**Speckle tracking echocardiographic assessment of Left ventricular global longitudinal strain in patients recovered from COVID-19**

**ABSTRACT:**

**Background:** The COVID-19 infection has firmly established itself as a pandemic that can affect many body systems, including the cardiovascular system.2D speckle tracking echocardiography (2D-STE) can diagnose early subclinical myocardial dysfunction, as many studies have reported an inverse correlation of increased cardiac biomarkers level with global longitudinal strain (GLS) values among COVID-19 patients. **Aim:** This study assessed the global Left ventricular strain using speckle tracking echocardiography in patients recently recovered from COVID-19 infection. **Patients and methods:** This study was done in Benha University Hospital from June 2022 to January 2023 and included 100 patients who had positive COVID-19 diagnosis proved by positive polymerase chain reaction (PCR) test of the nasopharyngeal swab within 30 ±5 days. **Results:** Patients were classified according to the upper laboratory limit of the hs-troponin (11.6) into two groups; with myocardial injury (hs-troponin > 11.6) and without myocardial injury (hs-troponin ≤ 11.6). Patients with myocardial injury had significantly lower EF and LVGLS (P < 0.001). No significant differences were observed regarding ECG abnormality, D-dimer, and TLC. Moreover, LVGLS showed significant negative correlations with age (P < 0.001), hs-troponin (P = 0.013), and D-dimer (P = 0.013). In contrast, it showed a significant positive correlation with EF (P < 0.001), and no significant correlation was observed with TLC (P = 0.408). **Conclusion:** Serial measurements of cardiac troponin and LVGLS following recovery from COVID‐19 infection has an incremental prognostic value and can be used to evaluate the progression of sub‐clinical LV dysfunction.

**Keywords:** COVID-19, myocardial injury, cardiac troponin, global longitudinal strain.

**Introduction:**

The COVID-19 infection, which occurs as a result of infection with the novel coronavirus SARS-CoV-2, is a highly infectious and pathogenic viral infection that emerged in China and spread as a pandemic across the whole world **(1)**. Genetic analysis revealed that SARS-CoV-2 is phenotypically and genetically related to acute respiratory syndrome-like (SARS-like) bat viruses. Corona viruses are enveloped, positive-stranded RNA viruses with a nucleocapsid, and the genomic structure is organized as a single stranded RNA of approximately 30 kb in length and with a 5′-cap structure and 3′-poly-A tail making it the largest RNA virus **(2).** Upon entry into the host, replication of the viral RNA starts with the synthesis of polyprotein 1a/1ab (pp1a/pp1ab). The transcription occurs through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of sub genomic RNAs (sgRNAs) sequences **(3).** COVID-19 is considered mainly as a respiratory viral illness as its causative agent, SARS-CoV-2, predominantly targets the respiratory and vascular systems. The pathogenesis of COVID- 19 induced pneumonia is best explained by two stages, an early and a late phase. **(4).**The early phase is characterized mainly by viral replication resulting in direct virus-mediated tissue damage **(5)**, while the late phase occurs later when the infected host cells trigger an immune response with the recruitment of T lymphocytes, neutrophils and monocytes that releases cytokines such as tumor necrosis factor-α (TNF α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), IL-6, IL-8, IL-12 and interferon (IFN)-γ **(6)**.However, it can affect all body systems, including the cardiovascular system. Acute myocardial injury, detected by elevated serum levels of cardiac biomarkers, heart failure, arrhythmias, myocarditis and acute coronary syndromes have been described as its common cardiovascular complications **(7)**. Recent studies have indicated that endothelial dysfunction is a main feature of COVID-19 infection. This relation is evidenced by the role of the vascular endothelium in the hyperinflammatory state, which is the major driver of cytokine storm in ARDS as well as multiple cardiovascular and COVID 19 related pathologies **(8)**. Also, the hypercoagulable state and disseminated intravascular coagulation observed in COVID-19 reflect a state of endothelial damage and enhances thrombosis by reduced endothelial integrity leading to exposure of prothrombotic subendothelial matrix, adhesion and aggregation of platelets with subsequent initiation of clotting cascades, thrombin activation, and fibrin production **(9).** Moreover, Acute viral infections including SARS, influenza and COVID-19 can trigger ACS and may directly cause inflammation in the coronary vasculature, in addition to causing systemic inflammation **(10)**. A post mortem study suggested that patients with COVID 19 infections had increased infiltration of atherosclerotic vascular plaques with macrophages and increased infiltration of the adventitia with T-cells, macrophages and dendritic cells **(11).** Oxygen supply demand mismatch is considered one of the possible mechanisms of COVID-19 induced ACS, as hypoxia and respiratory failure are considered the leading causes of death in COVID-19, accounting for about 60% of cases with fatal outcome **(12)**. The severe hypoxic state, combined with other factors such as: sepsis, anemia, tachyarrhythmias, hypotension, and shock can induce myocardial damage due to the mismatch between oxygen supply and demand in absence of significant atherothrombotic lesions, consistent with the diagnosis of type 2 MI **(13).** Given their high complexity and vulnerability, critically ill patients with COVID-19 are highly susceptible to the occurrence of type 2 MI, which strongly contributes to the high rate of in hospital mortality among COVID patients **(14).** Furthermore, myocardial infarction with nonobstructive coronary arteries (MINOCA) has been widely reported among COVID-19 patients. Several mechanisms have been proposed for these cases, including coronary vasospasm, plaque erosion and microthrombi. The exact mechanisms of MINOCA are largely under-investigated due to difficulties in performing invasive and noninvasive diagnostic work-up among COVID 19 patients including intravascular imaging, cardiac magnetic resonance and pharmacological provocative test **(15)**. 2D speckle tracking echocardiography (2D-STE) can diagnose subclinical myocardial dysfunction earlier than conventional echocardiography **(16)**. Recent studies have reported an inverse correlation of increased cardiac biomarkers level with global longitudinal strain (GLS) values in the population **(17)**. However, the level of cardiac involvement, if any, should be identified and which patient group is more risky, So that we can determine which patient group should be followed-up and treated for long-term cardiac involvement **(18)**.

**Patients and methods:**

**Study design:**

Analytical cross section study at Benha university hospital.

**Ethical consideration:**

Before doing echocardiography or taking blood samples, a written informed consent was taken from each patient.

**Patients:**

100 patients who were tested Positive for COVID 19 infection at Benha University hospital.

**Inclusion criteria:**

Patients who had COVID-19 diagnosis proved by positive polymerase chain reaction (PCR) test of the nasopharyngeal swab within 30 ±5 days.

**Exclusion criteria:**

\*Age is less than 18 years.

\*Patients presented with acute coronary syndrome.

\*Patients presented with acute heart failure.

\*Patients presented with rapid tachyarrhythmias including atrial fibrillation and ventricular arrhythmias.

\*Patients presented with renal failure (eGFR < 30 ml/min).

\*Patients presented with severe chronic obstructive pulmonary disease (COPD).

\*Patients with poor echogenicity

**Methods:**

**a) Written informed consent:**

It was taken before the start of the study. No risks will be found and any unexpected risk appearing during the study will be cleared to the patients and the committee on time.

**b) Complete history taking:**

Age, gender, hypertension, diabetes, smoking, dyslipidemia, history of IHD, onset and offset of COVID symptoms.

**c) Clinical examination**

Complete physical examination including: vital signs with general, chest, and cardiac examination.

**d) 12 Lead ECG.**

**e) Routine lab investigations:**

Serum creatinine, complete blood picture and high sensitive troponin (hs-TnI).

**F) Echocardiography:**

Echocardiographic examination was performed on patients within one month after discharge. Echocardiographic images were obtained and recorded by standard techniques. Left ventricular global longitudinal strain (LV-GLS) was analyzed by using the Qlab13 program. The mean GLS was calculated by averaging the peak GLS values of apical two-chamber, apical three-chamber, and apical four-chamber images.

**G) Statistical design:**

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Kolmogorov–Smirnov test, the Shapiro-Wilk test, and direct data visualization methods. Quantitative data were compared according to myocardial injury using the independent t-test or Mann-Whitney U test for normally and non-normally distributed quantitative data. Categorical data were compared using the Chi-square test. ROC analysis was done for LVGLS to predict myocardial injury. The area under the curve with a 95% confidence interval, best cutoff point, and diagnostic indices were calculated. Correlations were done using Pearson’s or Spearman’s correlation. Multivariate stepwise logistic regression analysis was done to predict myocardial injury. The odds ratios with 95% confidence intervals were calculated. All statistical tests were two-sided. P values less than 0.05 were considered significant.

**Research ethics committee: MD.4.6.2021**

**Results:**

Among the studied patients, the mean age was 54 ±15 years. More than half (58%) were females. Diabetes mellitus and hypertension were reported in 41% and 52%, respectively. Half the patients had dyslipidemia (50%), and half were smokers (50%). About one-third (41%) had a history of IHD. The median time from diagnosis was 13 days, ranging from 2-27 days **(Table 1).**

**Table (1) General characteristics of the studied patients**

|  |  |  |
| --- | --- | --- |
| **General characteristics** |  |  |
| **Age (years)** | Mean ±SD | 54 ±15 |
| **Sex** |  |  |
| **Males** | n (%) | 42 (42) |
| **Females** | n (%) | 58 (58) |
| **Diabetes mellitus** | n (%) | 41 (41) |
| **Hypertension** | n (%) | 52 (52) |
| **Dyslipidemia** | n (%) | 50 (50) |
| **Smoking** | n (%) | 50 (50) |
| **History of IHD** | n (%) | 41 (41) |
| **Time from diagnosis (days)** | Median (range) | 13 (2 - 27) |

Patients were classified according to the upper laboratory limit of the hs-troponin (11.6) into two groups; with myocardial injury (hs-troponin > 11.6) and without myocardial injury (hs-troponin ≤ 11.6). Patients with myocardial injury had significantly lower EF (58 ±3 vs. 63 ±1, P < 0.001) and LVGLS (-17.8 ±1.5 vs. -20.2 ±0.4, P < 0.001). No significant differences were observed regarding ECG abnormality (P = 0.292), D-dimer (P = 0.370), and TLC (P = 0.553) (Table 2).

**Table (2) Clinical characteristics of the studied patients according to myocardial injury**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Myocardial injury** |  |
|  |  | Yes (n = 76) | No (n = 24) | P-value |
| **ECG abnormality** | n (%) | 56 (73.7) | 15 (62.5) | 0.292 |
| **EF (%)** | Mean ±SD | 58 ±3 | 63 ±1 | <0.001\* |
| **LVGLS** | Mean ±SD | -17.8 ±1.5 | -20.2 ±0.4 | <0.001\* |
| **D Dimer** | Median (range) | 590 (132 - 1410) | 345 (273 - 1438) | 0.370 |
| **TLC** | Median (range) | 9 (3.2 - 18.5) | 7.5 (3.4 - 17.4) | 0.553 |

LVGLS showed significant negative correlations with age (r = -0.709, P < 0.001), hs-troponin (r = -0.924, P < 0.001), and D-dimer (r = -0.247, P = 0.013). In contrast, it showed a significant positive correlation with EF (r = 0.894, P < 0.001). No significant correlation was observed with TLC (P = 0.408) (Table 3).

**Table (3) Correlation between LVGLS and other parameters**

|  |  |
| --- | --- |
|  | **LVGLS** |
|  | R | P |
| **Age (years)** | -.709 | <0.001\* |
| **EF %** | .894 | <0.001\* |
| **hs-Troponin** | -.924 | <0.001\* |
| **D-dimer** | -.247 | 0.013\* |
| **TLC** | -0.084 | 0.408 |

**Discussion:**

Various studies have reported an inverse correlation of increased cardiac biomarkers level with global longitudinal strain (GLS) values among the patients with or without established cardiovascular disease. Studies in the literature had focused on the increase in cardiac troponin levels and cardiac involvement due to COVID-19 during hospitalization **(19)**.

The aim of the current study was to assess the global Left ventricular strain using speckle tracking echocardiography in patients recently recovered from COVID-19 infection.

In agreement with that results, **Zheng, et al** in 2020 analyzed 13 meta-analyses and examined 3027 patients with COVID-19 infection, and found that elevated troponin levels were significantly associated with disruption in the LV-GLS, and increased severity of the disease and mortality **(20)**.

Furthermore, **Özer, et al** in 2021 showed that among 127 post COVID-19 patients included in his study, patients with myocardial injury showed significantly lower EF (p=0.032), LVGLS (p=0.05) and higher LA diameter (p=0.01). However, in contrast to our study, he showed that patients with myocardial injury had also significantly higher levels of D Dimer and TLC (P=0.01) **(21)**.

As regard the LVGLS and its correlation with other parameters, **Mahajan,et al** in 2021 agreed with our results as he evaluated the LVGLS among 134 patients recovered from COVID-19 infection and found that  there was a significant correlation between cardiac troponins and LVGLS ( p < 0.0001) suggesting impaired LVGLS among patients with myocardial injury during index hospitalization with COVID‐19 infection **(22).**

While cardiac troponins during the acute COVID‐19 infection indicates myocardial inflammation and acute myocardial injury, LVGLS represents the clinical transformation of this myocardial injury into subclinical LV dysfunction **(23)**.

The reduction in LVGLS and elevation of cardiac troponin among COVID-19 patients may be due to various factors including viral infiltration of the myocardium that can lead to cardiomyocyte inflammation and death, respiratory failure and hypoxia that may cause myocardial injury, the immune response’s activation and the release of cytokine storm that will cause myocardial inflammation and finally, microvascular dysfunction, coronary plaque thrombosis and rupture due to hypercoagulable state can also cause myocardial injury and inflammation **(24)**.

**Conclusion:**

 serial measurements of cardiac troponin and LVGLS following recovery from COVID‐19 infection has an incremental prognostic value and can be the ideal way to evaluate the progression of sub‐clinical LV dysfunction.

**Study limitations:**

\*Larger sample size and longer follow up period are needed to confirm the results.

\*Further trials are needed to compare LVGLS and cardiac biomarkers with other inflammatory markers.

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