Received: 23 February 2022 | Revised: 11 June 2022 | Accepted: 11 July 2022

DOI: 10.1111/echo.15431

Echocardiography WILEY

ORIGINAL ARTICLE

The usefulness of speckle tracking echocardiography in identifying subclinical myocardial dysfunction in young adults recovered from mild COVID-19

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Abstract

Background: Myocardial strain assessed with speckle tracking echocardiography is a sensitive marker of cardiac dysfunction. Both left-ventricular global longitudinal strain (LV-GLS) and right ventricular longitudinal strain (RV-LS) were affected by severe SARS-CoV-2 infection. However, data about cardiac involvement in patients with asymptomatic/mild Coronavirus disease-19 (COVID-19) is still lacking.

Aim: To evaluate myocardial function using LV-GLS and RV-LS in patients with previous asymptomatic/mild COVID-19.

Methods: Forty young adults without previously known comorbidities/cardiovascular risk factors and with a confirmed diagnosis of asymptomatic or paucisymptomatic SARS-CoV-2 infection were retrospectively included. A 2D-transthoracic echocardiogram with speckle tracking analysis was performed at least 3 months after the diagnosis. Forty healthy subjects, matched for age, sex, and body surface area in a 1:1 ratio were used as the control group.

Results: Left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE) and RV-LS were comparable between the two groups. LV-GLS was significantly lower in the cases compared to the control group ($-22.7 \pm 1.6\%$ vs. $-25.7 \pm 2.3\%$; $p < .001$). Moreover, the prevalence of regional peak systolic strain below -16% in at least two segments was three times higher in patients with previous COVID-19 compared to controls (30% vs. 10%, $p = .02$). In multivariable logistic regression, previous COVID-19 infection was independently associated with reduced LV-GLS values ($p < .001$).

Conclusion: SARS-CoV-2 infection may affect left ventricular deformation in 30% of young adult patients despite an asymptomatic or only mildly symptomatic acute illness. Speckle-tracking echocardiography could help early identification of patients with subclinical cardiac involvement, with potential repercussions on risk stratification and management.

Elisa Gherbesi, Luca Bergamaschi, Carmine Pizzi and Alberto Barosi have contributed equally to this work.

KEYWORDS
COVID-19, myocardial strain, SARS-CoV-2, speckle tracking echocardiography

1 | INTRODUCTION

Towards the end of 2019, coronavirus disease 2019 (COVID-19), a viral infection caused by SARS-CoV-2, rapidly spread, causing a pandemic, with millions of people infected worldwide, resulting in a health emergency of global concern.

Despite its prevalent lung tropism, COVID-19 infection may be considered a multi-systemic disease involving different organs.[1–3] Notably, a significant amount of evidence has described cardiac involvement in COVID-19[4–7] showing that cardiac injury is associated with increased mortality.[8]

A recent study demonstrated that up to 78% of patients who recovered from COVID-19 have abnormal cardiac magnetic resonance (CMR) findings, primarily myocardial inflammation, and regional scar.[9] These alterations were irrespective of pre-existing conditions, severity, and overall course of the acute illness. They proved that long-term cardiac sequelae might be observed in patients without apparent myocardial involvement during the acute infection.[9]

Myocardial strain assessed by speckle tracking echocardiography is a sensitive marker of cardiac dysfunction, with long-term prognostic value in many cardiac conditions[10,11] especially in atherosclerotic/non-atherosclerotic coronary artery diseases.[12–14] Previous studies demonstrated a reduced left ventricular global longitudinal strain (LV-GLS) in patients with CMR-proven viral myocarditis and normal left ventricular ejection fraction (LVEF).[15] COVID-19 may alter both LV-GLS and right ventricular longitudinal strain (RV-LS), and these parameters were found to be independent predictors of mortality in hospitalized patients with severe disease.[16–19] On the other hand, there are less studies regarding cardiac involvement in COVID-19 asymptomatic patients or with mild diseases not requiring hospitalization.

2 | METHODS

2.1 | Study design and population

This single-center, retrospective, observational study enrolled young adults with previous asymptomatic or mildly symptomatic SARS-CoV-2 infection who were evaluated in the echo-Lab of Luigi Sacco - University Hospital (Milan, Italy) between November 2020 and August 2021, mostly referred for evaluation for not-agonistic sports activity.

The inclusion criteria were: (I) age between 15 and 40 years, (II) laboratory-confirmed SARS-CoV-2 infection by RNA detection in the upper respiratory tract swab test; (III) asymptomatic or mild infection (according to COVID-19 Treatment Guidelines of National Institutes of Health: Asymptomatic Infections are individuals who test positive for SARS-CoV-2 but who have no symptoms that are consistent with COVID-19; Mild Illnesses mean individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste, and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging[20]); (IV) trans-thoracic echocardiogram (TTE) performed >3 months after SARS-CoV-2 infection diagnosis.

Exclusion criteria were: known previous comorbidity or cardiovascular risk (CV) factors (including primary/ischemic cardiomyopathies, significant valve disease, atrial fibrillation, arterial hypertension, diabetes mellitus), suboptimal TTE image quality, or absence of EKG tracing.

A control group of 40 healthy subjects, matched for age, sex, and body surface area (BSA) in a 1:1 ratio, was recruited from the Outpatient Clinic of Luigi Sacco – University Hospital. Subjects were referred for palpitations, atypical chest pain, or innocent murmur; otherwise healthy, they were not taking any medication and exhibited a standard cardiac evaluation, EKG, and echocardiogram. The enrollment time of the control group was similar to the COVID-19 cases. The present study was conducted according to the principles of the Declaration of Helsinki. All patients were informed about their participation in the study and provided oral informed consent for the anonymous publication of scientific data. The need for written consent to participate in this research study was waived in view of the observational, retrospective, and anonymous nature of the study.

2.2 | Echocardiography and speckle tracking analysis

A complete conventional echocardiographic study (Epiq 7C, Philips Healthcare, Eindhoven, The Netherlands) was recorded at least 12 weeks after diagnosis.

Echocardiographic images were obtained, with standard transducer positions, in the parasternal long-axis, short-axis, and apical 4-, 2-, and 3-chamber views. Conventional echocardiographic measurements were done according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines.[21,22] LVEF was calculated using the modified Simpson biplane method. LV filling pressure was obtained by pulsed-wave Doppler from apical 4-chamber view with the sample volume positioned at the tips of the mitral valve, and by dividing the early (E) trans-mitral velocity wave by early annular diastolic velocity using TDI imaging to compute the E/E′ ratio.

Post-processing software evaluated speckle tracking echocardiography for longitudinal strain (TomTec-Arena version 2.41, TomTec, Unterschleißheim, Germany). Contour detection and tracking were

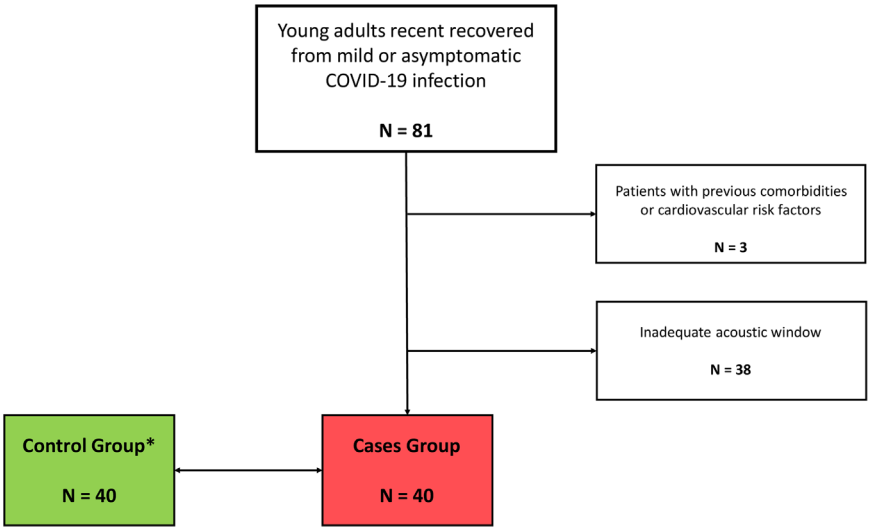

FIGURE 1 Study Flow chart. *Forty healthy subjects, matched for age, sex, and body surface area in a 1:1 ratio

done automatically by the software (AutoStrain). A frame rate of 50–70 frames per second was considered valid. In the case of false auto-tracking, speckle-tracking borders were manually corrected to ensure complete endo-epicardial tracking of entire segments. If it was not feasible to track 1 or more segments, the case was excluded.

LV was divided into 18 segments, providing the calculation of LV-GLS and a bull's eye display of time to peak longitudinal strain and end-systolic longitudinal strain.

Based on previous studies,[23,24] we considered reduced LV-GLS values as the presence of a GLS lower than −16% in ≥2 segments, a value significantly below the normality range proposed in a large meta-analysis.

For the right ventricular strain, RV free wall and interventricular septum were automatically divided into three segments: basal, mid, and apical. RV-LS was obtained from the average values of all six segments, while right free wall longitudinal strain (RFW-LS) was derived from the average values of three RV-free wall segments.

All strain analyses were performed separately and blinded to all clinical information. Therefore, we compared echocardiographic results with the control group.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 25.0, IBM Corporation, Armonk, NY). Continuous variables were reported as mean±standard deviation (SD) or as median [interquartile range, IQR] if normally or non-normally distributed, respectively; discrete variables were reported as absolute numbers and percentages. The normal distribution of continuous variables was assessed using the Shapiro–Wilks test and the equality of variance was tested between groups using Levene's test. In the case of departure from normality, nonparametric tests (Mann-Whitney *U* test) were used; in case of normal distribution of values, parametric tests (Student's *t*-test) to compare differences between the two groups were performed. Pearson $\chi 2$ test was used to compare categorical patient characteristics among groups. Multivariable logistic regression was performed to explore predictors of reduced GLS. Fifteen patients were randomly selected to test the intra-observer and inter-observer variability expressed as the Intra-class Correlation coefficient for LV-GLS and RV-LS. All *p* values were two sided, and values <.05 were considered statistically significant.

3 | RESULTS

As shown in Figure 1, out of 81 young adults who recently recovered from asymptomatic or mildly symptomatic SARS-CoV-2 infection, 3 patients were excluded due to concomitant CV risk factors, and 38 for an inadequate acoustic window. Therefore, the final sample included 40 patients (70% males, mean age 24.4 ± 8.4 years). Complete echocardiography was performed after a mean time of 15 ± 1.4 weeks since the SARS-CoV-2 infection onset (baseline time).

A control group of ambulatory individuals without SARS-CoV-2 infection were matched in a 1:1 ratio for age, gender, and body surface area (BSA).

Patient characteristics are summarized in Table 1. The comparison of demographic characteristics indicated that the two groups were similar in gender distribution, mean age, BSA, and body mass index (BMI).

3.1 | Standard echocardiographic evaluation

Standard echocardiographic parameters were similar between the study population and the control group. Subjects showed the same left ventricular function on conventional echocardiography, with no differences in LVEF, LV diastolic and systolic volume index, LV diastolic function and LV mass index, or relative wall thickness (Table 1).

Despite the expected impact of SARS-CoV-2 infection on the right chambers, no statistically significant differences were found between

TABLE 1 Demographic and echocardiographic findings

	Total *N* = 80	Prior SARS-CoV 2 infection *N* = 40	Control *N* = 40	*p*-value
Demographic data				
Age (years)	24.4 ± 7.4	24.4 ± 8.3	24.4 ± 6.8	.9
Male gender (n,%)	52 (65%)	28 (70%)	26 (59%)	.3
BSA (m^2)	1.8 ± .18	1.85 ± .17	1.79 ± .18	.1
BMI (kg/m^2)	22.9 ± 3.3	22.9 ± 2.8	22.9 ± 3.8	.2
Echocardiographic data				
LVEDD (mm)	45.8 ± 3.8	46.5 ± 3.3	45.1 ± 4.0	.07
LVEDVi (ml/m^2)	56.6 ± 10.8	57.3 ± 11.8	55.9 ± 9.9	.2
LVESD (mm)	29.9 ± 3.7	30.5 ± 3.3	29.4 ± 3.9	.1
LVESVi (ml/m^2)	20.9 ± 4.9	40.3 ± 10.5	36.9 ± 10.3	.1
IVSd (mm)	8.1 ± 1.3	8.1 ± 1.3	8.1 ± 1.3	.9
PWd (mm)	8.0 ± 1.2	8.0 ± 1.1	8.1 ± 1.3	.6
LVMI (gr/m^2)	66.3 ± 15.4	67.8 ± 15.7	64.9 ± 15.2	.4
RWT	.35 ± .05	.34 ± .04	.36 ± .05	.07
LAVi (ml/m^2)	22.7 ± 6.9	23.2 ± 7.8	22.2 ± 6.0	.5
E/A ratio	1.5 ± .5	1.6 ± .5	1.5 ± .5	.7
E/E' ratio	5.4 ± .9	5.2 ± .9	5.5 ± .9	.1
RV basal diameter (mm)	32.9 ± 4.9	33.3 ± 5.2	32.6 ± 4.7	.5
PAPs (mmHg)	24.0 ± 3.9	25.6 ± 3.6	23.2 ± 3.9	.08
TAPSE (mm)	24.0 ± 3.5	24.3 ± 3.7	23.7 ± 3.3	.5
LVEF (%)	63.6 ± 4.4	63.3 ± 4.1	63.9 ± 4.6	.5
LV-GLS (%)	−24.3 ± 2.4	-22.6 ± 2.3	−25.7 ± 1.6	<.001
RV-LS (%)	−23.4 ± 2.8	−23.2 ± 2.9	−23.6 ± 2.7	.5
RFWLS (%)	−26.9 ± 4.0	−26.5 ± 4.0	−27.2 ± 4.0	.4

Continuous variables are presented as mean ± SD while categorical ones as n (%).

Abbreviations: BSA, Body surface area; BMI, Body mass index; LVEDD, Left ventricular end-diastolic diameter ; LVEDVi, Left ventricle end-diastolic volume index; LVESD, Left ventricular end-systolic diameter; LVESVi, Left ventricle end-systolic volume index; IVSd, Interventricular septum thickness in end-diastole; PWd, Posterior wall thickness in end-diastole; LVMI, Left Ventricular mass index; RWT, Relative Wall Thickness; LA AP, left atrium anteroposterior diameter; LAVi, Left atrium volume index; RV, Right ventricle; PAPs, Pulmonary arterial systolic pressure; TAPSE, Tricuspid annular systolic excursion; LVEF, Left ventricle ejection fraction; LV-GLS, Left ventricle global longitudinal strain; RV-LS, Right ventricle longitudinal strain ; RFWLS, Right ventricle free wall longitudinal strain.

case and control groups. In particular, there were no differences in either TAPSE, S' wave at TDI or in right ventricular basal diameter size (33.3 ± 5.2 mm vs. 32.6 ± 4.7 mm cases vs. controls, $p = .5$). Moreover, no patient had direct or indirect signs of pulmonary hypertension (Table 1).

3.2 | Speckle tracking echocardiographic analysis

In contrast with standard echocardiographic findings, LV-GLS values differed significantly between case and control group (−22.7 ± 1.6% vs. −25.7 ± 2.3%, $p < .001$), even though absolute values were both within the normal range. Interestingly, reduced LV-GLS values lower than −16% in ≥2 segments were found in 30% of subjects with previous SARS-CoV-2 infection compared to 10% of the control group ($p = .02$) (Table 1).

Comparing the segmental strain values between the case and control group, the most significantly reduced values, below standard (in the grey zone of GLS between −16% and −18%) were detected in the infero-basal, infero-septal basal, and antero-septal basal segments (Figure 2).

Moreover, on multivariable logistic regression, previous SARS-CoV-2 infection was associated with reduced LV-GLS values ($p < .001$) (Table 2).

Finally, right ventricular strain values did not differ between patients with prior infection and the control subjects, with absolute values of both RV-LS and RFW-LS in the normal range (Table 1 and Figure 2).

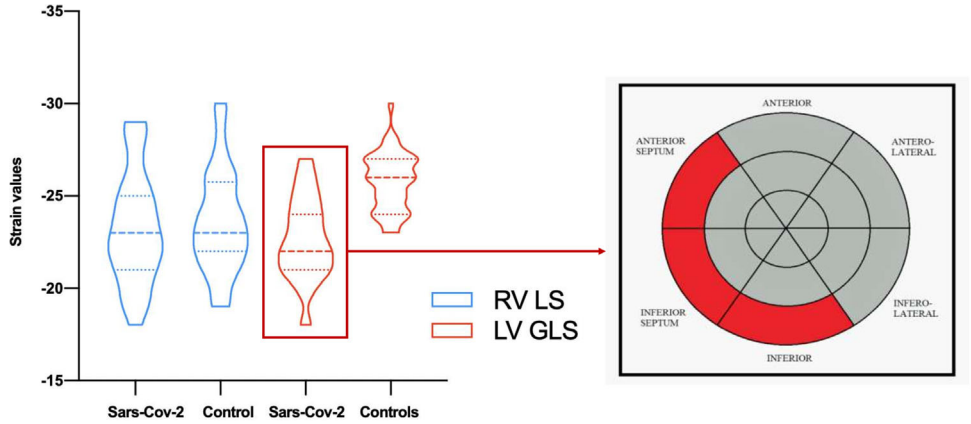

FIGURE 2 Left and right ventricular strain values in young adults recovered from mild COVID-19 versus controls. The violin plots show right (RV LS, blue) and left (LV GLS, orange) longitudinal strain differences in cases and controls. The LV-GLS Bull's Eye plot compares the segmental strain values between cases and controls: in red the segments with the most significantly reduced values, below standard

TABLE 2 Variables associated with reduced strain value (≥2 segments with GLS <16%)

	OR	95% CI	*p*-value
Previous SARS-CoV-2 infection[a]	8.8	3.04–25.3	<.001
Male gender	2.4	.65–8.64	.2
Age, years	1.03	.96–1.11	.3
BSA, m^2	.19	.05–7.01	.4

Abbreviations: BSA, Body Surface Area, m^2.
[a]Asymptomatic or mild symptomatic COVID-19.

3.3 | Observer variability

Fifteen patients were randomly chosen for the intra-and inter-observer variability analysis. Intra and inter-observer agreement for LV-GLS and RV-LS was evaluated. The intraclass correlation coefficients (ICC) for intra-observer variability were as follows: .96 (95% CI .89–.98) for LV-GLS; .95 (95% CI .87–.98) for RV-LS ($p < .05$ for both). ICCs for inter-observer variability were as follows: .94 (95% CI .85–.98) for LV-GLS; .93 (95% CI .83–.97) for RV-LS ($p < .05$ for both).

4 | DISCUSSION

To our knowledge, this is the first study to examine cardiac involvement assessed with two-dimensional speckle-tracking echocardiography (2D-STE) in young adult patients who recovered from asymptomatic or mildly symptomatic COVID-19. In summary, our main findings are: (I) 30% of cases exhibited a mild subclinical cardiac involvement detected only by speckle tracking echocardiography; (II) the number of patients with impaired LV-GLS was significantly higher in the COVID-19 group than in the healthy control subjects; (III) logistic regression analysis showed that recovery from COVID-19 was associated with impaired LV-GLS in our patient population; (IV) among healthy patients with similar LVEF on conventional echocardiography, 2D-STE allows the detection of subclinical LV dysfunction after the earlier phase of the disease.

Previous studies demonstrated that 2D-STE might enrich traditional echocardiographic assessment of LV function and overall prognosis in patients with severe SARS-CoV-2 infection.[16,17] The LV longitudinal deformation not only contributes to the ejection phase but also reflects disturbances in the twisting physiology, thereby compromising cardiac hemodynamics.[17]

Based on current evidence, SARS-CoV-2 infection can be associated with subtle LV systolic function and metabolic alterations.[25]

We found that young adult patients who recovered from asymptomatic or mildly symptomatic COVID-19 had detectable abnormalities of cardiac function using deformation analysis by 2-D STE as compared to the control group. The abnormalities of cardiac function were more significant in the infero-basal, infero-septal basal, and antero-septal basal segments (Figure 3). Our finding is consistent with several studies that reported a similar pattern of reduced LV-GLS in viral myocarditis.[26,27] Regarding COVID-19 related myocarditis, a direct cardiotropic localization of SARS-CoV-2 into myocytes has never been described. However, autoptic studies demonstrated findings (lymphocyte infiltrates and macrophagic response) compatible with viral myocarditis.[28]

The exact mechanism of cardiac involvement in COVID-19 remains unclear. However, it has been hypothesized that inflammatory response apoptosis and oxidative stress-mediated by ACE-2 receptor can play a role in COVID-19 related cardiac damage.[25] ACE-2 receptor (the receptor of SARS-CoV-2) is expressed in cardiac muscle cells, mainly in LV basal segment, cardiac fibroblasts, and the coronary vascular endothelium.[29] The dysregulation of ACE2 in COVID-19 patients increases the inflammatory cytokine regulating the cell signaling in inflammation and immune-related diseases.[29] In our study, the abnormalities in LV basal segment evaluated by 2D-STE can be explained by the above-mentioned mechanisms.

In severe cases of COVID-19 infection, such as acute respiratory distress syndrome with possible pulmonary thrombosis,[30] the right ventricle can be directly damaged, resulting in RV dysfunction due to

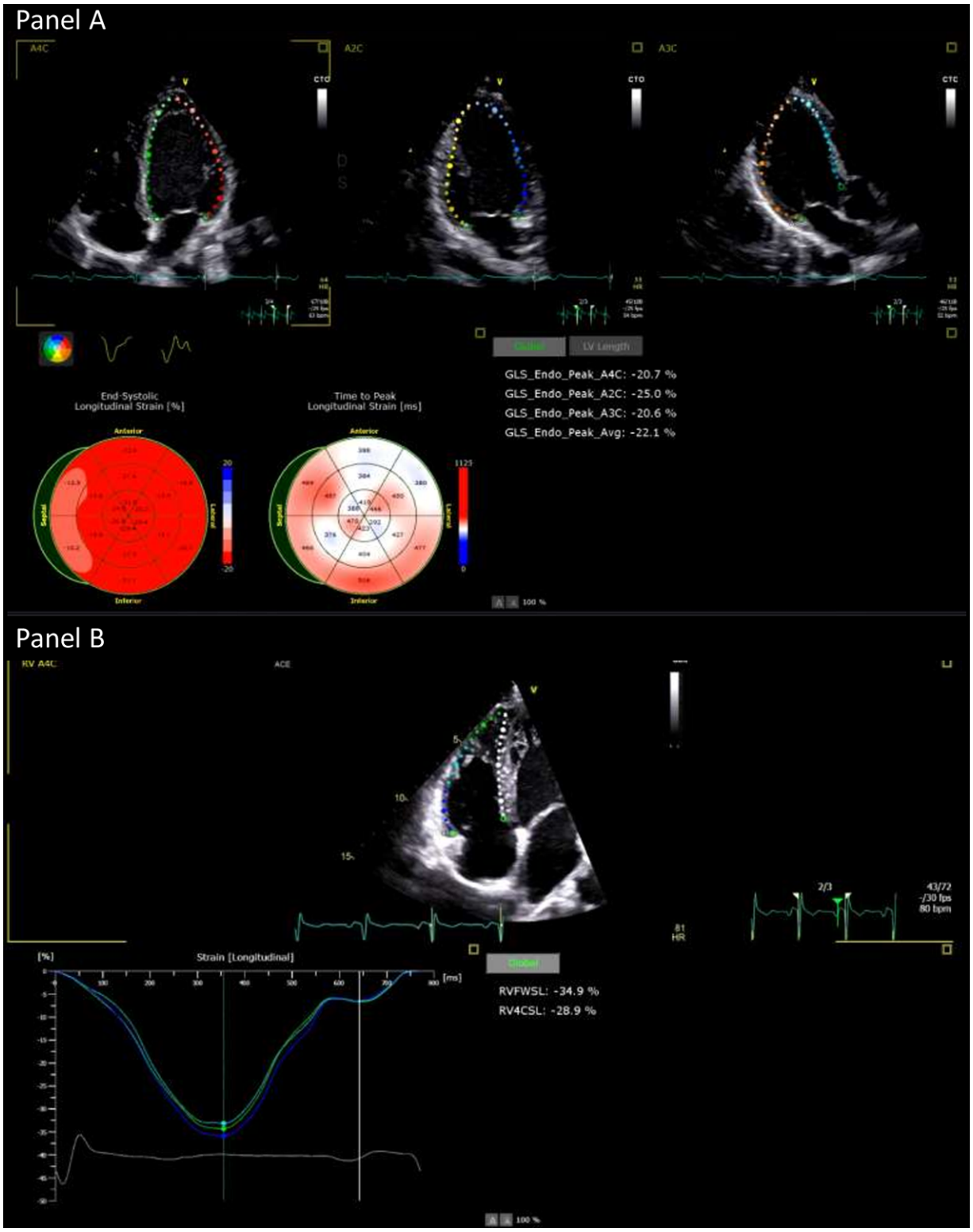

FIGURE 3 Speckle tracking echocardiography in a subject recently recovered from mild COVID-19 infection. (A) Strain echocardiographic evaluation of left ventricle showing normal absolute values of LV-GLS, but the basal segments presented significantly reduced values (light red in the GLS Bull's Eye plot on the left). (B) Speckle tracking echocardiographic evaluation of the right ventricle with absolute values of both RV-LS and RFW-LS in the normal range

increased pulmonary vascular resistance and RV afterload leading to decreased RV contractility and failure. Other possible mechanisms of RV dysfunction are hypoxia, inflammatory response, and autoimmune injury.[31,32] However, in our study, we found normal right ventricular standard echocardiographic parameters (including direct or indirect signs of pulmonary hypertension) and right ventricular strain values (both RV-LS and RFW-LS), without significant differences between cases and controls. Our results support that only in severe or complicated cases of SARS-CoV-2 infection the RV may be affected with varying degrees of dysfunction; conversely, in asymptomatic or mildly symptomatic patients an RV secondary injury is unlikely.

The long-term cardiac sequelae of COVID-19 in young subjects are not fully known. It is unclear whether these patients should have a dedicated follow-up, especially with echocardiography evaluations. According to a recent study, SARS-CoV-2 infection was related with myocardial deformation in LV mid-wall segments in about 25% of asymptomatic or mildly symptomatic children, lasting at least 3 months after the infection.[23] The different results in terms of LV-GLS distribution abnormalities between pediatric patients and our population can be explained by the age difference and also by different echocardiographic vendors. Our results are consistent with the one obtained with the study by Turan et al which reported subclinical LV dysfunction detected by LV-GLS in patients recovered from asymptomatic or mildly symptomatic COVID-19.33 However, this study differs from ours because they enrolled older patients and subjects with several comorbidities and cardiovascular risk factors.[33] Many of these conditions, such as mild hypertension, non-severe valvular heart disease, and pharmacological therapy, can impair LV-GLS. In addition, Turan et al. did not evaluate RV function by RV-LS and RFW-LS.[33]

In our study, a sensitive diagnostic method such as strain echocardiography detected a subclinical myocardial dysfunction in many patients who recovered from mild and/or asymptomatic SARS-CoV2 infection. As compared to the few studies available, we included a highly selected population of young adults without any other known factors able to influence myocardial deformation, suggesting that a comprehensive echocardiographic evaluation during cardiology follow-up could be considered in this setting.

5 | LIMITATIONS

The present study had some limitations which must be considered in interpreting the results. First, this is a single-center study and the sample size is relatively small. Nevertheless, we enrolled a consecutive sample of a specific outpatient population with good image quality.

We used 2D- STE, a validated and largely available method, but we can not exclude that three-dimensional STE, a more advanced one, could detect more subtle alterations.

We did not perform any laboratory tests, such as inflammatory markers, or cardiac magnetic resonance, which could help investigate the pathophysiology of cardiac involvement. However, these diagnostic evaluations are not currently recommended in this population of young adults with asymptomatic or mild previous Sars-CoV-2 infection. Moreover, in our study, we did not analyze left atrium strain and its relationship with new-onset atrial arrhythmias. Finally, this should be considered as pilot research evaluating the possible screening role of 2D-STE in this setting. Further studies are needed, including larger cohorts with combined echocardiography and cardiac magnetic resonance evaluation.

6 | CONCLUSION

SARS-CoV-2 infection may affect left ventricular deformation in 30% of young adult patients despite an asymptomatic or only mildly symptomatic acute illness. Although the clinical significance of these findings is unclear, speckle tracking echocardiography represents a precious tool in the early identification of patients with subclinical cardiac involvement.

Since long-term complications of COVID-19 are still unknown, myocardial deformation imaging could be important for risk stratification, therapeutic strategies and planning of long-term follow-up.

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How to cite this article: Gherbesi E, Bergamaschi L, Cusmano I, et al. The usefulness of speckle tracking echocardiography in identifying subclinical myocardial dysfunction in young adults recovered from mild COVID-19. *Echocardiography*. 2022;1-8. https://doi.org/10.1111/echo.15431