocardial abnormalities may lead to a variety of clinical presentations such as exercise intolerance, palpitations, chest pain, new-onset heart failure, or arrhythmia which may even be fatal. Hence, timely recognition and management of any residual myocardial damage in COVID-19 may be clinically important. Unfortunately, only limited long-term data is available regarding cardiovascular involvement in the convalescent phase of COVID-19 [8–13].

Recognition of residual myocardial involvement in patients convalescing from COVID-19 is challenging because most of the patients are asymptomatic. Moreover, in many patients the myocardial abnormalities are quite subtle and not recognizable with conventional diagnostic modalities such as standard echocardiography. A few studies have shown that cardiac magnetic resonance (CMR) imaging may reveal evidence of persistent myocardial injury and fibrosis in many such patients [8–11]. However, the wider use of CMR is not practical due to its cost and other logistic challenges. In this context, strain imaging could be a useful tool for diagnosing subclinical myocardial dysfunction [12–14]. The present study was therefore sought to characterize the extent of residual myocardial dysfunction using strain imaging in patients who had recently recovered from COVID-19.

Materials and methods

This study included 472 consecutive patients with previous COVID-19, presenting to cardiac outpatient clinic for various indications during the period from January 2021 to January 2022. The patients were recruited if they met all the following inclusion criteria- (1) age between 20 and 80 years, (2) documented previous COVID-19 with positive reverse transcriptase polymerase chain reaction for SARS-CoV-2, (3) no previous documented cardiac illness except arterial hypertension, and (4) willing to participate in the study. We also recruited 100 control subjects who were free from any major systemic illness and were matched with the post-COVID patients for age, gender, diabetes mellitus and hypertension.

All subjects underwent detailed clinical assessment and echocardiography. Clinical assessment included history regarding presence or absence of major cardiovascular risk factors and any symptoms. For post-COVID subjects, we also collected information about the following- any pre-existing respiratory illness, the reason for current presentation, duration since their COVID-19 episode and the details of the previous COVID-19 episode including the need for

hospitalization, oxygen requirement, need for ventilatory support, use of remdesivir and steroids. Physical examination included measurement of vital signs and body mass index (BMI), and other relevant systemic examination.

Echocardiography

All subjects underwent a standard transthoracic echocardiography examination using a 2.5–4.0 MHz transducer connected to a commercially available ultrasound system (Vivid S60, GE Vingmed Ultrasound AS, Horten, Norway). The scanning was performed by a single experienced operator, with the patients in the left lateral position.

Standard echocardiographic measurements were obtained following the recommendations of the American Society of Echocardiography [15]. Left ventricular (LV) ejection fraction (EF) was calculated from the apical four- and two-chamber views using the Simpson's biplane method. The lower limit of normal LVEF was taken as 52% for men and 54% for women, as recommended by the American Society of Echocardiography [15]. Mitral inflow pattern was assessed using pulse-wave Doppler with sample volume placed between the tips of the mitral leaflets in the apical four-chamber view. Tissue Doppler imaging was used for measuring early diastolic mitral annular velocity (e') at the medial mitral annulus. The ratio of early diastolic mitral inflow velocity (E) to mitral annular e' (E/e') was used for analysis. Pulmonary artery systolic pressure (PASP) was derived by adding estimated right atrial pressure to the peak tricuspid regurgitation gradient.

Speckle-tracking echocardiography was used for estimating LV global longitudinal strain (GLS). Standard gray-scale images in three apical views (apical two-, three- and four-chamber views) were obtained and analyzed offline on a dedicated workstation (EchoPAC PC, version 202, GE Medical). The average of peak systolic longitudinal strain of all myocardial segments in the three views was taken as LV GLS and used for analysis.

The study was approved by the institutional review board and the ethics committee.

Statistical analysis

The baseline characteristics and other descriptive variables were summarized using standard statistical tools such as mean \pm standard deviation, median with interquartile range, or counts and proportions as appropriate. The categorical variables were compared using Chi-square test and continuous variables using independent t-Test or analysis of variance. A multiple linear regression analysis was performed to determine the independent predictors of LV GLS at the time of current presentation. Two-sided p -value < 0.05 was

Table 1 Clinical characteristics of the post-COVID population (N = 472)

Parameter	Findings
Age, years	54.0 ± 13.4
Male gender	269 (57.0)
Hypertension	267 (56.6)
Diabetes mellitus	149 (31.6)
Pre-existing obstructive airway disease	34 (7.2)
Body-mass index, kg/m ²	26.0 ± 4.5
Current presentation	
Asymptomatic	78 (16.5)
Palpitations	17 (3.6)
Exertional dyspnea/ breathing difficulty	285 (60.4)
Generalized weakness	56 (11.9)
Chest pain	28 (5.9)
Duration post-COVID	
Mean duration, weeks	18.9 ± 13.9
12 weeks or less	240 (50.8)
> 12 weeks	232 (49.2)
Hospitalized	138 (29.2)
Oxygen requirement	
None	336 (71.2)
Low-flow	88 (18.6)
High-flow	48 (10.2)
Ventilator requirement	
None	456 (96.6)
Non-invasive ventilation	9 (1.9)
Invasive ventilation	7 (1.5)
Steroid use	184 (39.0)
Remdesivir	15 (3.2)

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses

COVID- coronavirus disease

considered statistically significant. All analyses were performed using SPSS version 20.0.

Results

The study included 472 post-COVID subjects (age 54.0 ± 13.4 years, 57% men) and 100 controls (age 53.9 ± 13.6 years, 53% men).

Clinical characteristics of the post-COVID subjects

Table 1 describes clinical characteristics of the post-COVID subjects. Exertional dyspnea or breathing difficulty at rest were the commonest reasons (3 out of every 5 cases) for current clinical presentation, while chest pain, palpitations and generalized weakness were the other reasons. Nearly one-sixth of all subjects had presented for unrelated reasons. Both hypertension and diabetes were commonly present in the patients, but only a few had pre-existing obstructive airway disease.

Table 2 Comparison of post-COVID patients with controls

Parameter	Controls (n = 100)	Post-COVID (n = 472)	P value
Age, years	53.9 ± 13.6	54.0 ± 13.4	0.96
Male gender	53 (53.0)	269 (57.0)	0.27
Hypertension	50 (50.0)	267 (56.6)	0.14
Diabetes mellitus	40 (40.0)	149 (31.6)	0.07
Body-mass index, kg/m ²	26.1 ± 4.8	26.0 ± 4.5	0.75
Left ventricular ejection fraction, %	63.2 ± 2.2	61.9 ± 4.6	0.007
Left ventricular global longitudinal strain, %	-19.9 ± 2.6	-17.6 ± 3.4	< 0.001
Estimated pulmonary artery systolic pressure, mmHg	38.2 ± 7.1	38.7 ± 8.2	0.54
Mitral inflow E/e' ratio	11.9 ± 3.8	11.2 ± 3.3	0.03

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses.

COVID- coronavirus disease, E- mitral inflow early diastolic velocity, e'- mitral annular early diastolic velocity.

The median duration since COVID-19 was 12.0 weeks (interquartile range 9.0–26.0 weeks). Majority of the subjects had had relatively mild infection. Less than one third needed hospitalization and almost the same proportion required oxygen support. Non-invasive or invasive ventilation was used in < 5% subjects. A sizeable proportion (39%) received steroids whereas remdesivir was hardly used.

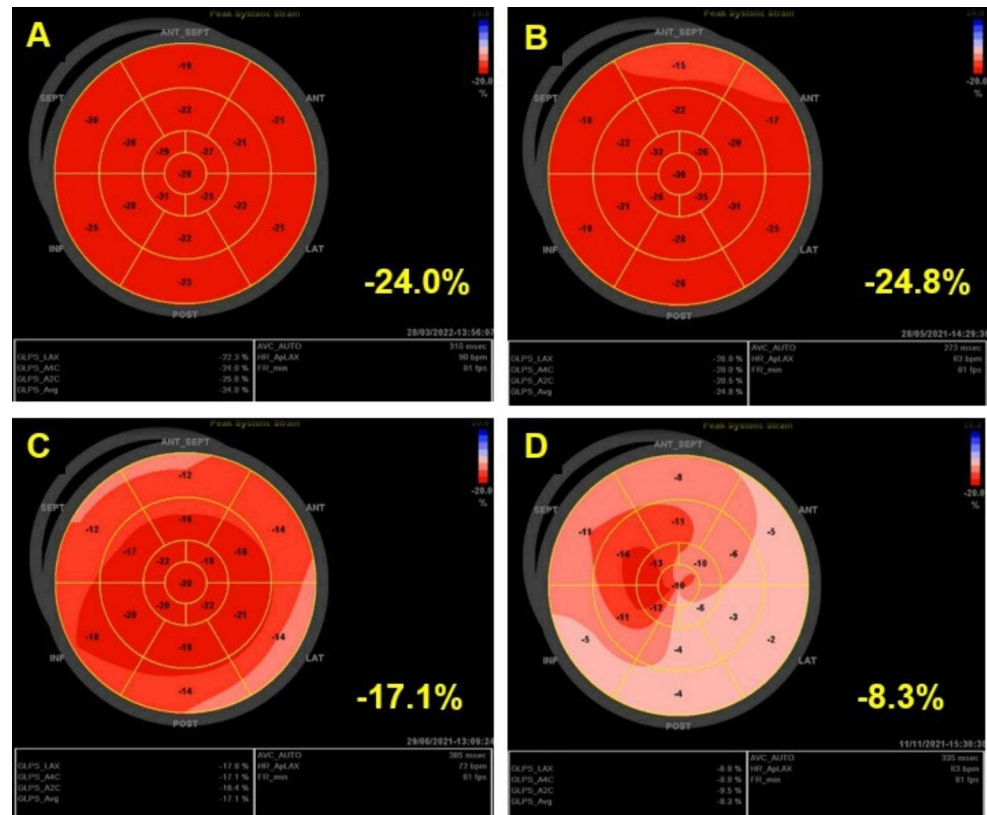
Comparison with controls

As compared to controls, the post-COVID subjects had significantly lower LVEF and LV GLS, whereas mitral E/e' was significantly higher (Table 2) (Fig. 1). This was despite the absence of any significant difference between the two groups in age, gender, BMI and the prevalence of hypertension or diabetes mellitus. The estimated PASP also was not different between the two groups. Most (> 95%) of the patients with previous COVID-19 had normal LVEF. However, GLS was abnormal in 18.4% subjects (using mean minus two standard deviations of the GLS value in controls as the reference).

Post-COVID subjects categorized according to the duration since the initial COVID-19 episode

Compared to the patients presenting beyond 12 weeks, those who had presented early after their initial COVID-19 episode were more often symptomatic and were more likely to have received steroids previously. However, there was no difference in the co-morbidities, and the need for hospitalization or oxygen use (Table 3). The LVEF and GLS also did not differ between the two groups. However, GLS

Fig. 1 Representative examples of global longitudinal strain (GLS) bull's eye plots in study patients and controls. (A) Controls; (B, C, D) Patients with previous coronavirus disease 2019 with GLS values in the highest, middle and lowest tertile, respectively



much lower in symptomatic patients as compared to those who were asymptomatic at the time of current presentation ($-17.3 \pm 3.4\%$ vs. $-19.4 \pm 2.7\%$, $P < 0.001$).

Post-COVID subjects categorized according to the need for hospitalization for the initial COVID-19 episode

Of the 472 subjects, 138 (29.2) had required hospitalization for their initial COVID-19 episode. Men were more likely to be hospitalized than women (Table 4). In addition, those requiring hospitalization had a higher burden of co-morbidities. Furthermore, as expected, the patient treated in hospital had greater use of steroids, remdesivir, oxygen therapy and ventilatory support.

The majority of the patients who were hospitalized initially had now presented with some symptoms. The LVEF was marginally lower in them, as compared to the other group, but LV GLS was significantly reduced. They also had higher PASP.

Post-COVID subjects categorized into tertiles of left ventricular global longitudinal strain

When grouped into LV GLS tertiles (Fig. 1), the subjects with the worst GLS were older, more likely to be men, and had higher BMI and a higher prevalence of hypertension

and diabetes mellitus (Table 5). They also had more severe initial infection with greater need for hospitalization, oxygen therapy and steroids. The patients with the lowest GLS had lower LVEF but mitral E/e' and PASP were not different. The need for hospitalization was independently associated with lower GLS in a multiple linear regression analysis which also included baseline comorbidities (Table 6).

Discussion

Coronavirus disease 2019, caused by SARS-CoV-2, is the greatest pandemic of our time and has already resulted in more than 515 million infections and more than 6 million deaths [16]. Although COVID-19 is predominantly a respiratory disease, myocardial involvement is not uncommon [1–4, 6]. In many patients, the myocardial injury occurring during the acute phase of COVID-19 may lead to long-term sequelae such myocardial fibrosis and/or persistent myocardial inflammation. These residual myocardial abnormalities can cause a variety of clinical presentations including arrhythmia, which may even be fatal. Besides this, in some patients, COVID-19 may also result in the development of a new-onset cardiomyopathy, particularly during the convalescent phase after the initial infection. Given the sheer magnitude of COVID-19 cases, any such myocardial

Table 3 Clinical and echocardiographic characteristics of the post-COVID population divided according to the duration since the COVID episode

Parameter	12 weeks or less (N=240)	> 12 weeks (N=232)	P value
Age, years	53.1 ± 13.0	54.9 ± 13.8	0.14
Male gender	128 (53.3)	141 (60.8)	0.06
Hypertension	130 (54.2)	137 (59.1)	0.28
Diabetes mellitus	70 (29.2)	79 (34.1)	0.25
Pre-existing obstructive airway disease	21 (8.8)	13 (5.6)	0.28
Body-mass index, kg/m ²	25.7 ± 4.3	26.3 ± 4.6	0.17
Asymptomatic at presentation	24 (10.0)	54 (23.3)	<0.001
Duration post-COVID, weeks	7.7 ± 3.1	30.4 ± 10.9	<0.001
Hospitalized	71 (29.6)	67 (28.9)	0.87
Oxygen requirement			
None	172 (71.7)	164 (70.7)	0.55
Low-flow	41 (17.1)	47 (20.3)	
High-flow	27 (11.3)	21 (9.1)	
Ventilator requirement			
None	232 (96.7)	224 (96.6)	0.88
Non-invasive ventilation	5 (2.1)	4 (1.7)	
Invasive ventilation	3 (1.3)	4 (1.7)	
Steroid use	107 (44.6)	77 (33.2)	0.011
Remdesivir	9 (3.8)	6 (2.6)	0.47
Left ventricular ejection fraction, %	62.1 ± 4.1	61.6 ± 5.1	0.23
Left ventricular global longitudinal strain, %	-17.4 ± 3.4	-17.9 ± 3.4	0.16

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses.

COVID- coronavirus disease, E- mitral inflow early diastolic velocity, e'- mitral annular early diastolic velocity.

involvement is a matter of concern with major public health implications.

There are several different mechanisms responsible for myocardial involvement in COVID-19. The virus acts through angiotensin converting enzyme-2 receptors, which are found predominantly in alveolar and myocardial tissue [17]. Hence, SARS-CoV-2 may cause myocardial injury through direct invasion. In a recent study, 39 consecutive patients who died of COVID-19 and underwent autopsy were included. SARS-CoV-2 could be detected in 24 of the 39 (61.5%) patients [7]. Similarly, viral genome could also be detected in the myocardial tissue of many patients dying of severe acute respiratory distress caused by the older coronavirus [18]. These findings support the role of direct myocardial invasion in causing myocardial injury in coronavirus infections. Despite this evidence, indirect mechanisms such as myocardial inflammation, vasculitis, thrombosis, myocardial infarction, or secondary effects of hypoxia, hemodynamic instability and systemic stress appear to be the more

Table 4 Clinical and echocardiographic characteristics of the post-COVID population divided according to the need for hospitalization during COVID

Parameter	Not hospitalized (N=334)	Hospitalized (N=138)	P value
Age, years	53.3 ± 13.5	55.6 ± 13.0	0.10
Male gender	180 (53.9)	89 (64.5)	0.034
Hypertension	178 (53.3)	89 (64.5)	0.026
Diabetes mellitus	93 (27.8)	56 (40.6)	0.007
Pre-existing obstructive airway disease	21 (6.3)	13 (9.4)	0.16
Body-mass index, kg/m ²	25.8 ± 4.6	26.3 ± 4.2	0.25
Asymptomatic at presentation	69 (20.7)	9 (6.5)	<0.001
Duration post-COVID, weeks	18.8 ± 13.7	19.1 ± 14.3	0.81
Oxygen requirement			
None	312 (93.4)	24 (17.4)	<0.001
Low-flow	21 (6.3)	67 (48.6)	
High-flow	1 (0.3)	47 (34.1)	
Ventilator requirement			
None	334 (100.0)	122 (88.4)	<0.001
Non-invasive ventilation	0 (0.0)	9 (6.5)	
Invasive ventilation	0 (0.0)	7 (5.1)	
Steroid use	63 (18.9)	121 (87.7)	<0.001
Remdesivir	1 (0.3)	14 (10.1)	<0.001
Left ventricular ejection fraction, %	62.1 ± 4.2	61.3 ± 5.6	0.08
Left ventricular global longitudinal strain, %	-18.2 ± 3.3	-16.3 ± 3.2	<0.001
Estimated pulmonary artery systolic pressure, mmHg	37.8 ± 7.8	40.1 ± 8.8	<0.001
Mitral inflow E/e' ratio	11.0 ± 3.3	11.4 ± 3.3	0.26

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses.

COVID- coronavirus disease, E- mitral inflow early diastolic velocity, e'- mitral annular early diastolic velocity.

dominant mechanisms responsible for myocardial injury in COVID-19 [1–4, 6].

The long-term follow-up of the patients suffering myocardial injury during the acute phase of COVID-19 is important due to its potential to cause undesirable consequences. In a study of 502 patients with biopsy-proven inflammatory carditis occurring before the onset of COVID-19 pandemic, up to 6.6% of the patients developed sudden cardiac death or life threatening arrhythmia [19]. Higher incidence of atrial and ventricular arrhythmias was observed in patients with active or preceding myocarditis [20]. Other autopsy series have shown that in a significant number of patients with sudden cardiac death with grossly normal appearing heart, myocarditis could be identified on histological examination [21, 22]. Thus, myocarditis is an important substrate for sudden cardiac death, esp. in the young age group [23]. These observations are equally pertinent to patients recovering from COVID-19. It can be assumed that among patients

Table 5 Clinical and echocardiographic characteristics of the post-COVID population divided according to the global longitudinal tertiles

Parameter	Highest tertile	Intermedi-	Lowest tertile	P value
	(-19.1% or more negative, N = 158)	ate tertile (N = 159)	(Less negative than -16.3%, N = 155)	
Age, years	50.8 ± 13.7	53.7 ± 12.9	57.6 ± 12.9	<0.001
Male gender	56 (35.4)	102 (64.2)	111 (71.6)	<0.001
Hypertension	72 (45.6)	95 (59.7)	100 (64.5)	0.002
Diabetes mellitus	39 (24.7)	47 (29.6)	63 (40.6)	0.008
Pre-existing obstructive airway disease	7 (4.4)	12 (7.5)	15 (9.7)	0.49
Body-mass index, kg/m ²	25.2 ± 4.3	26.2 ± 4.4	26.6 ± 4.7	0.022
Asymptomatic at presentation	41 (25.9)	30 (18.9)	7 (4.5)	<0.001
Duration post-COVID				
Mean duration, weeks	18.6 ± 13.4	19.4 ± 13.6	18.5 ± 14.6	0.84
> 12 weeks	82 (51.9)	80 (50.3)	70 (45.2)	0.46
Hospitalized	30 (19.0)	38 (23.9)	70 (45.2)	<0.001
Oxygen requirement				
None	123 (77.8)	124 (78.0)	89 (57.4)	<0.001
Low-flow	26 (16.5)	24 (15.1)	38 (24.5)	
High-flow	9 (5.7)	11 (6.9)	28 (18.1)	
Ventilator requirement				
None	152 (96.2)	156 (98.1)	148 (95.5)	0.18
Non-invasive ventilation	4 (2.5)	3 (1.9)	2 (1.3)	
Invasive ventilation	2 (1.3)	0 (0.0)	5 (3.2)	
Steroid use	52 (32.9)	53 (33.3)	79 (51.0)	0.001
Remdesivir	3 (1.9)	4 (2.5)	8 (5.2)	0.22
Left ventricular ejection fraction, %	63.0 ± 2.6	62.1 ± 2.9	60.4 ± 6.8	<0.001
Left ventricular global longitudinal strain, %	-21.2 ± 1.6	-17.7 ± 0.8	-13.9 ± 2.1	<0.001
Estimated pulmonary artery systolic pressure, mmHg	38.0 ± 8.2	39.4 ± 8.0	38.7 ± 8.4	0.34
Mitral inflow E/e' ratio	10.9 ± 2.8	10.9 ± 3.1	11.6 ± 3.8	0.11

Continuous values are reported as mean ± standard deviation and categorical values as actual numbers with percentages in parentheses. COVID- coronavirus disease, E- mitral inflow early diastolic velocity, e'- mitral annular early diastolic velocity.

Table 6 Multiple regression analysis to determine independent predictors of global longitudinal strain in the post-COVID patients

	Unstandardized coefficients		Standardized coefficients			95% confidence interval for B	
	B	Standard error	Beta	t	P value	Lower bound	Upper bound
(Constant)	-21.56	0.62		-35.01	<0.001	-22.77	-20.35
Age	0.041	0.012	0.16	3.39	0.01	0.017	0.064
Male gender	1.77	0.29	0.26	6.1	<0.001	1.20	2.34
Diabetes mellitus	0.13	0.33	0.018	0.40	0.69	-0.51	0.77
Hypertension	0.37	0.33	0.054	1.13	0.26	-0.27	1.01
Hospitalization	1.56	0.32	0.21	4.91	<0.001	0.94	2.19

Dependent variable- global longitudinal strain. Since global longitudinal strain is described with a minus sign, a positive value of beta indicates inverse relationship with the predicting variable.

COVID- coronavirus disease.

with recovered myocarditis, myocardial infarction or other cardiac injury due to COVID-19, a sizeable proportion might be having subclinical cardiovascular abnormalities. Such patients continue to be at risk for fatal arrhythmias despite apparently recovered cardiac function. Timely recognition of such residual myocardial involvement in patients convalescing from COVID-19 is therefore crucial.

Unfortunately, at present there is only limited information available about the long-term cardiovascular complications of COVID-19. This is due to several reasons. First, COVID-19 has been a relatively new disease; more time is required for studying its long-term complications. Second, most of the patients with residual myocardial involvement are asymptomatic. And lastly, the evidence of residual

myocardial involvement in most of the patients is too subtle to be recognized by the conventional diagnostic modalities.

CMR is a very useful tool for detecting subclinical myocardial inflammation and/or fibrosis. Puntman et al. published a prospective observational study after the first wave of COVID-19 illness [8]. Hundred patients who had recently recovered from COVID-19 were included. Nearly 78% of them had cardiovascular involvement. Late gadolinium enhancement (LGE) and parametric mapping with CMR were found to be the most sensitive markers to diagnose early cardiac damage. Another study evaluated 47 patients at three months after recovering from moderate to severe COVID-19 [9]. The evidence of myocardial injury was present in nearly one-third of the patients. Yet another study evaluated healthcare workers with history of mild COVID-19 [24]. In this study, no residual or permanent cardiovascular abnormalities were found in CMR performed at 6 months after the initial infection.

Although CMR is a useful cardiac imaging modality, its limited availability, higher cost and technical challenges render it unsuitable for wider use for post-COVID cardiac surveillance. Echocardiography is much better suited for this purpose with GLS being a reliable and sensitive measure of subclinical myocardial dysfunction.

Only a few studies have reported GLS in patients recently recovered from COVID-19 [12–14]. A study from North India included 134 subjects within 30–45 days after recovery from COVID-19 [12]. Only those with normal LVEF were included in this study. Subclinical LV systolic dysfunction, defined as GLS less than the mean value in controls, was seen in 29.9% subjects. Another study included 100 patients recovered from COVID-19 at a median delay of 130 days. Overall GLS was not reduced in post-COVID patients, but the basal segmental longitudinal strain was found to be lower [13]. Yet another study included 86 COVID-19 survivors late (median time interval 327 days) after recovery. Compared with controls, no significant difference was found in any of the echocardiographic parameters, including GLS [14].

In our study, we recruited patients at a median interval of 12 weeks after the initial infection. Much like the previous studies, we also found that GLS was significantly reduced in post-COVID patients as compared to controls. Majority of our patients had LVEF within normal range yet had significantly reduced GLS implying high prevalence of subclinical LV systolic dysfunction. Furthermore, the patients presenting with one or more symptoms had much lower GLS as compared to those who were asymptomatic. These findings show the utility of GLS in the evaluation of the post-COVID population and suggest that GLS should be measured in every symptomatic post-COVID patient to detect underlying myocardial dysfunction.

We also observed that the impairment of GLS correlated well with the severity of the initial illness. The patients with the worst GLS had more severe initial infection with greater need for hospitalization, oxygen therapy and steroids. They also had a higher burden of comorbidities. This supports the robustness of GLS as a measure of myocardial injury.

The prevalence of impaired GLS in our study was much higher than what was reported in the study by Mahajan et al. cited above [12]. This may be because we did not limit our recruitment to patients with documented normal LVEF. Moreover, we also did not exclude patients with diabetes mellitus or hypertension. Our findings are thus more representative of the population that seeks medical advice following their initial COVID-19 infection. It is also noteworthy that unlike the study by Mahajan et al., we used mean minus two standard deviations of GLS in the controls as the threshold to define impaired GLS. This should be a more appropriate cut-off than any value below the mean GLS. We found that 18.4% of the post-COVID subjects in our study had abnormal GLS using this definition.

Limitations

Our study had several limitations that merit attention. First, this was a hospital-based study which recruited patients who had presented to the hospital for some or other reason. Hence, the true prevalence of residual post-COVID myocardial abnormalities cannot be determined from this study. Second, most of our patients had had mild form of COVID illness, which limits generalizability of our study findings. Third, in our patients, we did not have a direct information about the extent of myocardial injury during the initial episode of COVID-19 and therefore, had to rely on other markers of disease severity, such as the need for hospitalization, oxygen use, and ventilatory requirement. Fourth, echocardiography was the only diagnostic modality used in this study and the findings were not corroborated with any other imaging tool such as CMR. Fifth, due to logistic reasons, we could not systematically assess the right ventricular systolic function in our patients. Also, as per the practice at our center, we measured only the medial e' , instead of lateral e' or mean e' . However, since most of our patients had had mild COVID illness, we believe these omissions did not appreciably impact the main findings of our study. Sixth, we did not have any baseline echocardiography data for our patients and hence, it was not possible to determine if the echocardiography abnormalities found during the present evaluation were pre-existing or new. To overcome this, we included controls who were matched for age, gender and two common cardiovascular risk factors (namely diabetes and hypertension) which are also the common reasons for subclinical LV systolic dysfunction. We believe,

inclusion of such subjects as controls allowed us to better assess the true prevalence of LV myocardial dysfunction in post-COVID patients than in the previous studies [12, 13]. Lastly, our study was initiated at a time when COVID vaccination had not become available in India. However, during the later stages of the study, we had patients who had received COVID vaccine, albeit the first dose only. Unfortunately, we could not systematically capture this information in this study.

Conclusion

This study shows that impairment of LV systolic and diastolic function is common among subjects recovering from previous COVID-19 episode. The patients with more severe initial infection have more marked impairment of LV function and this impairment persists even after several months of recovery from the initial infection. Routine measurement of GLS is important since subclinical LV systolic dysfunction is common in these patients.

Author contributions AD collected all the data. MB analyzed the data. AD and MB wrote the manuscript, edited it as necessary, and reviewed the final version.

Competing interests The authors declare no competing interests.

References

- Akhmerov A, Marban E (2020) COVID-19 and the heart. *Circ Res* 126:1443–1455
- Zheng YY, Ma YT, Zhang JY, Xie X (2020) COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 17:259–260
- Chang WT, Toh HS, Liao CT, Yu WL (2021) Cardiac involvement of COVID-19: a Comprehensive Review. *Am J Med Sci* 361:14–22
- Sharma YP, Agstam S, Yadav A, Gupta A, Gupta A (2021) Cardiovascular manifestations of COVID-19: an evidence-based narrative review. *Indian J Med Res* 153:7–16
- Liu PP, Blet A, Smyth D, Li H (2020) The Science Underlying COVID-19: implications for the Cardiovascular System. *Circulation* 142:68–78
- Bansal M (2020) Cardiovascular disease and COVID-19. *Diabetes & metabolic syndrome* 14:247–250
- Lindner D, Fitzek A, Brauningner H et al (2020) Association of Cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol* 5:1281–1285
- Puntmann VO, Carerj ML, Wieters I et al (2020) Outcomes of Cardiovascular magnetic resonance imaging in patients recently recovered from Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol* 5:1265–1273
- Wang H, Li R, Zhou Z et al (2021) Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 23:14
- Daniels CJ, Rajpal S, Greenshields JT et al (2021) Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: results from the big ten COVID-19 Cardiac Registry. *JAMA Cardiol*
- Chudgar P, Burkule N, Lakshmvienkateshiah S, Kamat N (2021) Role of Cardiac magnetic resonance imaging in Assessment of Cardiovascular Abnormalities in patients with Coronavirus Disease 2019: our experience and review of literature. *J Indian Acad Echocardiography Cardiovasc Imaging* 5:150–157
- Mahajan S, Kunal S, Shah B et al (2021) Left ventricular global longitudinal strain in COVID-19 recovered patients. *Echocardiography* 38:1722–1730
- Caiado LDC, Azevedo NC, Azevedo RRC, Caiado BR (2022) Cardiac involvement in patients recovered from COVID-19 identified using left ventricular longitudinal strain. *J Echocardiogr* 20:51–56
- Gao YP, Zhou W, Huang PN et al (2021) Normalized Cardiac structure and function in COVID-19 Survivors Late after Recovery. *Front Cardiovasc Med* 8:756790
- Lang RM, Badano LP, Mor-Avi V et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 28:1–39e14
- WHO Coronavirus (COVID-19) Dashboard (2022) Available at: <https://covid19.who.int/>. Last accessed: May 5,
- Chen L, Li X, Chen M, Feng Y, Xiong C (2020) The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 116:1097–1100
- Oudit GY, Kassiri Z, Jiang C et al (2009) SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest* 39:618–625
- Marc-Alexander O, Christoph M, Chen TH et al (2018) Predictors of long-term outcome in patients with biopsy proven inflammatory cardiomyopathy. *J Geriatr Cardiol* 15:363–371
- Peretto G, Sala S, Rizzo S et al (2020) Ventricular arrhythmias in myocarditis: characterization and Relationships with myocardial inflammation. *J Am Coll Cardiol* 75:1046–1057
- Junttila MJ, Hookana E, Kaikkonen KS, Kortelainen ML, Myerburg RJ, Huikuri HV. Temporal Trends in the clinical and pathological characteristics of victims of Sudden Cardiac Death in the absence of previously identified Heart Disease. *Circ Arrhythm Electrophysiol* 2016;9.
- Tseng ZH, Olgin JE, Vittinghoff E et al (2018) Prospective countywide surveillance and autopsy characterization of Sudden Cardiac Death: POST SCD study. *Circulation* 137:2689–2700
- Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO (2009) Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation* 119:1085–1092
- Joy G, Artico J, Kurdi H et al (2021) Prospective case-control study of Cardiovascular Abnormalities 6 months following mild COVID-19 in Healthcare Workers. *JACC Cardiovasc Imaging*

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