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Subclinical left ventricular dysfunction in COVID-19

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ABSTRACT

Background: Coronavirus Disease-2019 (COVID-19) is associated with cardiovascular injury, but left ventricular (LV) function is largely preserved. We aimed to evaluate for subclinical LV dysfunction in patients with COVID-19 through myocardial strain analysis.

Methods: We performed a single-center retrospective cohort study of all patients hospitalized with COVID-19 who underwent echocardiography. Traditional echocardiographic and global longitudinal strain (GLS) values were compared with prior and subsequent echocardiograms.

Results: Among 96 patients hospitalized with COVID-19 with complete echocardiograms, 67 (70%) had adequate image quality for strain analysis. The cohort was predominantly male (63%) and 18% had prevalent cardiovascular disease (CVD). Echocardiograms were largely normal with median [IQR] LV ejection fraction (EF) 62% [56%, 68%]. However, median GLS was abnormal in 91% (−13.5% [−15.0%, −10.8%]). When stratified by CVD, both groups had abnormal GLS, but presence of CVD was associated with worse median GLS (-11.6% [−13.4%, −7.2%] vs −13.9% [−15.0%, −11.3%], p = 0.03). There was no difference in EF or GLS when stratified by symptoms or need for intensive care. Compared to pre-COVID-19 echocardiograms, EF was unchanged, but median GLS was significantly worse (−15% [−16%, −14%] vs −12% [−14%, −10%], p = 0.003). Serial echocardiograms showed no significant changes in GLS or EF overall, however patients who died had stable or worsening GLS, while those who survived to discharge home showed improved GLS.

Conclusions: Patients with COVID-19 had evidence of subclinical cardiac dysfunction manifested by reduced GLS despite preserved EF. These findings were observed regardless of history of CVD, presence of COVID-19 symptoms, or severity of illness.

1. Introduction

Coronavirus Disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily causes respiratory failure. However, there is a growing body of evidence demonstrating cardiac involvement, including myocarditis, cardiomyopathy and arrhythmias [1]. Myocardial and epicardial inflammation have been observed on cardiac magnetic resonance imaging (MRI) and postmortem evaluations [2–5]. Myocardial injury, based on cardiac biomarker elevation, has also been observed in patients with COVID-19, and is associated with increased mortality risk [6–9]. Myocardial strain analysis by speckle-tracking echocardiography has been shown to identify abnormal left ventricular (LV) function and subclinical cardiac injury even in the presence of normal ejection fraction (EF). Strain has previously been shown to be abnormal in severe sepsis and septic shock, and has been associated with higher mortality despite preserved LV EF [10–12]. Viral myocarditis is also associated with reduced strain, with improvement after treatment [13]. Influenza has been associated with abnormalities in regional longitudinal strain, but not global longitudinal strain (GLS) [14]. Despite evidence of cardiac involvement of COVID-19 by biomarker elevation, cardiac MRI, and postmortem examinations, most patients with COVID-19 have normal systolic function by traditional echocardiographic metrics [15]. We hypothesized that patients with COVID-19 have evidence of LV dysfunction by speckle-tracking echocardiography and strain analysis, even in the absence of abnormalities in EF and other echocardiographic parameters.

2. Methods

We designed a retrospective cohort study including all patients diagnosed with SARS-CoV-2 infection by positive polymerase chain

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reaction (PCR) testing between January 1, 2020 and September 9, 2020 at University of California San Diego (UCSD) Health who had echocardiograms performed during a hospital visit that were of adequate quality for strain analysis. At our institution, echocardiography in COVID-19 patients was performed selectively after screening by a cardiologist to ensure clinical necessity and minimize staff exposure. Patients were identified via extraction from the electronic health record [16], with confirmation of SARS-CoV-2 diagnosis and timing of echocardiogram by manual chart review. Variables collected included demographics, SARS-CoV-2 testing, comorbidities, medications, critical care interventions such as mechanical ventilation, and vital status. Obesity was defined as body mass index $\geq$ 30 kg/m^2. Cardiovascular disease (CVD) was defined as history of coronary artery disease, peripheral arterial disease, stroke or transient ischemic attack, or heart failure. The primary outcome was GLS on initial echocardiogram during hospitalization for SARS-CoV-2. The study was approved by the UCSD Human Research Protection Program and conforms to the Declaration of Helsinki guidelines.

Echocardiograms were obtained in standard parasternal and apical views using a variety of commercially available instruments. Adequate quality required obtaining requisite views for strain analysis and having two or fewer endocardial borders obscured by dropout or artifact**.** Echocardiographic measurements were obtained according to American Society of Echocardiography (ASE) cardiac chamber quantification guidelines [17]. LV EF and left atrial (LA) volume indexed to body surface area were measured using the Simpson's biplane method from the apical views. Normal EF was defined as $\geq$50%. LV dimensions, transmitral early (E) and late (A) pulsed wave tissue Doppler velocity of the septal and lateral mitral annulus (e'), E/A and E/e' ratios were assessed using 2016 ASE diastology guidelines [18]. Heart rate, mean arterial blood pressure, patient level of care and clinical characteristics at the time of echocardiogram were collected by manual chart review.

Myocardial strain analysis was completed using EchoInsight v.3.2.3.5564 (Epsilon Imaging, Ann Arbor, MI, USA). For 2D strain analysis, standard 2D gray-scale tracking included the three standard apical views (two, three, and four-chamber views). Longitudinal strain (LS) was measured globally and regionally (basal, mid, apex) in all patients. Myocardial strain was measured independently by two readers (H.S.B and Q.M.B.) for each echocardiogram. Normal GLS was defined as ≤ -18% which is the value used in our clinical laboratory.

Patient and echocardiographic characteristics on hospital presentation, as well as clinical outcomes, are presented as means and standard deviations for continuous, normally distributed variables, or medians and interquartile range (IQR) for skewed variables; and as frequencies with percentages for categorical variables. Analyses were performed before and after stratification by history of CVD, level of care at time of echocardiogram (intensive care unit [ICU] vs non-ICU), and presence of symptoms associated with COVID-19. Continuous variables were compared using student's t tests or Mann-Whitney U tests for skewed distributions, and categorical variables were compared using chi square tests. Among those with multiple echocardiograms, comparison of baseline cardiovascular comorbidities was made using chi square tests. Comparisons were made between the echocardiograms during the index hospital visit and the baseline echocardiograms prior to admission, as well as follow-up echocardiograms, using paired t tests and Wilcoxon tests as appropriate. Spearman correlations were computed to assess inter-observer variability, as well as the association between global longitudinal strain (GLS) and biomarkers. Statistical analysis was performed using SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA). All tests utilized two-sided p-values with statistical significance defined as $p < 0.05$.

3. Results

Overall, 96 patients with positive SARS-CoV-2 testing had an echocardiogram performed during the COVID-19 hospital visit; of these, 29 were excluded due to inadequate quality for strain analysis, resulting in a study cohort of 67 patients. The number of echocardiograms per month on patients with COVID-19 increased over the first 6 months, while the proportion that were excluded due to poor quality or missing views decreased over time Figure Supplementary figure 1 (Supplemental Figure).

The study cohort (Table 1) was middle aged (mean 57 ± 17 years), and predominantly male (67%) and Hispanic (61%). There was a high prevalence of medical comorbidities including obesity (64%), hypertension (40%), diabetes mellitus (34%) and CVD (18%, including 13% with history of heart failure). Median initial and peak highly sensitive troponin T (hsTnT) were not significantly elevated, although median hsTnT at time of echocardiogram was elevated. Median N-terminal pro-B-type natriuretic peptide (NT-proBNP) and D-dimer were elevated while median procalcitonin and C-reactive protein (CRP) were not. All but one patient required hospital admission; most patients were admitted for symptoms related to COVID-19 (93%), required ICU admission (84%), and required intubation and/or ventilator support (75%). Median ICU length of stay was 45 [16–88] days. Many patients required venovenous extra-corporeal membranous oxygenation (V-V ECMO, 24%) or had renal failure requiring continuous renal replacement therapy (CRRT, 19%). No patients were on venoarterial extra-corporeal membranous oxygenation (V-A ECMO). At the time of final data collection, 33% of patients had died, 33% were discharged home, 32% were discharged to an acute care facility, skilled nursing facility or rehab facility, and 1 patient (2%) remained hospitalized (Table 1).

Inter-observer agreement for strain measurements as assessed by Spearman correlation was 85%. Most echocardiograms were performed in the ICU (75%) and for an indication of either COVID-19 symptoms/disease (67%) or SARS-CoV-2 positivity (5%). Further detail from the ordering physicians regarding clinical indication for echocardiograms was limited, but information regarding patient clinical characteristics at the time of echocardiogram was collected. At the time of examination, 88% of patients were symptomatic from COVID-19, 82% required oxygen support (61% on ventilator), 40% had acute respiratory distress syndrome (ARDS), 15% were on V-V ECMO, and 9% had clinical evidence of heart failure. Mean arterial blood pressure ranged from 62 to 114 mm Hg (median 79 [73–88] mm Hg) and heart rate ranged from 43 to 125 beats per minute (median 89 [72–101] beats per minute). LV EF on initial echocardiogram was normal in 94% of patients with a median of 62% [56%–68%]. Conversely, GLS was abnormal in 91% of patients, with a median of −13.5% [−15.0% to −10.8%]. Of the 6 patients with normal GLS, all had normal LV EF; of the 61 patients with abnormal strain, 57 (93%) had normal LV EF (Table 2). There was no significant correlation between GLS and hsTnT levels whether on initial evaluation, peak value, or at the time of echocardiogram ($r = -0.008$, $p = 0.96$, $n = 35$; $r = -0.11$, $p = 0.46$, $n = 47$; $r = -0.21$, $p = 0.45$, $n = 15$, respectively). NT-proBNP was also not significantly correlated with GLS ($r = 0.08$, $p = 0.66$, $n = 38$).

In those with a history of CVD, median LV EF was normal, but lower than in those without CVD (56.0% [37.0%–65.0%] vs 64.0% [57.0%–69.0%], $p = 0.03$). Similarly, median GLS was worse in those with CVD compared to those without CVD, though GLS was abnormal in both groups (−11.6% [−13.4% to −7.2%] vs −13.9% [−15.0% to −11.3%], $p = 0.03$). There was no difference in LV EF or GLS in ICU patients compared with non-ICU patients, nor did GLS differ in those with and without symptoms associated with SARS-CoV-2

Table 1
Study cohort characteristics.

	Study Cohort (n = 67)
Age (years)	57 ± 17
Male, n (%)	42 (63)
BMI (kg/m^2)	30 ± 6 (n = 57)
Race / Ethnicity, n (%)	
Asian	2 (3)
Black	3 (5)
Hispanic or Latino	41 (61)
White	15 (22)
Other or more than one race	5 (8)
Medical Comorbidities, n (%)	
Cardiovascular Disease	12 (18)
Heart Failure	9 (13)
Coronary artery disease	8 (12)
Prior PCI	0 (0)
Prior CABG	3 (5)
PAD	6 (9)
Hypertension	27 (40)
Diabetes Mellitus	23 (34)
Obesity	43 (64)
Stroke	5 (8)
Atrial Fibrillation / Flutter	10 (15)
Chronic Kidney Disease	7 (10)
Asthma	4 (6)
Chronic Obstructive Pulmonary Disease	1 (2)
Active Smoker	2 (3)
Malignancy	7 (10)
Prior Organ Transplant	2 (3)
Rheumatologic Disease	5 (8)
HIV	2 (3)
Home Medications	
ACE-I / ARB	26 (39)
Beta Blocker	13 (19)
Diuretic	15 (22)
MRA	2 (3)
Aspirin	25 (37)
Statin	18 (27)
NSAIDs	13 (19)
Initial Labs	
Creatinine (mg/dL)	0.9 [0.7–1.2]
Estimated GFR (mL/min/1.73 m^2)	88 ± 47
hsTnT, Initial (ng/L)	18 [6–47] (n = 35)
hsTnT, Peak (ng/L)	21 [7–66](n = 47)
hsTnT, Time of Echocardiogram (ng/L)	48 [19–251] (n = 15)
NT-proBNP (pg/mL)	1321 [230–5472] (n = 38)
D-dimer-HS (ng/mL)	743 [319–4563] (n = 45)
Procalcitonin (ng/mL)	0.3 [0.1–1.2] (n = 56)
C-Reactive Protein (mg/dL)	12 [5–24] (n = 47)
Clinical Outcomes	
Presentation	
Emergency Department, n (%)	32 (48)
Transfer, n (%)	14 (21)
Unknown, n (%)	21 (31)
Hospital Admission, n (%)	66 (99)
Admission for COVID-19, n (%)	62 (93)
Required ICU, n (%)	56 (84)
Required Intubation / Ventilator, n (%)	50 (75)
Required V-V ECMO, n (%)	16 (24)
Renal Failure Requiring CRRT, n (%)	13 (19)
Length of Stay (Days)	23 [14–36]
ICU Length of Stay (Days)	45 [16–88] (n = 56)
Disposition, n (%)	
Death	22 (33)
Discharged (non-healthcare facility)	22 (33)
Acute care facility	15 (22)
SNF / Rehab	7 (10)
Remain Admitted	1 (2)

Values are presented as mean ± standard deviation, median [IQR] or n (%). ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker, BMI = Body Mass Index, CABG = coronary artery bypass graft surgery, CRRT = continuous renal replacement therapy, GFR = glomerular filtration rate, hsTnT = = high-sensitivity troponin T, ICU = intensive care unit, LTAC = long-term acute care facility, MRA = mineralcorticoid-receptor antagonist, NSAID = non-steroidal anti-inflammatory drug, NT-proBNP = brain-terminal B-type natriuretic peptide, PAD = peripheral arterial disease, PCI = percutaneous coronary intervention, SNF = skilled nursing facility, V-V ECMO = veno-ovenous extra-corporeal membranous oxygenation.

Table 2
Initial Echocardiographic Parameters.

Echocardiogram Location, n (%)	
Emergency Department	3 (5)
Floor, non-ICU	14 (21)
ICU	50 (75)
Echocardiogram Indication	
Coronavirus positive	3 (5)
COVID-19	45 (67)
Other	19 (28)
Clinical Features at Time of Echocardiogram	
Symptomatic	59 (88)
Requiring oxygen therapy	55 (82)
Requiring mechanical ventilation	41 (61)
ARDS	38 (57)
Shock requiring vasopressor therapy	27 (40)
Requiring V-V ECMO	10 (15)
Heart failure	6 (9)
Cardiac ischemia	2 (3)
Heart Rate (BPM) at Time of Echocardiogram	89 [72–101]
Median MAP (mm Hg) at Time of Echocardiogram	79 [73–88] (n = 59)
LV EF (%)	62 [56–68]
LVIDd (cm)	4.7 [4.2–4.9]
LVIDs (cm)	3.0 [2.5–3.3] (n = 62)
LA Volume Index (mL/m^2)	22 [18–30] (n = 55)
Global Longitudinal Strain (%)	−13.5 [-15.0 to −10.8]
Abnormal Global Longitudinal Strain, n (%)	61 (91)
Reduced LV EF among abnormal GLS, n (%)	4 (7)
E/A ratio	1.0 [0.8–1.4] (n = 53)
Lateral E' (m/s)	0.10 ± 0.04 (n = 54)
LV Diastolic Function Category, n (%)	
Normal	23 (34)
Mild	16 (24)
Pseudonormal	2 (3)
Indeterminate	16 (24)
Unavailable	10 (15)
RVSP (mmHg)	37 [30–46] (n = 46)
TAPSE (cm)	1.8 [1.5–2.2] (n = 53)

Values are presented as mean ± standard deviation, median [IQR] or n (%). ARDS = acute respiratory distress syndrome, BPM = beats per minutes, EF = ejection fraction, ICU = intensive care unit, LA = left atrium, LV = left ventricle, LVIDd = left ventricular end-diastolic dimension, LVIDs = left-ventricular end-systolic dimension, MAP = mean arterial blood pressure, RVSP = right ventricular systolic pressure, TAPSE = tricuspid annular plane systolic excursion, V-V ECMO = venovenous extracorporeal membranous oxygenation.

infection. GLS was worse and EF was preserved in both conditions (Fig. 1).

A baseline echocardiogram, prior to SARS-CoV-2 diagnosis, was available in 14 patients. Those with a baseline echocardiogram were significantly more likely to have cardiovascular disease (50% vs 9.4%, p < 0.001) and more likely to have heart failure (29% vs 9%, p = 0.08) and coronary artery disease (29% vs 7.5%, p = 0.05) with borderline statistical significance (Supplemental Table 1). Heart rate and mean arterial blood pressure at the time of echocardiograms performed during hospital visit compared to prior echocardiograms did not differ significantly. LV EF, LV dimensions and other standard echocardiographic measurements also did not differ between hospital visit and baseline examinations (Table 3). Median GLS, however, did differ significantly during hospital visit compared with baseline (−12.3% [−14.5% to −10.5%] vs −15.1% [−16.4% to −14.2%], respectively, p = 0.003, Fig. 1). When restricting comparison to patients with a prior (baseline) echocardiogram within 1 year prior to SARS-CoV-2 hospitalization, there was no significant difference in LV EF (65.0% [61.0%–70.0%] at baseline vs 62.0% [54.0%–69.0%] during hospital visit, p = 0.23), but there was a strong trend toward worsening in median GLS during hospital visit compared to baseline (−11.1% [−14.4% to −10.5%] vs −15.1% [−15.3% to −12.8%], p = 0.06).

Finally, serial echocardiograms were compared in 12 patients who had at least one follow-up echocardiogram available. The median time to follow-up echocardiogram was 12.5 [8.0–29.3] days. With the exception of right ventricular systolic pressure (RVSP), all echocardiographic parameters, including GLS, were not significantly different between follow-up and initial echocardiogram done during the same hospital visit in the overall group (Supplemental Table 2). We also tracked serial echocardiograms from prior to and beyond hospitalization, when available (Supplemental Table 3). Patients who died demonstrated stable or worsening GLS on serial echocardiograms, those who were discharged home demonstrated improvement, and those who remain hospitalized or were discharged to an acute care facility had stable GLS.

4. Discussion

In this retrospective cohort study of predominantly critically ill patients diagnosed with SARS-CoV-2, LV systolic function, evaluated by global longitudinal strain, was reduced in over 90% of patients, while standard echocardiographic parameters such as LV EF and LV volumes remained normal. GLS was consistently worse when compared to baseline echocardiograms, and when stratified by history of CVD, the presence of COVID-19 symptoms, and critical illness. Importantly, there was no correlation between strain measurements and cardiovascular biomarkers. Taken together, these findings suggest that patients with SARS-CoV-2 infection have subclinical LV systolic dysfunction not adequately captured by traditional echocardiographic parameters, though the clinical impact of these findings requires further study.

Our study population was middle aged, predominantly male and with a high proportion of Hispanics and a high prevalence of medical comorbidities. Median initial and peak cardiac troponin levels were not significantly elevated and did not correlate with GLS. Patients in this cohort were screened for clinical appropriateness for echocardiograms, which is reflected in the severity of disease and clinical outcomes seen. However, 33% were discharged home and 32% were discharged to an acute or subacute care facility. Additionally, while 84% of patients required ICU care during their admission, 25% of initial echocardiograms were performed outside the ICU. Our results also demonstrate that the number of echocardiograms increased each month over the course of the pandemic through June, paralleling the increase in incident cases and a greater appreciation of cardiac involvement in the disorder.

GLS was also abnormal when stratifying by history of CVD, disease severity, and the presence of COVID-19 symptoms. While GLS was worse in the group with prior CVD, it did not differ when comparing ICU and non-ICU patients or in those with asymptomatic vs symptomatic SARS-CoV-2 infection. GLS has previously been shown to be abnormal in patients with severe sepsis and septic shock; however, patients with uncomplicated sepsis, other critical illness such as from major trauma and patients with influenza did not have abnormal GLS [11,12,15], suggesting that abnormal GLS is not observed simply as a response to hospitalization, acute illness or critical illness. Our findings, in the context of these prior studies, suggest that LV systolic dysfunction may be related to COVID-19 and not just a nonspecific response to systemic inflammation, sepsis or critical illness. Our findings were also generally sustained over time, as GLS did not differ in the overall group between follow-up and initial echocardiograms. However, GLS improved in those patients with serial echocardiograms who recovered and were discharged home, while it worsened or was unchanged in those who died, though patient numbers are inadequate for statistical analysis or to draw definitive conclusions. This was true despite the need for ICU level of care in most patients who had serial echocardiograms, which suggests that GLS may reflect a true phenomenon of cardiac involvement of COVID-19. However, the

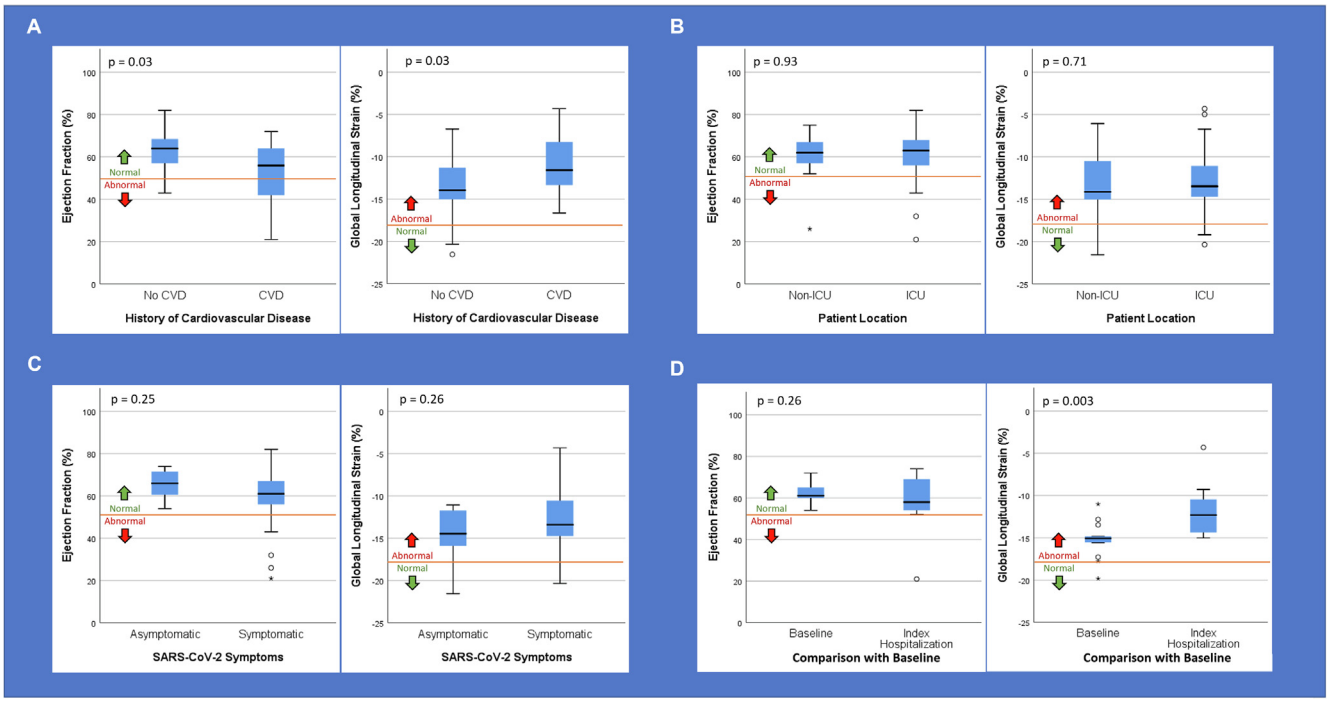

Fig. 1. Left Ventricular Ejection Fraction and Global Longitudinal Strain Stratified by (A) History of Cardiovascular Disease, (B) Presence of Critical Illness, (C) Asymptomatic versus Symptomatic SARS-CoV-2 Infection, and (D) Baseline versus Hospitalization Echocardiogram. Circles represent outliers, Asterisks represent extremes. CVD = Cardiovascular Disease, ICU = intensive care unit.

Table 3
SARS-CoV-2 Echocardiogram Compared with Baseline.

	Prior Echocardiogram (n = 14)	SARS-CoV-2 Echocardiogram (n = 14)	p
Heart rate (BPM)	78 [67–94]	88 [72–100]	0.07
Median MAP (mm Hg)	91 [79–101] (n = 4)	83 [72–92] (n = 4)	0.14
LV EF (%)	61 [60–66]	58 [53–69]	0.26
LVIDd (cm)	4.6 [4.0–5.3]	4.5 [3.6–5.0]	0.70
LVIDs (cm)	3.1 [2.4–3.7] (n = 11)	3.0 [2.8–3.2] (n = 11)	0.86
LA volume index (mL/m^2)	32 [23–42] (n = 8)	30 [21–30] (n = 8)	0.61
Global longitudinal strain (%)	−15.1 [-16.4 to −14.2]	−12.3 [-14.5 to −10.4]	0.003
E/A ratio	1.1 [0.7–1.5] (n = 8)	1.3 [0.7–1.4] (n = 8)	0.61
Lateral E' (m/s)	0.08 ± 0.03 (n = 5)	0.08 ± 0.03 (n = 5)	0.69
RVSP (mmHg)	29 [25–47] (n = 8)	33 [24–37] (n = 8)	0.48
TAPSE (cm)	2.1 [1.7–2.6] (n = 6)	1.5 [1.2–2.2] (n = 6)	0.08

Values are presented as mean ± SD, median [IQR] or n (%). BPM = beats per minutes, EF = ejection fraction, LA = left atrium, LV = left ventricle, LVIDd = left ventricular end-diastolic dimension, LVIDs = left-ventricular end-systolic dimension, MAP = mean arterial blood pressure, RVSP = right ventricular systolic pressure, TAPSE = tricuspid annular plane systolic excursion

degree of GLS abnormality may not reflect the severity of the overall disease process.

COVID-19 has been associated with a variety of cardiovascular abnormalities. Pathologic examination and imaging studies using cardiac MRI have demonstrated evidence of myocardial injury [2–5]. However, we found that most patients undergoing echocardiography had preserved LV EF and otherwise relatively normal echocardiograms. Our study did, however, demonstrate cardiac involvement in the form of abnormal strain in nearly all patients with echocardiograms done for a clinical indication. Further, our data suggests that such involvement may be common in patients with SARS-CoV-2 infection, whether or not they are symptomatic from their infection, have a history of CVD, or are critically ill. The clinical significance of abnormal strain in COVID-19 patients is uncertain. Future studies in unselected COVID-19 patients would be required to determine if abnormal strain is an adverse prognostic marker. In addition, potential therapeutic strategies to improve strain will need to be evaluated to assess their role in outcomes. Finally, the implications of abnormal strain in regard to the persistence of myocardial abnormalities after recovery of infection, the so-called Long Haul Syndrome, remain to be defined.

Our study has several strengths. Each study was read independently by two readers with good inter-observer variability, with consistent findings in serial echocardiograms. Our cohort had high disease severity by its nature, but our findings were consistent regardless of ICU status or patient symptoms, suggesting that abnormal LV function by strain is related to the underlying disease process rather than disease severity or critical illness. Additionally, strain analysis is subject to variations in heart rate and blood pressure, but we did not find any difference in these metrics.

Our study also has notable limitations including a relatively small sample size, which reflects the burden of COVID-19 at UCSD. However, to our knowledge, this is one of the most comprehensive studies of echocardiographic parameters to date. Age- and sex-matched controls were not collected, as the primary intent of this study was to describe the pattern of disease in COVID-19 patients. Accordingly, we used published normal values for strain as the standard against which we compared measurements in our study cohort. While reported normal values for strain have shown small differences in independent studies, the measurements in our study population were substantially beneath the lower limit of normal in most reports [19]. Our study was subject to selection bias for an inherently sicker population as patients were only included if they were hospitalized and an echocardiogram was deemed clinically necessary. Therefore, our data may not apply to all COVID-19 patients. Those with a prior echocardiogram had abnormal GLS at

baseline. However, this data was only available in a subset of patients, and was likely due to the higher prevalence of baseline cardiovascular disease in these patients. Despite the abnormal baseline GLS, GLS was significantly worse during SARS-CoV-2 infection while EF was not. Echocardiograms were performed by different sonographers on different machines, which is the practice in most clinical laboratories. As this may lead to variations in quality and strain measurements, echocardiographic images were rigorously scrutinized to ensure sufficient quality by two physicians. Limited serial echocardiographic data were available and whether the observed trends correlate with COVID-19 trajectory warrants further study. Additionally, the indication for repeat echocardiogram was often not clear, limiting our ability to make definitive conclusions. Finally, strain analysis was completed using software from a single vendor and therefore may not be generalizable to all methods of strain assessment.

In conclusion, many patients with SARS-CoV-2 infection with echocardiograms done in the hospital have abnormal LV systolic function as assessed by GLS despite normal LV EF, regardless of history of CVD, severity of disease, or presence of COVID-19 symptoms. These findings should be interpreted with caution as this is a retrospective cohort study with a selection bias for a critically ill population. Additionally, the short- and long-term implications of this finding for therapy and prognosis remains undefined.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100770.

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