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Assessment of Left Ventricular Function by Global Longitudinal Strain in Patients Recovered from Covid -19

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ABSTRACT

Background: Patients with COVID-19 infection may have an additional marker of outcomes with left ventricular (LV) strain evaluation by transthoracic echocardiography (TTE).

Objective: This study aimed to use two-dimensional (2D) speckle-tracking echocardiography to evaluate left ventricular (LV) global longitudinal strain (GLS) in order to identify subclinical cardiac impairment among recovered cases from Covid-19 infection.

Patients and methods: A case-control study in the isolation Hospital, Zagazig University in the duration from October 2021 to March 2022. We included 110 patients that were categorized in 2 groups according to clinical, radiological, laboratory and echocardiographic parameters: **Group I:** included patients recovered from Covid-19 (Study group). **Group II:** Non-Covid patients (Control group). This group included healthy subjects who have not encountered Covid-19 infection. **Results:** When comparing both groups, significant differences were found regarding echocardiographic data using speckle tracking. LVGLS was significantly decreased in cases compared to controls (19.18 ± 2.76 vs 21.58 ± 1.35, P<0.001), AP2GLS (18.90 ± 2.47 vs 21.58 ± 1.35, P<0.001), AP3GLS (20.28 ± 2.98 vs 21.94 ± 3.13, P = 0.005). A statistically difference existed between the two groups with respect to GLS, with all controls having a GLS value greater than −18 and 27.35% of cases had decreased GLS < −18%.

Conclusion: As a primary method, it's nearly as secure as the more traditional median sternotomy for mitral valve repair. Excellent cosmetic outcomes can be achieved without the need for additional groin incisions and the risks associated with them.

Keywords: Left ventricular function, Global longitudinal strain, Covid -19 infection.

INTRODUCTION

Since December 2019, when it was first detected, the 2019 coronavirus illness (COVID-19) has killed more than 1.9 million people around the world. Although our collective knowledge of COVID-19 illness pathogenesis, progression, and treatment has been expanding, it is still inadequate. An increase in mortality has been linked to heart damage caused by COVID-19 infection [(1)]. Acute respiratory distress syndrome, the respiratory system is the most heavily affected by SARS-CoV-2 (the agent of COVID-19), but other organs, notably the cardiovascular system, play important roles in the development of the disease [(2)].

Eighteen to twenty-eight percent of patients with COVID-19 have been documented to experience acute cardiac damage, as characterized by increased high-sensitivity cardiac troponin-I levels, which are associated with poorer clinical outcomes**.** Subclinical myocardial dysfunction has been shown to affect outcomes in COVID-19 patients, although our knowledge of this phenomenon is still restricted. Two-dimensional (2D) speckle-tracking strain measurement by transthoracic echocardiography is a predictor of cardiovascular events that can be detected before they become clinically apparent [(3)].

Monitoring cardiotoxic effects of chemotherapy and predicting morbidity and mortality in heart failure have both made use of LV strain assessment [(4)]. Acute myocardial injury has been linked to respiratory viral illnesses like influenza and acute respiratory distress syndrome (ARDS), but there is a severe dearth of data clarifying the specific roles of these pathogens in myocardial strain [(5)].

Transthoracic echocardiography (TTE) evaluation of left ventricular strain is a useful supplemental marker of outcomes in individuals with COVID-19 infection. Echocardiography using a method called strain by speckle tracking makes use of 2-dimensional grey scale pictures to assess global and localized left ventricular function. Systolic function can be evaluated using peak global longitudinal strain (GLS) [(6)].

Abnormal global longitudinal strain (GLS) in the left ventricle (LV) may indicate subclinical involvement of heart among COVID-19 cases. Long-term predictive usefulness of LV-GLS has been demonstrated across a variety of cardiac diseases, involving valvular disease as well as heart failure, suggesting that it is a precise measure of dysfunction of left ventricle. In addition, there is mounting proof that aberrant LV-GLS can detect myocardial damage before a decrease in LV ejection fraction occurs (EF). Given the lack of information about the long-term effects of COVID-19, it is essential to quickly identify individuals who may be at increased risk [(3)].

Moreover, in post hoc analysis, GLS had higher intra- and inter-observer repeatability than LVEF. In addition, GLS analysis is feasible in the vast majority of patients, and GLS measurements can be made just as quickly as LVEF measurements [(7)].

This study goal was evaluation of left ventricular (LV) global longitudinal strain (GLS) by using two-dimensional (2D) speckle-tracking echocardiography in

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order to detect subclinical myocardial impairment among cases who had previously been infected with Covid-19 and recovered.

PATIENTS AND METHODS

We performed our study in the isolation Hospital of Zagazig University in the duration from October 2021 to March 2022. We included 110 patients who were divided into 2 groups according to clinical, radiological, laboratory and echocardiographic parameters:

Group I: included patients recovered from Covid-19 (Study group)

Group II: Non-Covid patients (Control group). This group included healthy subjects who have not encountered Covid-19 infection.

Both real-time reverse transcription polymerase chain reaction (rRT-PCR) from nasal swabs as well as a chest computed tomography (CT) scan showed the presence of the COVID-19 virus.

Patients who had negative results from RT-PCR on a nasopharyngeal swab or radiographic evidence from chest CT scan were determined to have recovered from Covid-19. The following conditions were met for patients to be released:

- Maintaining a normal temperature for more than three days:
- Two negative RT-PCR findings in a row, with at least 24 hours between them.
- Improvement in breathing conditions.
- A period of isolation of at least 14 days is required.

At the one-month mark following release, an echocardiographic checkup was performed. Biochemistry results were acquired from a retrospective examination of patients hospitalised with COVID-19 infection and including blood glucose, complete blood count, renal function test, and C-reactive protein (CRP).

Exclusion criteria:

- Patients suffering from coronary artery disease (CAD).
- Heart failure patients.
- Valvular heart disease patients or who had cardiomyopathy.
- Non-sinus rhythm, including atrial fibrillation (AF) or paced rhythm.
- Diabetes mellitus: Any patient with HbA1c ≥ 6.5%, RBS ≥ 200mg/dl, FBS ≥126 mg/dl, 2-hours post prandial glucose in venous plasma ≥ 200 mg/dl [8].
- Hypertension: The latest American College of Cardiology/American Heart Association Recommendations for treating hypertension. Hypertension is now defined as systolic blood pressure that is greater than 130/80 mmHg, according to Canadian recommendations [9].
- Chronic renal failure
- Chronic liver disease.

All studied groups underwent the following:

1. History taking: A thorough and detailed history was taken, as regards the age, sex, class of functional capacity as defined by the New York Heart Association (NYHA).

2- Clinical examination: A complete clinical general and local cardiological examination was performed.

3- Lab investigations: Fasting blood sugar, complete blood count (CBC), liver function tests, serum electrolytes, kidney function tests, and prothrombin time and concentration.

4- Electrocardiogram (ECG).

5- Plain chest x-ray posteroanterior view in the erect position.

6- Echocardiography: During the COVID-19 epidemic, all TTEs were done and analysed in accordance with the published standards of the American Society of Echocardiography (ASE) for bedside focused investigation.

Through the use of a modified Simpson's biplane technique, we assessed LV ejection fraction (EF), ESV, and EDV in apical two and four chamber views of the heart. In the apical four-chamber and apical two-chamber views at end-diastole and end-systole, volume was measured by following the blood-tissue contact. A line drawn virtually across the mitral valve annulus's level completes the design [10]. After that, we used speckle tracking echocardiography to measure the global longitudinal strain in the left ventricle (LVGLS). Apical 4-, 3-, and 2-chamber views were used to capture images, with the latter two being analyzed offline, automatically, with commercially available software. A polar plot (Bulls' eye) provided visual and quantitative representations of regional LV function through the use of color-coded values of peak-systolic strain over 17 segments [11]. When it was available, we compared our findings to those from the index TTE study done during the COVID-19 hospitalization.

Ethical consent:

Institutional Review Board (IRB) approval from Zagazig University approved this study, and patients provided written informed consents. For this investigation, we followed the (Declaration of Helsinki), the guidelines established by the World Medical Association for the conduct of research involving human subjects.

Statistical analysis

IBM's SPSS program, version 20.0, was used to analyse the data submitted into the computer. IBM Corp., Armonk, NY. Quantitative data were summarized using percentages and charts. To ensure a normally distributed sample, the Kolmogorov-Smirnov test was used. The data were summarized using basic statistical methods: range (low and high), mean (average), standard deviation (SD), median (middle), and interquartile range (interq) (IQR). Chi square test

(χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). The importance of the data was determined by applying a cutoff of 5% to the total. P value ≤ 0.05 was considered significant.

RESULTS

Table (1) showed that age was 42.9 ± 11.42 and 44.20 ± 7.07 in case and control respectively with non-significant difference among groups. Also, there was no significant difference regarding sex. Weight was distributed as 76.47 ± 6.76 vs78.36 ± 8.72 (P = 0.207), height was 169.41 ± 6.86 vs 167.78 ± 6.88 (P = 0.215) and BMI was 27.66 ± 2.10 vs 28.03 ± 4.48 (P = 0.212). Systolic BP was 119.0 ± 10.06 vs 116.27 ± 11.6 (P 0.192) diastolic BP was 73.81 ± 11.86 vs 75.45 ± 5.79 (P 0.360) and they did not differ significantly among both groups. When comparing patients and controls, there was a statistically significant difference in HR which was 97.43 ± 7.93 vs 78.12 ± 10.24 in controls (p<0.001**).

Lymphocytes were significantly lower among cases 1.3 ± 0.45 vs. 2.12 ± 0.45 (P = 0.00) but CRP and D dimer were significantly higher among cases, CRP was 17.92 ± 6.58 vs 6.36 ± 2.13 (P <0.001**), D dimer was 3.94 ± 1.35 vs 0.65 ± 0.25 (P <0.001**).

Table (1): Demographic, vital signs and laboratory investigations of the studied groups

			Cases	Control	t/ X^2	P
Age (years)			42.9±11.42	44.20±7.07	0.712	0.478
Weight (kg)			76.47±6.76	78.36±8.72	1.270	0.207
Height (cm)			169.41±6.86	167.78±6.88	1.248	
BMI (kg/m^2)			27.66±2.10	28.03±4.48	1.259	0.212
SEX	**Male**	**N**	38	30		
		%	69.1%	54.5%		
	Female	**N**	17	25	2.46	0.11
		%	30.9%	45.5%		
Smoker	**Yes**	**N**	39	39		
		%	70.9%	70.9%		
	No	**N**	16	16	0.0	1.0
SBP(mmHg)			119.0±10.06	116.27±11.6	1.312	0.192
DBP(mmHg)			73.81±11.86	75.45±5.79	0.919	0.360
HR			97.43±7.93	78.12±10.24	11.05	<0.001**
CRP(mg/L)			17.92±6.58	6.36±2.13	6.134	<0.001**
Lymphocytes (mm^3)			1.3±0.45	2.12±0.45	6.619	<0.001**
D_DIMER (ng/mL FEU)			3.94±1.35	0.65±0.25	10.020	<0.001**

Table (2) showed that recovery from Covid-19 was associated with significant differences in echocardiographic data compared to normal participants (controls). There were decreased values of LVGLS in cases compared to control (19.18 ± 2.76 vs 21.58 ± 1.35, P <0.001**), AP2GLS (18.90 ± 2.47 vs 21.58 ± 1.35, <0.001**), AP3GLS (20.28 ± 2.98 vs 21.94 ± 3.13, P 0.005*), AP4GLS (20.67 ± 2.74 vs 21.08 ± 2.85, P 0.132).

Table (2): ECHO findings of the studied groups

	Cases	Control	t	P
LVGLS	19.18±2.76	21.98±1.12	6.982	<0.001**
AP2GLS	18.90±2.47	21.58±1.35	7.016	<0.001**
AP3GLS	20.28±2.98	21.94±3.13	2.847	0.005*
AP4GLS	20.67±2.74	21.08±2.85	1.442	0.132
LVEF	63.82±8.54	65.26±5.66	1.789	0.075
LVEDV	97.10±21.26	90.63±20.69	1.508	0.135
LVESV	38.60±8.89	35.50±8.25	1.677	0.096

LVEF Left ventricular ejection fraction, LV-GLS Left ventricular global longitudinal strain, LVEDV Left ventricular end-diastolic volume, LVESV Left ventricular end-systolic volume.

Table (3) showed that all of the controls had GLS values greater than or equal to 18, hence there was a huge gap between the two groups statistically but only (72.75%) of cases had normal GLS >18 and (27.35%) had decreased **GLS< 18.**

Table (3): Global longitudinal strain distribution between studied groups

			Group		X^2	P
			Case	Control		
GLS	**GLS >18**	**N**	40	55		
		%	72.7%	100.0%		
	GLS<18	**N**	15	0	**17.36**	**<0.00****
		%	27.3%	0.0%		
Total		**N**	55	55		
		%	100.0%	100.0%		

Table (4) showed that HR, CRP and D dimer were significantly higher among cases with GLS < 18. HR was 94.32 ± 6.24 Vs. 105.7 ± 5.73 among those with GLS > 18 versus those with GLS < 18 ($p < 0.01$**)**.** CRP was found to be 11.33 ± 10.90 vs. 17.29 ± 13.62 and D dimer (2.08 ± 0.85 vs 3.68 ± 1.32), in patients with GLS >18 compared to patients with GLS <18 ($p < 0.01$**). Lymphocytes were significantly lower in cases with GLS <18. It was found to be 1.79 ± 0.61 vs 1.21 ± 0.45) in patients with GLS >18 compared to those with a GLS lesser than 18 ($p < 0.01$**).

Table (4): Univariate analysis of different predictors between cases with normal GLS and decreased GLS

	GLS >18	**GLS <18**		
Age (years)	43.04±9.04	46.80±11.73	1.433	0.155
BMI (kg/m^2)	27.35±3.73	27.34±2.18	0.009	0.993
SBP (mmHg)	117.26±10.81	120.0±11.80	0.900	0.370
DBP (mmHg)	74.31±9.52	76.66±7.94	0.906	0.367
HR	94.32±6.24	105.7±5.73	-6.15	<0.001**
CRP (mg/L)	11.33±1.90	17.29±3.73	2.450	0.021*
Lymphocytes (mm^3)	1.79±0.41	1.21±0.45	2.804	0.006*
D_DIMER (ng/mL FEU)	2.08±0.53	3.68±0.83	2.480	0.015*

Lymphocytes number, CRP and HR were significant predictors for LV GLS among covid 19 patients (Table 5).

Table (5): multivariate liner regression analysis for detection of predictors of LV GLS dysfunction among cases

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
LVGLS	**CRP**	7545.188	27	279.45	2.88	**0.004***
	Lymphocytes	27.617	27	1.02	3.95	**<0.001***
	D DIMER	205.715	27	7.61	1.88	0.053
	HR	2379.361	27	88.124	2.323	**0.016***

Table (6) showed that statistically, LV GLS was positively correlated with HR, CRP, and D dimer. C-reactive protein and D Dimer also had a positive connection (Figures 1 & 2).

Table (6): Correlation between HR, CRP, lymphocytes, D dimer and LV GLS among cases

Items		**LVGLS**	**CRP**	**D DIMER**
HR	R	**-0.551**	.028	.156
	P	**<0.001***	.842	.254
	N	55	55	55
CRP	R	**-.283***	1	**.648****
	P	**.036**		**0.001**
	N	55	55	55
Lymphocytes	R	-.002	-.210	.076
	P	.989	.123	.579
	N	55	55	55
D DIMER	R	**-.269***	.648**	1
	P	**0.04**	.000	
	N	55	55	55

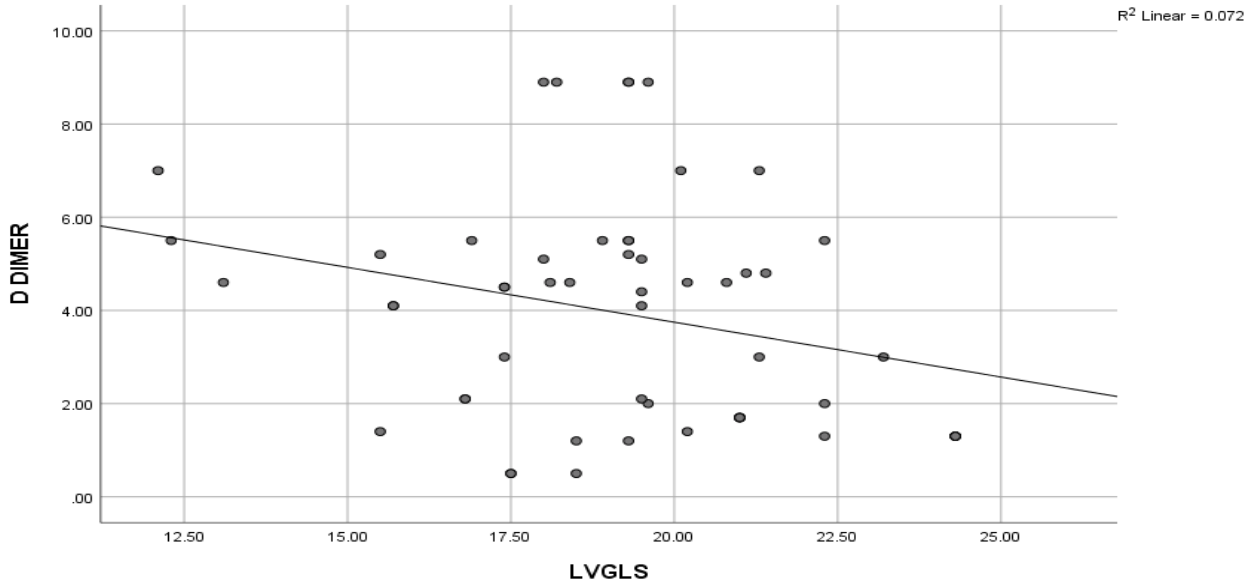

Figure (1): Scatter diagram showing negative correlation between LV GLS and D dimer

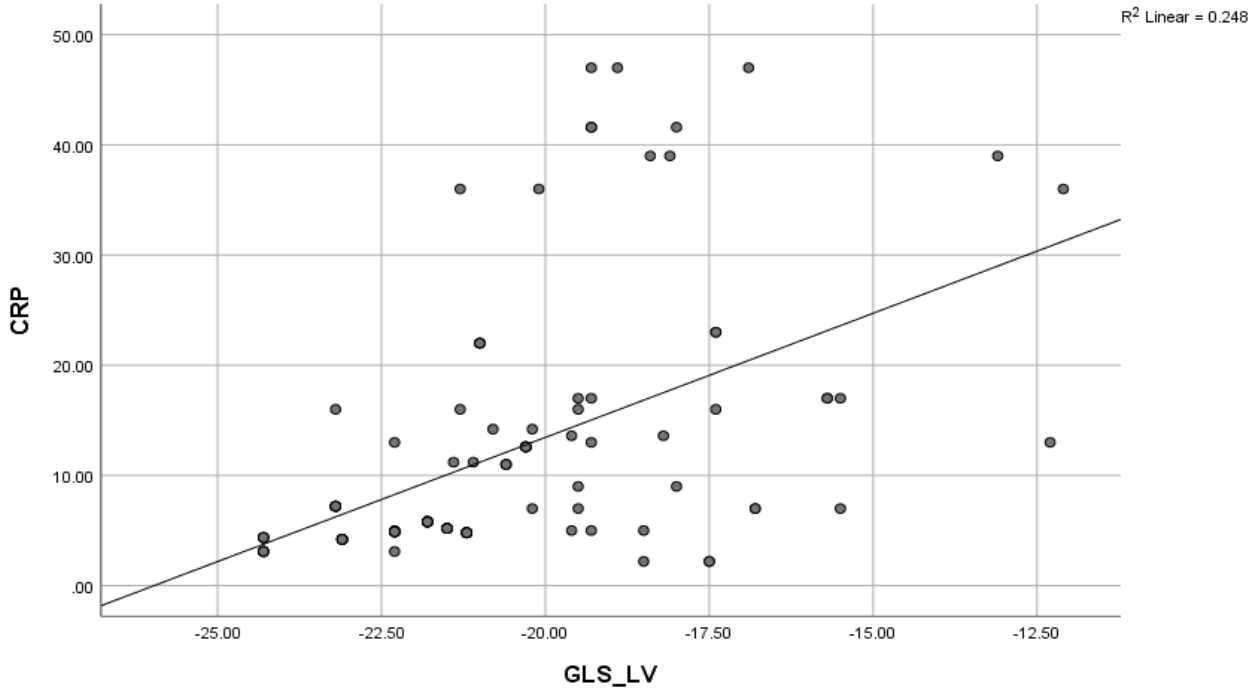

Figure (2): Scatter diagram illustrating positive correlation between LV GLS and CRP level

Table (7) showed that HR at the level > 101 was 80.0% sensitive and 95.0% specific with overall accuracy 87.3% (95% CI). CRP at the level > 13 was 54.5% sensitive and 52.7% specific with overall accuracy 46.4% (95% CI) (Figure 3).

Table (7): Validity of HR and CRP as predictors in cases with decreased LV GLS

Items	AUC	95%CI	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP	0.493	0.320-0.665	13.5	54.5%	52.7%	53.5%	53.7%	49.4%
HR	0.928	.858-0.999	>101	80.0%	95.0%	93.6%	82.5%	87.3%

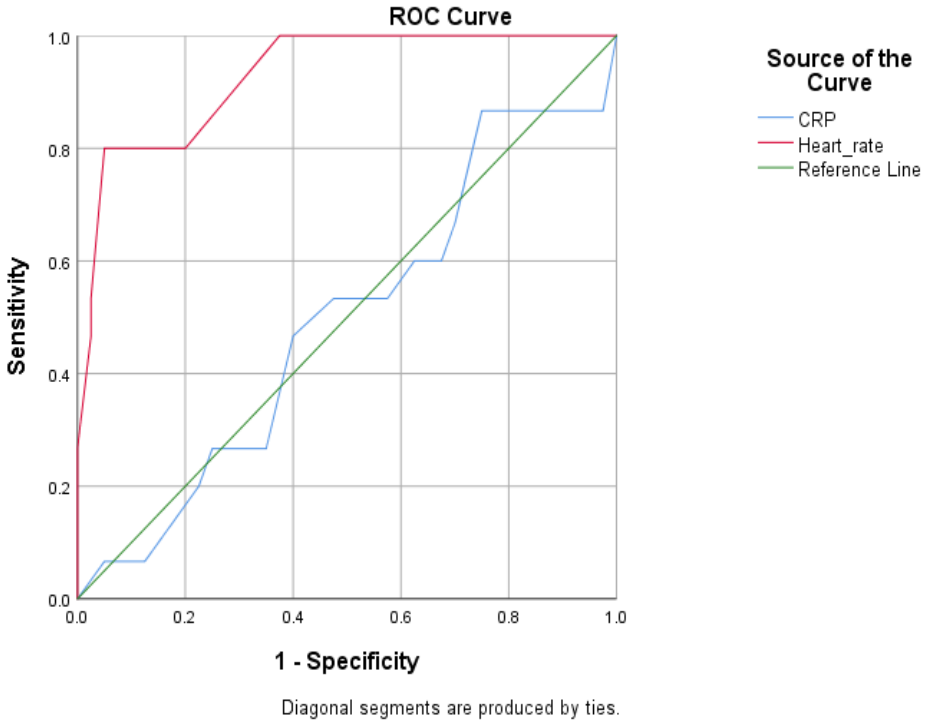

Figure (3): ROC curve Validity of HR and CRP as predictors in cases with decreased LV GLS.

DISCUSSION

Examination of segmental longitudinal strain (LS) patterns can aid in the diagnosis of heart diseases when a pathognomonic defect is detected in addition to clinical evidence, such as the apical-sparing strain reduction seen in cardiac amyloidosis. The basal left ventricular LS of COVID-19 inpatients consistently reduced on STE [(3)].

In the current study we found that both groups; cases and controls were matched regarding age, weight, BMI, height and sex data with no significant difference between them. SBP, DBP and HR did not differ significantly between groups. However, heart rate (HR) was significantly higher in the study group compared to controls. Moreover, Comparing the study group to a control group, the study group had considerably higher levels of CRP and D-dimer. Lymphocytes were significantly lower among cases.

Turan *et al.* [(12)] illustrated that the study population consisted of 70 people (37 females and 33 males, with a mean age of 43.59 11.83 years). Seventy healthy adults (34 women and 36 men, with a mean age of 46.66 16.58) served as the comparison group. Serum levels of haemoglobin, hematocrit, mean corpuscular volume (MCV), and albumin were comparable between the two groups with only the hematocrit being significantly lower in the control group. Compared to the control group, the people with COVID-19 had lower levels of hemoglobin, hematocrit, and mean corpuscular volume (MCV), and greater levels of plasma albumin.

Using speckle tracking, we found that there were statistically significant differences between the two groups in this investigation using echocardiographic data. The incidence of global LVGLS, AP2GLS, AP3GLS were lower in cases than in controls. However, in terms of AP4GLS, there was no discernible difference between the two groups. Also, LVEF assessed by Simpson's biplane method did not show difference between the two groups.

Turan *et al.* [(12)] reported that ECHO examinations were performed and a median (interquartile range) of 23 (11-89) days after a COVID-19 diagnosis was made. No significant relationship was seen between any of the classical ECHO parameters and the duration of time since the first patient diagnosis of COVID-19 (LV-GLS: r = 0.006, p = 0.96; similarly, p > 0.05 was seen for all of the other traditional ECHO parameters). Both the COVID-19 and control groups showed identical classical ECHO characteristics, such as peak late mitral filling velocity (A wave), peak late diastolic myocardial velocity (A'), and tricuspid lateral annular systolic velocity (S'). The COVID-19 cohort's A, A', and S' wave velocities were higher than those of the COVID-18 cohort.

Mahajan *et al.* [(13)] documented C-reactive protein (p = 0.006) and interleukin-6 (p = 0.002) levels, total leukocyte count (p = 0.003), and hemoglobin (p = 0.004) were all substantially greater in the group with severe COVID-19 sickness than in the group with mild disease.

Regarding LV Global longitudinal strain (GLS) value, our current findings clearly revealed that classification of patients according to GLS value in accordance to latest recommendations of European guidelines where a change in segmental strain was considered to have occurred when the number dropped below -18%. We found that there was highly statistically significant difference between both groups regarding GLS with all controls having normal GLS value > −18 and 27.35% of cases having decreased GLS < −18%. **Özer *et al.* [14]** revealed that 28 patients (37.8%) had LV-GLS values above -18. Sixteen (57.1%) of these individuals had myocardial damage, while 12 (26.1%) did not (p = 0.014). Myocardial damage was associated with greater mean LVGLS values than non-injury (-17.7 2.6 vs. -18.9 1.8, p = 0.051). Also, there was a correlation between troponin concentrations and LV-GLS scores (r = 0.22, p = 0.045).

In the current study we performed multiple linear regression analysis of potential predictors of decreased LV GLS among patients recovered from COVID-19 that revealed statistically significant difference among both groups regarding heart rate, CRP, lymphocyte number and D-dimer level. **Turan *et al.* [12]** reported that although both were significantly higher in COVID-19 survivors compared to controls (p = 0.02, p = 0.04, respectively), those who included the grey zone of the cut-off value (absolute value 18) had a significantly higher proportion of patients with LV-GLS deterioration (42.9% vs. 5.7%, respectively) in their analysis. According to the most recent in-depth findings and most recent expert consensus, the study established LV-GLS cut-off values. Low-risk asymptomatic outpatients made up the majority of the study population. In addition, their study had a control group of healthy people of the same age and gender, which is not something you see in a lot of other studies. These variations could account for the relatively low incidence of left ventricular dysfunction.

In the present study on multivariate regression analysis, we found that only HR, CRP and lymphocyte number remained significant and could be used as predictors for LV dysfunction in patients recovered from COVID-19. **Turan *et al.* [12]** demonstrated that recovery from COVID-19 might be used to anticipate the presence of LV -GLS (absolute value 18) in a multivariate logistic regression study (OR, 0.133 (0.038-0.461); 95% CI, p = 0.001). One other predictor was age (p = 0.039). The levels of C-reactive protein and the standard inflammation marker were similar in the control and COVID-19 groups. **Zheng *et al.* [15]** showed meta-analysis of 13 studies found that elevated troponin and D-Dimer levels in COVID-19 patients were linked to substantial morbidity and mortality. Patients hospitalised with COVID-19 often have elevated troponin levels, which is linked to myocardial damage and mortality.

Our current findings regarding correlation analysis between HR, CRP, lymphocyte number and LV GLS clearly revealed that there was statistically significant negative correlation between LV GLS and HR and CRP. We performed scatter diagram that confirmed the negative correlation between HR and CRP and LV GLS. To a similar extent, **Mahajan *et al.* [13]** found a positive correlation between IL-6 levels among active COVID-19 infection and LVGLS after recovery from the virus. Further, cardiac troponins were significantly correlated with LVGLS (r =.41; p 0.0001) indicating that patients with myocardial damage at the time of their index hospitalization for COVID-19 likely had compromised LVGLS.

Here, we used ROC curve analysis to determine the best cutoff value for predicting LV dysfunction in cured COVID-19 patients. This was done for both HR and CRP. We found that HR >101 bpm was 80.0% sensitive and 95.0% specific with AUC 92% (95% CI: 0.858-0.999) and CRP >13.5 mg/dl was 54.5% sensitive and 52.7% specific with AUC 49.3% (95% CI: 0.320-0.665) to predict LV dysfunction.

Li and colleagues [16] in 75 out of 77 patients diagnosed with acute myopericarditis had echo-bright areas within the LV wall on transthoracic echocardiography (TTE), Myocarditis was confirmed by CMRI in these regions with a sensitivity of 95%, specificity of 93%, and a positive predictive value of 95.2%. Our patients' segmental myocardial brightness was connected to the aberrant segments via GLS in 74% of cases.

CONCLUSION

Patients with minimal cardiac risk who had recovered with home quarantine and had no symptoms may nevertheless have subclinical LV dysfunction which could be detected by LV-GLS in the early recovery period. The importance of these patients' cardiovascular follow up may be higher than previously appreciated. Larger studies with longer follow-up periods are necessary to verify our findings and develop reliable methods for predicting cardiac occurrences in the future.

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