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Prevalence of abnormal left ventricular global longitudinal strain by speckle tracking echocardiography and its prognostic value in patients with COVID-19

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ABSTRACT

Importance Although cardiac injury is a known complication of COVID-19 infection, there is no established tool to predict cardiac involvement and in-hospital mortality in this patient population.

Objective To assess if left ventricular global longitudinal strain (LV-GLS) can detect cardiac involvement and be used as a risk-stratifying parameter for hospitalised patients with COVID-19.

Main outcomes and measures In-hospital mortality.

Results We found a statistically significant association between LV-GLS and in-hospital mortality (adjusted OR (aOR)=1.09; 95% CI 1.0 to 1.19, p=0.050). Furthermore, right ventricular fractional area change was significantly associated with in-hospital mortality (aOR=1.04; 95% CI 1.0 to 1.08, p=0.043). Troponin level had no statistically significant association with in-hospital mortality (aOR=3.43; 95% CI 0.78 to 15.03, p=0.101).

Conclusion and relevance LV-GLS can be a useful parameter for cardiovascular risk assessment in hospitalised patients with COVID-19 infection.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Left ventricular global longitudinal strain (LV-GLS) serves as a highly sensitive marker of myocardial function, capable of detecting subtle changes in cardiac performance even before conventional measures, such as the assessment of left ventricular ejection fraction, manifest abnormalities.
⇒ It has firmly established its utility in the timely detection of cardiotoxicity associated with specific cancer therapies, as well as in the evaluation of infiltrative cardiomyopathies.
⇒ However, its precise role in assessing early cardiac involvement in COVID-19 remains an area where its clinical application is not yet firmly established.

WHAT THIS STUDY ADDS

⇒ In this pilot study of 131 patients with COVID-19 admitted to the hospital between March 2020 and April 2020, 89 (67.9%) patients had an abnormal LV-GLS.
⇒ There was a significant association between abnormal longitudinal strain and in-hospital mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This pilot study has identified abnormal left ventricular longitudinal strain as a sensitive prognostic indicator for in-hospital mortality in patients with COVID-19.
⇒ The presence of a readily available bedside cardiac imaging tool for the detection of subclinical left ventricular dysfunction stands as a valuable resource within this patient demographic, with the potential for broad utilisation across diverse medical institutions.

INTRODUCTION

COVID-19 infection, caused by SARS-CoV-2, started at the end of 2019 in Wuhan, China and was declared a global pandemic by the WHO on 11 March 2020.[1] Cardiac injury is prevalent among hospitalised patients with COVID-19 and has been detected using troponin levels and found to be primarily associated with in-hospital mortality.[2] Echocardiography remains the mainstay imaging modality for the assessment of cardiac structures and left ventricular (LV) functions, however, two-dimensional speckle tracking echocardiography (2D-STE) is helpful in evaluating subclinical impairment of myocardium earlier and more accurately than conventional echocardiography. LV global longitudinal strain (LV-GLS) has been demonstrated to provide an accurate and reproducible estimate of global LV function and myocardial tissue damage. LV-GLS has been used in clinical practice for its diagnostic and prognostic significance independent of LV ejection fraction (LVEF) in cardio-oncology, valvular

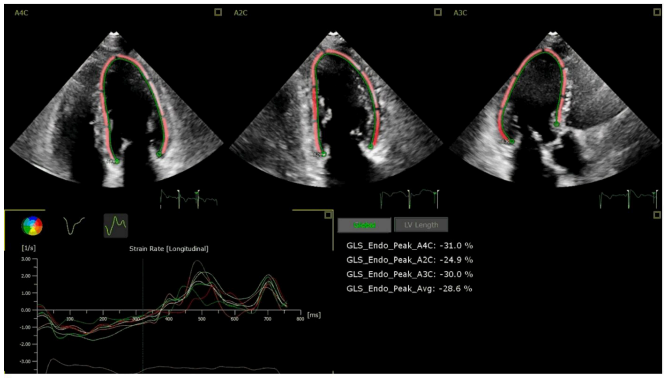

Figure 1 Assessment of left ventricular global longitudinal strain (GLS) using TOMEC software.

heart diseases, and ischaemic and non-ischaemic cardiomyopathies.[3 4] The aim of this pilot study is to evaluate if LV-GLS is abnormal in COVID-19 infection and its correlation with troponin levels which are currently used as marker of cardiac injury in this patient population.

PATIENTS AND METHODS

Methods

Charts were collected of patients who were diagnosed with COVID-19 infection from 22 March 2020 through 24 April 2020 at Steward Healthcare hospitals in Massachusetts. 131 patients were identified. COVID-19 infection was confirmed by PCR testing. An echocardiography study was performed for all included patientsVerified.

Echocardiographic assessment

Two-dimensional and Doppler echocardiography studies were performed. Global longitudinal strain was performed for the included patients using Tomtec software (figure 1.). Parameters for the global longitudinal strain were adjusted manually when needed. LVEF, right ventricular fractional area change (RVFAC) and several other measurements were collected. We defined an abnormal LV-GLS cut-off value of −18.0%.[5]

Clinical data collection

For the included patients, charts were retrospectively reviewed, and relevant data were collected. Collected data included age, gender, race, body mass index (BMI) and past medical history (smoking, hypertension, diabetes, hyperlipidaemia, coronary artery disease, congestive heart failure, cerebrovascular accidents, chronic kidney disease, atrial fibrillation and other comorbidities). Furthermore, laboratory data were collected for the included patients (leucocyte count, troponin, creatinine phosphokinase, B-natriuretic protein, liver function tests and inflammatory markers). Current medications information, length of stay, intensive care length of stay and ventilated days were also collected for all included patients. Congestive heart failure was defined as symptoms or signs caused by a structural/or functional cardiac pathology corroborated by objective evidence of cardiogenic pulmonary or systemic congestion or elevated natriuretic peptide levels. Peak troponin level was taken for the analysis and abnormal troponin levels were defined as conventional troponin I levels exceeding 0.04 ng/mL[6]

Statistical analysis

Data were expressed as mean values±SD, and frequencies were denoted in percentages. Independent two-sample t-tests were used for the comparison of continuous variables measurements, and χ^2 test for categorical variables. Multivariable logistic regression analysis of the association between global longitudinal strain and in-hospital mortality was performed. The model was adjusted for patient's age, gender, race, BMI, included comorbidities (smoking, chronic obstructive pulmonary disease/asthma, hypertension, hyperlipidaemia, obstructive sleep apnoea, history of myocardial infarction, coronary artery disease, prior coronary artery bypass grafting (CABG), diabetes mellitus, congestive heart failure, cerebrovascular accidents, chronic kidney disease and atrial fibrillation). Furthermore, multivariable logistic regression of the associated RVFAC was performed. A value of $p<0.05$ was considered statistically significant. SPSS V.25 software (IBM Corp, Armonk, New York, USA) was used for all statistical analyses.

RESULTS

A total of 131 patients with COVID-19 infection were identified. Out of 131 patients, 89 (67.9%) had abnormal LV-GLS and 42 (32.1%) had normal LV-GLS. There was no difference in terms of age, gender or ejection fraction between both groups ($p\geq0.091$ for both). Patients with abnormal strain had higher likelihood of having diabetes mellitus and congestive heart failure ($p\leq0.007$ for both). Both groups had comparable prevalence of smoking, hypertension, hyperlipidaemia, obstructive sleep apnoea, history of coronary artery disease (MI, CABG), chronic kidney disease, cerebrovascular accidents and atrial fibrillation. The abnormal strain group was more likely to be on β-blocker therapy and antiplatelet therapy as well as having abnormal right ventricular function (table 1). Pearson correlation to investigate the presence of correlation between troponin values and LV-GLS showed a weak correlation between troponin values and LV-GLS (correlation coefficient=0.26, p=0.014).

A definitive multivariate logistic regression analysis was conducted to investigate the potential association between LV-GLS and in-hospital mortality. After adjusting for the patient's age, gender, race and comorbidities, we found a statistically significant association between LV-GLS and in-hospital mortality (adjusted OR (aOR)=1.09; 95% CI 1.0 to 1.19, p=0.050). Furthermore, RVFAC was also statistically significantly associated with in-hospital mortality (aOR=1.04; 95% CI 1.0 to 1.08, p=0.043). However, troponin level had no statistically significant association with in-hospital mortality (aOR=3.43; 95% CI 0.78 to 15.03, p=0.101) (table 2).

Table 1 Baseline characteristics of patients with COVID-19 without abnormal left ventricular strain compared with those with abnormal left ventricular strain

	Overall	Abnormal strain	Normal strain	P value
LV-GLS (mean±SD)	−16.67±5.39	−13.92±4.25	−22.42±1.85	
Age, years (mean±SD)	68.58±14.54	68.96±14.23	69.40±15.04	0.871
BMI, kg/m^2 (mean±SD)	28.38±6.81	28.38±6.29	28.51±8.29	<0.001
Ejection fraction (mean±SD)	57.48±13.31	54.11±14.81	63.74±6.26	0.918
Female, %	38.2	33.7	47.6	0.091
Smoking, %	9.2	7.9	11.9	0.327
COPD/asthma, %	17.6	21.3	9.5	0.075
Hypertension, %	70.2	74.2	61.9	0.111
Hyperlipidemia, %	51.1	56.2	40.5	0.068
Obstructive sleep apnea, %	4.6	6.7	0.0	0.093
Hx of CAD %	15.4	19.3	7.1	0.057
Hx of CABG/PCI, %	8.4	10.1	4.8	0.251
DM2, %	42.7	50.6	26.2	0.007
CHF, %	14.5	20.2	2.4	0.004
CVA, %	7.6	9.0	4.8	0.321
CKD, %	23.7	28.1	14.3	0.062
Atrial fibrillation, %	18.3	21.3	11.9	0.143
Statins, %	44.5	44.9	43.8	0.543
β-blockers, %	28.8	35.4	12.5	0.012
Antiplatelets, %	26.1	31.6	12.5	0.029
Calcium channel blockers, %	23.6	26.9	15.6	0.154
Diuretics, %	26.1	30.4	15.6	0.083
Anticoagulation, %	42.6	44.8	38.1	0.297
Hydroxychloroquine/azithromycin, %	66.2	69.7	58.5	0.148
Steroids, %	19.1	19.1	19.0	0.598
Pressors, %	45.8	50.6	35.7	0.080
Vented, %	42.3	44.3	38.1	0.316
Dilated LA, %	16.9	18.2	14.3	0.388
More than mild LVF, %	30.8	35.2	21.4	0.080
Abnormal RV function, %	14.5	1.91	4.8	0.022
Dilated RV, %	23.7	25.8	19.0	0.266
Mitral valve abnormality, %	10.7	12.4	7.1	0.282
Aortic stenosis, %	9.2	11.2	4.8	0.194
Tricuspid valve abnormality, %	26.0	27.0	23.8	0.437
Troponin I (mean) ng/ml		0.530	0.135	0.001

BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; DM2, diabetes mellitus type 2; LA, left atrium; LVF, left ventricular function; LV-GLS, left ventricular global longitudinal strain; PCI, percutaneous coronary intervention; RV, right ventricle.

DISCUSSION

To our knowledge, the current study has the biggest cohort sample of all previous studies that looked into abnormal LV-GLS in patients with COVID-19 . The major finding in our pilot study was the high prevalence of abnormal LV-GLS denoting subclinical LV dysfunction in patients admitted with COVID-19 infection. We observed that 67.9% of our study cohort had abnormal LV-GLS. Only diabetes and congestive heart failure were more prevalent in the group with abnormal LV-GLS, however there was comparable prevalence of other cardiovascular disease risk factors between both groups with normal and abnormal LV-GLS.

Table 2 Multivariable regression of mortality and clinical characteristics of patients with COVID-19

	OR	Lower bound	Upper bound	P value
LV strain	1.090	1.000	1.189	0.050
Troponin	3.438	0.787	15.030	0.101
RVFAC	1.040	1.001	1.081	0.043

LV, left ventricle; RVFAC, right ventricular fractional area change.

We were also able to demonstrate a statistically significant association between abnormal LV-GLS and in-hospital mortality in this patient population. Interestingly, there was no statistically significant association between troponin levels and in-hospital mortality.

LV-GLS determination using 2D-STE is an objective, reproducible method to evaluate and predict subclinical myocardial dysfunction because of its ability to detect myocardial fibrosis early in various cardiac pathologies.[3] Few studies have investigated the prevalence of abnormal LV-GLS and its prognostic value in COVID-19 infection.[7–10] Janus *et al* showed similar results to our study with increased mortality observed with reduction in LV-GLS.[10] The study conducted by Baycan *et al* demonstrated similar results to ours with significant association between abnormal LV-GLS and in-hospital mortality.[8] The study conducted by Croft *et al* observed lower mean LV-GLS of patients with COVID-19 when compared with the normal healthy population, however different to our study, it showed that reduced LV-GLS was not a significant predictor of in-hospital mortality, with only severe LV-GLS reduction showing a trend towards predicting mortality.[7] The discrepancy between the different study findings can possibly be attributed to the difference in the severity of COVID-19 illness between the different study cohorts.

While our study only investigated LV-GLS in patients with COVID-19, recent studies have concluded that right ventricular longitudinal strain is an important predictor of in-hospital mortality in patients with COVID-19[11 12]

The reduced LV-GLS in patients with COVID-19 denotes myocardial injury which may be secondary to direct or indirect mechanisms. Direct mechanism involves the invasion of SARS-CoV-2 on the myocytes causing acute cardiac injury and myocarditis. The direct cardiac injury is thought to be facilitated by the upregulation of the ACE 2 receptor on myocytes.[13] Immune-mediated myocardial inflammation may also occur through activation of the innate immune system with the release of proinflammatory cytokines. In severe COVID-19 infection, the released proinflammatory cytokines like interleukin (IL) 6, IL-2 and TNF-α can lead to cytokine release syndrome and trigger myocardial inflammation.[14] Myocardial injury can result from respiratory failure and hypoxia.[13] Our study emphasises the importance of abnormal LV-GLS as a prognostic echocardiographic marker of mortality within this patient population. Nevertheless, it is important to note that our study did not definitely identify the aetiology of abnormal LV-GLS in this patient cohort. The causative factors are likely multifactorial arising from both direct and indirect myocardial effects or involvement, as described at the previous section. It is also noteworthy that our study did not identify a direct association between troponin levels and mortality. Elevated troponin levels in patients with COVID-19 are a common finding and suggest a potential cardiac involvement. While elevated troponin levels can indicate cardiac distress, they alone may not serve as a sensitive predictor of mortality in COVID-19.

Limitations

Although our study had a slightly bigger study sample, compared with the previously published studies that aimed to address this subject, our small study sample size limits the strength of our conclusions. Ideally, prospective studies with larger sample sizes are required to further investigate if LV-GLS by 2D-STE can be reliably used for subclinical myocardial dysfunction in patients with COVID-19. Moreover, the difference in the severity of COVID-19 infection between the two groups with normal and abnormal LV-GLS was not included.

Clinical implication

LV-GLS is a practical and precise imaging tool that can be employed for the assessment of cardiac involvement, serving as a sensitive predictor of mortality in patients hospitalised due to COVID-19 infection. Despite cardiac magnetic resonance (CMR) being the gold standard to detect subclinical LV dysfunction,[8] echocardiogram is more widely available and less challenging to obtain than CMR. The availability of a cardiac imaging tool at the bedside to detect subclinical LV dysfunction is definitely helpful in this patient population.

CONCLUSION

Abnormal LV-GLS in hospitalised patients with COVID-19 not only suggests potential subclinical cardiac involvement but also serves as a potentially sensitive predictor of in-hospital mortality. Patients with reduced LV-GLS need closer monitoring for the development of cardiovascular adverse events.

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Contributors SH: Guarantor, Conceptualised and planned the research project. Collaborated with AB, MM and MN, in collecting patient data. AB: Assisted in project planning and contributed to the data collection efforts. MM: Assisted in project planning and participated in data collection. MN: Played a role in project planning and contributed to the data collection process. YA: Conducted the statistical analysis. MS: Drafted and wrote the manuscript.

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