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Longitudinal Strain Assessment Of Myocardial Dysfunction In Covid–19 Patients: Correlating Clinical Symptoms And Laboratory Results At Admission And Four Months Post–Treatment

Lies Dina Liastuti,[1] Ines Vidal Tanto,[1] Aditya Rachman,[1] Marselly Maria Robot,[1] Bambang Dwiputra,[1] Rina Ariani,[1] Siska Suridanda Danny,[1] Taofan Taofan,[1] Renan Sukmawan.[1]

Abstract

Background: Myocardial dysfunction is increasingly recognized as a complication of COVID-19 infection, with significant implications for patient prognosis and long-term cardiovascular health. Longitudinal strain, measured via echocardiography, is a sensitive marker of myocardial function that may provide valuable insights into cardiac involvement in COVID-19 patients. This study aimed to assess myocardial dysfunction using longitudinal strain analysis in COVID-19 patients, correlating clinical symptoms and laboratory results at admission and four months post-treatment.

Methods: This study compared clinical and laboratory parameters in COVID-19 patients post-recovery, both with and without myocardial dysfunction. Adult COVID-19 survivors were included if they were hospitalized and met specific criteria. Independent variables included clinical factors and laboratory results at admission, while the dependent variable was myocardial dysfunction assessed through longitudinal strain of the left and right ventricles using speckle tracking echocardiography. The study was conducted at the National Cardiovascular Center Harapan Kita (RSJPDHK - FKUI) /Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, Jakarta.

Results: This study examined the cardiovascular health of 162 participants three months after infection with COVID-19. Those with comorbidities had the lowest LV GLS levels. Admission factors such as obesity, SpO2, and PaO2 levels were linked to decreased LV GLS levels. These findings suggest that these admission factors may predict the progression of COVID-19 syndrome and its implications for cardiovascular health.

Conclusion: COVID-19 patients with cardiovascular comorbidities have lower LV GLS values. Coronary artery disease (CAD) status during admission affects LV GLS values 3-6 months after COVID-19 infection, indicating myocardial dysfunction. Basal lateral LV-GLS correlates with obesity status, SpO2, and PaO2 during admission. It is crucial to closely monitor COVID-19 patients with cardiovascular comorbidities and recognize the implications of CAD status on myocardial function post-infection.

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Keywords: *COVID-19, echocardiography, fibrosis, admission factor.*

[1] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia / National Cardiovascular Center Harapan Kita, Jakarta, Indonesia

Correspondence:
Lies Dina Liastuti,
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Indonesia / National Cardiovascular Center Harapan Kita, Jakarta, Indonesia.
Email: dinaliastuti.research@gmail.com

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially identified in Wuhan, China, in December 2019, is the causative agent of coronavirus disease 2019 (COVID-19)1. This single-stranded RNA virus, a successor to the SARS-CoV-1 virus responsible for the 2002–2004 outbreak, spreads rapidly from person to person, facilitated by its high transmission rate, even among asymptomatic individuals.[2]

Beyond its acute effects on the cardiovascular system, COVID-19 presents the potential for long-term implications, notably through post-COVID-19 syndrome. Studies indicate that discharged COVID-19 patients commonly experience cardiac abnormalities and myocardial inflammation. Echocardiographic monitoring, particularly through the measurement of LV-GLS and RV-LS, has become increasingly vital for assessing cardiovascular manifestations in post-COVID-19 syndrome, offering objective and accurate insights. While myocardial dysfunction, especially in the right and left ventricles, is frequently encountered during acute COVID-19, research linking clinical and laboratory factors at admission with myocardial dysfunction measured by LV-GLS and RV-LS during the 3-6 month period post-treatment is scarce. Further investigation is crucial to better predict cardiovascular involvement in COVID-19 patients, facilitating the implementation of appropriate preventive measures.

This study aims to evaluate the disparities in LV-GLS and RV-LS values, serving as markers of myocardial dysfunction, among patients with cardiovascular comorbidities 3-6 months post-COVID-19 infection compared to a control group. The hypothesis posits significant differences in GLS between the subject and control groups, alongside a correlation between clinical and laboratory factors at admission and myocardial dysfunction measured by LV-GLS and RV-LS. By shedding light on cardiovascular involvement in post-recovery COVID-19 patients, this study seeks to enhance the ability to predict the risk of myocardial dysfunction.

Method

This study is a cross-sectional observational study aimed at comparing clinical and laboratory parameters in post-recovery COVID-19 patients with and without myocardial dysfunction, assessed through ventricular strain. Study subjects were selected using consecutive sampling methods at the National Cardiovascular Center Harapan Kita (RSJPDHK - FKUI) / Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, Jakarta. Medical record data were collected from COVID-19 inpatients from June to July 2021, while LV-GLS and RV-LS data were collected from October 2021 to January 2022. All patients signed informed consent before enrollment.

The target population consisted of adult COVID-19 survivors with a history of hospitalization, accessible at RSJPDHK. Inclusion criteria included patients aged over 18 years, confirmed COVID-19 by PCR method, with left ventricular ejection fraction over 50%, TAPSE over 1.7, and willingness to participate in the study by signing an informed consent form. Exclusion criteria included unwillingness to participate, inability to be contacted, death before 12 weeks post-COVID-19 treatment, as well as various cardiovascular conditions and specific underlying diseases. Cardiovascular controls were patients with cardiovascular comorbidities, while healthy controls were adult patients without a history of cardiovascular comorbidities and without COVID-19.

This study utilized independent variables including clinical factors (age, gender, obesity, diabetes, hypertension, smoking habits, SpO2) and laboratory factors (Ct-value, PaO2, hsTropT, NT-proBNP, CRP, D-dimer) at admission, with the dependent variable being myocardial dysfunction assessed through longitudinal strain of the left and right ventricles on speckle tracking echocardiography.

Results

Out of 162 subjects meeting the study criteria, 100 individuals had cardiovascular comorbidities and a history of COVID-19 (subjects group), while 31 individuals each had cardiovascular comorbidities without a history of COVID-19 (control group 1), and no history of COVID-19 or cardiovascular comorbidities (control group 2), as shown in **Table 1**: Patients' Demographic, Clinical, and Laboratory Characteristics. The mean age of the subjects was 62 years, with males comprising 62% of the total sample. There were no significant differences in mean age and

Table 1. Patients' Demographic, Clinical, and Laboratory Characteristics .

Variable (s)*	CV and COVID-19 (Subject Group)	CV without COVID-19 (Control 1)	Healthy Subjects (Control 2)	p-value (Subjects vs Control 1)	p -value (Subjects vs Control 2)	p -value (Control 1 vs Control 2)
Age (mean ± SD)	53.57 ±	52.48 ±	51.00 ±	0.59	0.41	0.599
Sex, n %	13.20	5.37	5.17	0.67	0.59	0.689
• Male	63 (63%)	20 (64.5%)	19 (61.3%)			
• Female	37 (37%)	11 (35.5%)	12 (38.7%)			
Diabetes Mellitus, n (%)				0.64	<0.001*	<0.001*
• Yes	69 (69%)	20 (64,5%)				
• No	31 (31%)	11 (35,5%)				
Hypertension, n (%)				0.78	<0.001*	<0.001*
• Yes	64 (64%)	19 (61.3%)	0 (0%)			
• No	36 (36%)	12 (38.7%)	31 (100%)			
Dyslipidemia, n (%)						
• Yes	14 (14%)	5 (16.1%)	0 (0%)			
• No	86 (86%)	26 (83.9%)	31 (100%)			
Smoking, n (%)				0.88	0.022*	0.020*
• Yes	15 (15%)	5 (16.1%)	0 (0%)			
• No	85 (85%)	26 (83.9%)	31 (100%)			
CAD, n (%)						
• Yes	36 (36%)	14 (45.2%)	0 (0%)			
• No	64 (64%)	17 (54.8%)	31 (100%)			
Obesity, n (%)						
• Yes	58 (58%)	17 (54.8%)	0 (0%)			
• No	42 (42%)	14 (45.2%)	31 (100%)			
SaO2, % (median ± IQR)	87 ± 12	-	-	-	-	-
CT value, (median ± IQR)	18 ± 5	-	-	-	-	-
Lactate, mg/dl (median ± IQR)	2.8 ± 0.60	-	-	-	-	-
PaO2, mmHg (median ± IQR)	87.5 ± 10.0	-	-	-	-	-

Abbreviations : CV, cardiovascular cormobidities; CAD, coronary artery disease; SaO2, peripheral oxygen saturation; CT-value, cycle-threshold value; PaO2, partial pressure of oxygen. aNumerical data are presented with mean ± SD if normally distributed or median ± IQR if non-normally distributed. bBivariate analysis was done with independent T-test/Mann-Whitney depending on the distribution of data
*p-value <0.05 is considered statiscally significant.

Table 2. Global Strain Measurement Of The Three Groups .

Variablea	CV and COVID-19 (Subjects group)	CV without COVID-19 (Control 1)	Healthy Subjects (Control 2)	p-value (case vs control 1)	p-value (case vs control 2)	p-value control 1 vs control 2)
LV-GLS (mean ±SB)	-16.17 ± 3.379	-19.48 ± 1.141	-21.48 ± 1.777	<0.001*	<0.001*	<0.001*
RV-LS (median, [IQR])	-20.65 [-33.5 - 1.7]	-20.80 [-27.1 - -18.7]	-22.5 [-24.3 - -16.9]	0.778*	<0.001*	<0.001*

Abbreviations: CV, cardiovascular comorbidities; LV-GLS, left-ventricular global longitudinal strain; RV-FWS, right ventricular Free Wall Strain. aNumerical data are presented with mean ± SD if normally distributed or median ± IQR if non-normally distributed. BBivariate analysis was done with independent T-test/Mann-Whitney depending on the distribution of data.*p-value<0.05 is considered statistically significant.

Table 3. Bivariate Analysis between Admission Factors and LVGLS.

Variables	P Value Bivariate Analysis
Clinical Sign	
Hypertension	0.99
Diabetes Mellitus	0.63
Dyslipidemia	0.76
Smoking	0.28
Coronary Artery Disease	0.057*
Obesity	0.75
SpO2 (%)	0.97
Laboratorium	
PaO2(mmHg)	0.81
Lactate (mg/dl)	0.19*
CT value	0.71

LV GLS is the dependent variable. Depending on the form and distribution of the data, independent t-tests or simple linear regression are used. *Bivariate analysis results are considered significant for p-values less than 0.25.

gender proportions among the three groups. Although there were no significant differences in the proportions of subjects with diabetes, hypertension, dyslipidemia, smoking, coronary artery disease, and obesity status between the subjects and control group 1, there were significant differences in control group 2, indicating no difference compared to the other two groups.

LV-GLS and RF-FWS values of each group are shown in **Table 2**: Global strain measurements of the three groups. Univariate analysis revealed a statistically significant difference in LV-GLS values between the three groups, with the subjects group having the lowest values. Meanwhile, there is no significant difference in RV-FWS values between the subjects and the control I group. Healthy subjects (control 2) have the highest RV-FWS values compared with the subjects and the control I groups. **Figure 1a-b** shows examples of GLS findings of control 1 and 2 groups. In the control 1 group, slight decreases in GLS values were observed mainly at the posterior and septal regions. Meanwhile, in recovered COVID-19 patients with cardiovascular comorbidities, the decrease in GLS values was found to be scattered across different heart regions (**Figure 2a-d**).

Subjects were consecutively recruited from COVID-19 patients treated in June-July 2021 at the National Cardiovascular Center Harapan Kita

Table 4. Relationship between Admission Factors and LVGLS in the Case Group.

Variablea	Linear Regression Equationa		
	Unstandardized B Coefficient	t	P Value
Constant	-14.202		
Clinical Sign			
CAD	-1.46	-2.102	0.038*
Laboratory			
Lactate (mg/dl)	-0.50	-1.55	0.125

LV GLS is the dependent variable.
*Statistically significant findings, p-value < 0.05.

(RSJPDHK). Demographic, clinical, and laboratory data were collected. LV-GLS and RV-LS measurements were conducted using Vivid E9 echocardiography and M5Sc transducer 3-6 months after patients tested negative for the COVID-19 PCR swab. Statistical analysis was performed using IBM SPSS v26.0, including data examination, univariate analysis, and multivariate analysis with multiple linear regression, with main variables selected based on literature and a backward method.

Multivariate Analysis of Factors at Admission Influencing LV GLS and Lateral LV GLS Segments.

Multivariate linear regression analysis indicates that CAD status significantly influences LV GLS negatively ($p < 0.038$, 95% CI). The graph shows a positive correlation between CT value and LV GLS ($y = 14.99 + 0.05x$), although this correlation is not statistically significant ($p = 0.784$). In the subjects group, obesity, SpO2 value, and PaO2 at admission significantly affect the basal lateral LV GLS ($p < 0.05$, 95% CI), with an R^2 value of 0.086. However, no factors were found to influence the mid and apical lateral segments. The backward method resulted in the gradual elimination of variables for the mid and apical lateral segments, with specific details provided in the relevant table.

Table 3: Bivariate Analysis between Admission Factors and LV GLS explains that LV GLS is the dependent variable. Depending on the form and distribution of the data, independent t-tests or simple linear regression are used. Bivariate analysis results are considered significant for p-values less than 0.25, highlighting initial associations between admission factors and LV GLS.

Table 4: Relationship between Admission Factors and LV GLS in the Subjects Group shows the association between various admission factors and LV GLS. In this table, LV GLS is the dependent variable, and statistically significant findings are indicated by p-values less than 0.05. This table provides insight into which admission factors are most strongly associated with changes in LV GLS in the subjects group.

Table 5: Relationship between Admission Factors and Basal Lateral LV GLS Segment in the Subjects Group presents the analysis focusing on the basal lateral segment of LV GLS. The dependent variable is the basal lateral LV-GLS segment, and multivariate linear regression is used to identify significant predictors. Statistically significant results are indicated by p-values less than 0.05, revealing key admission factors that influence the basal lateral segment of LV GLS.

Table 6: Relationship between Admission Factors and Mid Lateral LV GLS Segment in the Subjects Group presents the analysis focusing on the mid lateral segment of LV GLS. Using multivariate linear regression, it identifies significant predictors, with the mid lateral LV-GLS segment as the dependent variable. Significant predictors are determined by p-values less than 0.05, highlighting key admission factors influencing this segment of LV GLS.

Table 7: Relationship between Admission Factors and Apical Lateral LV GLS Segment in the Subjects Group shows the analysis for the apical lateral segment of LV GLS. The dependent variable is the apical lateral LV-GLS segment, with multivariate linear regression applied to determine significant relationships. Statistically significant results, indicated by p-values less than 0.05, identify important admission factors affecting the apical lateral segment of LV GLS.

Table 5. Relationship between Admission Factors and Basal Lateral LV GLS Segment in the Case Group.

Variable	Linear Regression Coefficienta					
	Model 1 (Full Model)b R2 = 0.13			Model 8 (Final Model)b R2 = 0.086		
	Unstandardized B Coefficient	t	P Value	Unstandardized B Coefficient	t	P Value
Constant		–44.88			-23.11	
Clinical Sign						
Hypertension	-1.95	-0.68	0.50	-	-	-
Diabetes Melitus	3.81	0.27	0.20	-	-	-
Dyslipidemia	-0.75	0.38	0.70	-	-	-
Smoking	-1.19	-0.63	0.53	-	-	-
CAD	2.36	-1.70	0.18	-	-	-
Obesity	4.57	2.08	0.04*	3.02	0.36	0.58
SpO2	0.25	1.17	0.24	-	-	-
Laboratorium						
PaO2 (mmHg)	-0.053	-1.70	0.093	-0.039	0.16	0.55
Lactate (mg/dl)	-0.38	-0.54	0.59	-	-	-
CT Value	0.59	2.04	0.04	0.364	0.74	0.71

Dependent Variable: Basal Lateral LV-GLS Segment. bMultivariate analysis using linear regression. *Statistically significant result, p-value < 0.05.

Discussion

This study highlights that patients with cardiovascular comorbidities and concurrent COVID-19 infection exhibit notably lower LV-GLS values compared to both healthy individuals and those with cardiovascular comorbidities but without COVID-19 infection. LV-GLS testing demonstrates the capacity to objectively identify endomyocardial fibrosis alongside subclinical myocardial injury.[5] COVID-19, known as a major cause of endothelial inflammation, microvascular thrombosis, and multi-organ failure, often manifests with disturbances in the cardiovascular system.

Upon discharge from the hospital, a substantial proportion of COVID-19 patients display cardiac abnormalities and myocardial inflammation, with approximately 29% experiencing ventricular remodeling three months post-discharge. Subclinical myocardial damage and fibrosis, detectable through GLS examination, commonly occur. While some studies have noted significant differences in LV-GLS between control groups and COVID-19 patients, this disparity isn't reflected in left ventricular ejection fraction. The mechanism underlying myocardial fibrosis in COVID-19 implicates an exaggerated immune response, elevated angiotensin II levels, and direct viral invasion leading to myocarditis and fibrosis.[6]

Notably, this study reveals that ischemic heart disease (CAD) status upon hospital admission significantly impacts LV GLS values in the subjects group, suggesting a link between CAD comorbidities during acute COVID-19 infection and increased cardiovascular complications during long-term follow-up. Endothelial dysfunction, a common pathway in COVID-19 and CAD, may exacerbate complications in COVID-19 patients with underlying CAD. Additionally, while no significant correlation was found between LV-GLS and RV-LS with various clinical and laboratory factors upon admission, a positive correlation was observed between CT value upon admission and LV GLS level, indicating

Table 6. Relationship between Admission Factors and Mid Lateral LV GLS Segment in the Case Group.

Variable	Linear Regression Coefficienta					
	Model 1 (Full Model)b R2 = 0.114			Model 8 (Final Model)b R2 = 0.058		
	Unstandardized B Coefficient	t	P Value	Unstandardized B Coefficient	t	P Value
Constant		–44.88			-23.11	
Clinical Sign						
Hypertension	-1.95	-0.68	0.50	-	-	-
Diabetes Melitus	3.81	0.27	0.20	-	-	-
Dyslipidemia	-0.75	0.38	0.70	-	-	-
Smoking	-1.19	-0.63	0.53	-	-	-
CAD	2.36	-1.70	0.18	-	-	-
Obesity	4.57	2.08	0.04*	3.02	0.36	0.58
SpO2	0.25	1.17	0.24	-	-	-
Laboratorium						
PaO2 (mmHg)	-0.053	-1.70	0.093	-0.039	0.16	0.55
Lactate (mg/dl)	-0.38	-0.54	0.59	-	-	-
CT Value	0.59	2.04	0.04	0.364	0.74	0.71

Dependent Variable: Mid Lateral LV-GLS Segment. bMultivariate analysis using linear regression. *Statistically significant result, p-value < 0.05.

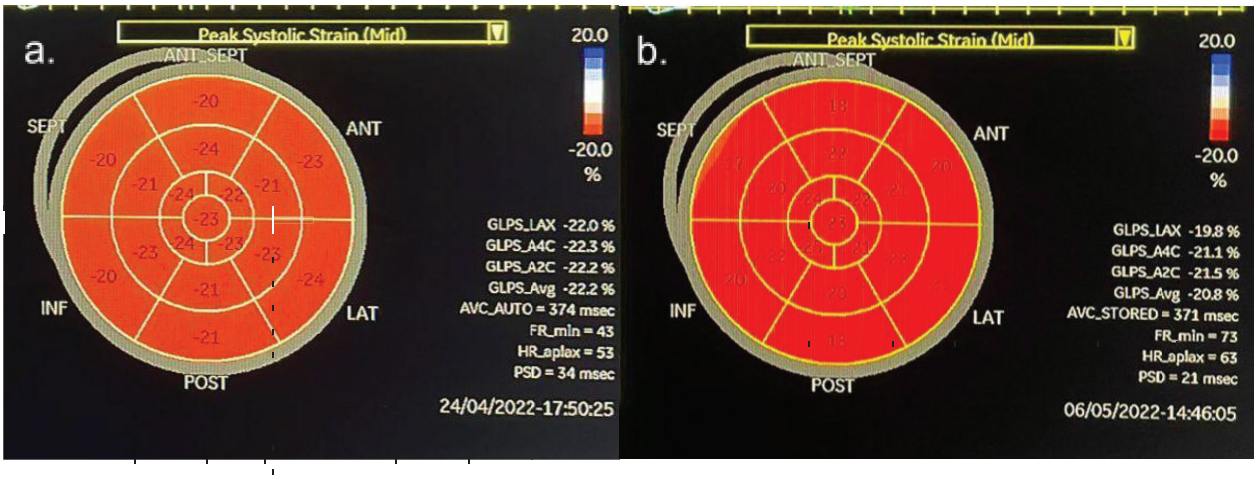

Figure 2. Planning for viewing mitral leaflets: anterior-septal (1 and 2), inferior-septal (3). Anterior tricuspid valve prolapse was noticed without tricuspid annular disjunction

Table 7. Relationship between Admission Factors and Apical Lateral LV GLS Segment in the Case Group.

Variable	Linear Regression Coefficienta					
	Model 1 (Full Model)b R2 = 0.105			Model 10 (Final Model)b R2 = 0.029		
	Unstandardized B Coefficient	t	P Value	Unstandardized B Coefficient	t	P Value
Constant		–44.26			-19.48	
Clinical Sign						
Hypertension	-3.21	-1.20	0.23	-	-	-
Diabetes Melitus	4.48	1.63	0.11	-	-	-
Dyslipidemia	-1.17	-0.64	0.52	-	-	-
Smoking	-0.42	-0.24	0.81	-	-	-
CAD	-0.22	-0.14	0.89	-	-	-
Obesity	2.50	1.22	0.22	-	-	-
SpO2	0.21	1.02	1.02	-	-	-
Laboratorium						
PaO2 (mmHg)	0.001	0.05	0.96	-	-	-
Lactate (mg/dl)	1.01	1.54	0.13	-	-	-
CT Value	0.37	1.38	1.38	0.267	1.69	0.95

Dependent Variable: Apical Lateral LV-GLS Segment. Multivariate analysis using linear regression. *Statistically significant result, p-value < 0.05, p-value < 0.05.

a potential association with disease severity[7].

Furthermore, subanalysis suggests a correlation between low oxygen levels and decreased LV-GLS in COVID-19 patients, particularly in the basal lateral region of the myocardium where COVID-19 receptors are predominantly distributed. This underscores the potential contributions of obesity and low oxygen levels to cardiac remodeling, especially in regions with heightened COVID-19 receptor expression.[8]

Our study has several limitations. Firstly, this is a single-center study with a relatively small sample size. Secondly, no baseline data regarding echocardiography strain values before COVID-19 infection. To minimize bias, a comparison was made with other demographic and risk-factors-matched cohorts of patients. Lastly, some admission factor variables data were significantly missing (e.g., CRP, d-dimer, NT-proBNP, troponin). Hence these could not be included in the multivariate analysis.

Conclusion

Patients with a history of COVID-19 and cardiovascular comorbidities demonstrate significantly lower LV-GLS values compared to both control groups. Furthermore, CAD status upon admission significantly influences LV GLS values 3-6 months after COVID-19 infection, serving as an important parameter for assessing myocardial dysfunction. Sub-analysis reveals correlations between obesity status, SpO2, and PaO2 upon admission with basal lateral LV-GLS. These findings underscore the importance of closely monitoring patients with a history of COVID-19 and cardiovascular comorbidities, as well as recognizing the implications of CAD status on myocardial function post-infection.

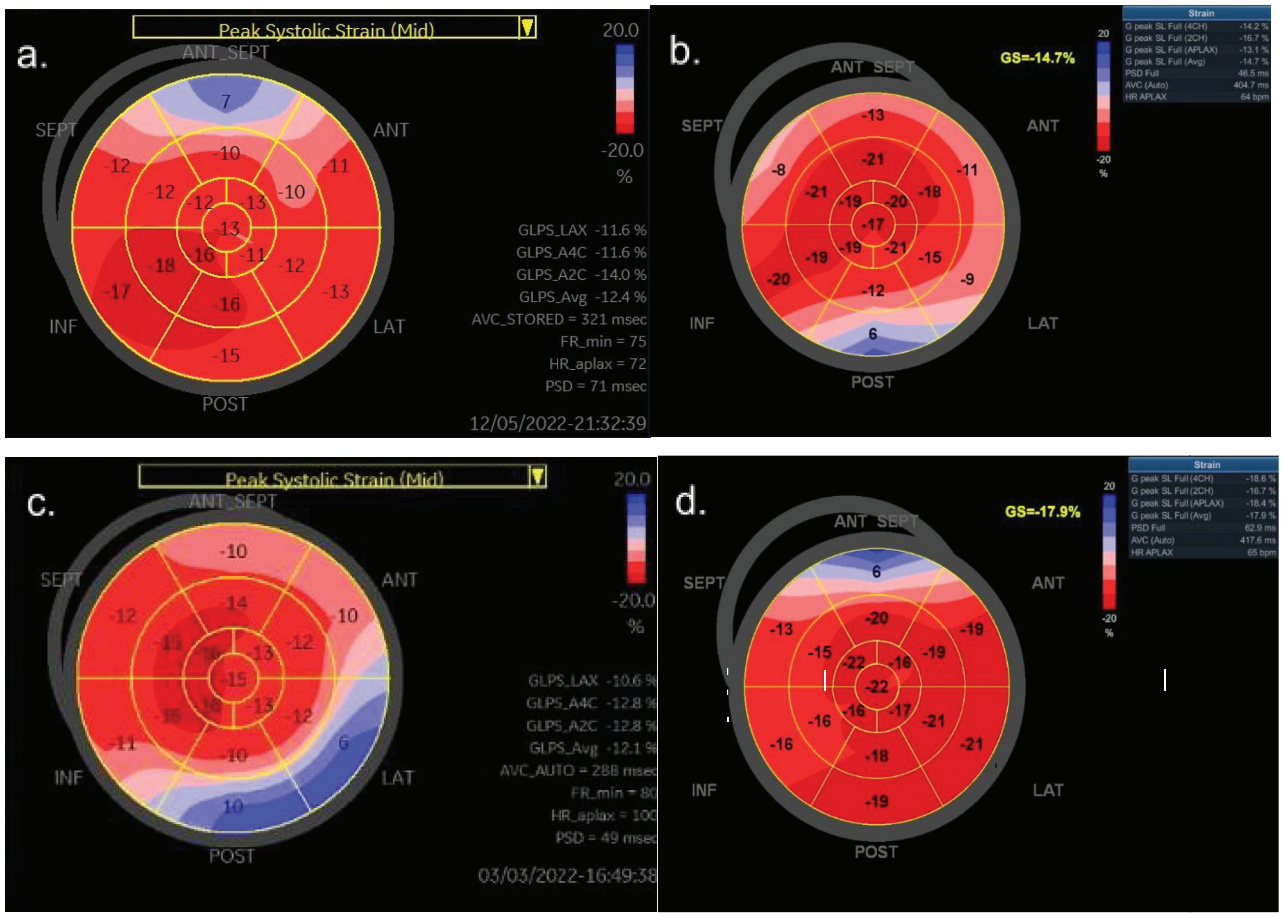

Figure 2. Planning for viewing mitral leaflets: anterior-septal (1 and 2), inferior-septal (3). Anterior tricuspid valve prolapse was noticed without tricuspid annular disjunction

List of Abbreviations

SARS COV 2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID - 19	Coronavirus Disease Of 2019
LV GLS	Left Ventricular Global Longitudinal Strain
RVLS	Right Ventricular Longitudinal Strain
PCR	Polymerase Chain Reaction
CT value	Cycle Threshold Value
CAD	Coronary Artery Disease
TAPSE	Tricuspid Annular Plane Systolic Excursion
NT-proBNP	N-Terminal Pro–B-Type Natriuretic Peptide
CRP	C-Reactive Protein

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