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Global longitudinal strain score predicts all cause death in patients with chronic total occlusion with preserved ejection fraction

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Abstract. – OBJECTIVE: Change in LVEF is one of the most important indicators of prognosis in CTO cases. Studies in patients with CTO have shown improvement in LVEF approximately at 3 and 6 months after successful PCI. It has been shown that LV global longitudinal strain (GLS) starts to improve even 1 day after CTO-PCI. We aimed at investigating the effect of subclinical echocardiographic involvement on all-cause mortality in the group with CTO and preserved ejection fraction by evaluating the LV GLS score.

PATIENTS AND METHODS: Patients with LVEF ≥ 50% were considered to have preserved ejection fraction and were included in the study. The endpoint of the study was all-cause death. For this retrospective study, 1,171 patients with coronary angiography who had had CTO in any of their vessels were screened.

RESULTS: A total of 86 consecutive patients were reviewed in the study. The optimum GLS score cut-off value (≥ 14.18) for predicting mortality was determined using receiver operating characteristic (ROC) curve analysis (AUC: 0.897, sensitivity 87.5%, specificity 81.5% *p*<0.001). At a mean follow-up of 49 months, a significant difference was found between the two groups in all-cause mortality determined by the GLS score [2 (3.4%) *vs.* 14 (51.9%), *p*<0.001]. A significant difference in mortality was observed between the group with a low GLS score and the group with a high GLS score, according to Kaplan-Meier analysis. The effect of GLS score in predicting all-cause mortality was demonstrated in multivariate cox regression analysis (Low GLS score; OR: 6.36 95%CI (1.039-39.013), *p*=0.045). Cox regression multivariate analysis and the effect of GLS score in predicting mortality were observed [Low GLS score; OR: 6.368 95%CI (1.039-39.013), *p*=0.045].

CONCLUSIONS: As a predictor, GLS may be a valuable marker of cardiac subclinical dysfunction for all caused mortality in CTO patients.

Key Words:
Chronic total occlusion, Strain Echocardiography, GLS.

Introduction

Chronic total occlusion (CTO) of the coronary artery, as previously defined, is defined angiographically as a TIMI grade 0 or 1 of antegrade flow for more than one month[1]. In the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, which grouped patients as coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), 27% of those randomized had CTO in at least one coronary artery[2]. In addition, the prevalence of CTO was found to be higher than 59% in a bypass enrollment group[3].

Change in left ventricular ejection fraction (LVEF) is one of the most important indicators of prognosis in CTO cases. In patients with cardiovascular disease, myocardial dysfunction may occur even if overall LVEF is maintained. Studies[4,5] in patients with CTO have shown improvements in LVEF approximately 3 and 6 months after successful PCI. It has been shown that LV global longitudinal strain (GLS) starts to improve even 1 day after CTO-PCI. It is expected that a tool that shows a positive effect so early regardless of the treatment can be used to determine the prognosis of the disease.

It has been found[6] that the GLS, which evaluates longitudinal myocardial deformation, is more sensitive in detecting myocardial contractility changes before there is a change in global LV parameters and is also less variable when compared to LVEF and wall motion analysis. In patients with cardiovascular disease, even if overall LVEF is preserved, the GLS score may be associated with prognosis[7].

CTO, which is an angiographic finding that is so common and can often hide clinically, has been discussed from many different perspectives. Considering the possibility of diagnosis, it would not be a wrong approach to even attribute all-cause mortality in this group to CTO.

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In our study, we aimed at investigating the effect of subclinical echocardiographic involvement on all-cause mortality in the group with CTO and preserved ejection fraction by evaluating the LV GLS score.

Patients and Methods

Patients

For this retrospective, single-center and cross-sectional study, 1,171 patients who underwent coronary angiography for any reason and were found to have CTO in any coronary artery in our University's Department of Cardiology between December 2012 and December 2019 were screened. Left ventricular longitudinal strain echocardiography records of 126 patients were accessed. Patients with LVEF ≥ 50% were considered to have preserved ejection fraction and were included in the study. The endpoint of the study was determined as all-cause death. All patients had a positive study of functional ischemia. A comprehensive basic clinical history and physical examination, 12-lead electrocardiography, and transthoracic echocardiography were performed in all patients. Data on clinical features such as hypertension, diabetes mellitus and smoking status were obtained from electronic medical records. Incomplete medical histories of the patients were obtained through telephone interviews.

Patients under 18 years of age, with a CTO artery diameter of < 2 mm, with severe heart valve diseases and a history of bypass surgery, were included in the study.

This study was approved by the local ethics committee and was performed according to approved guidelines. We conducted our study with the informed consent of the patients.

Transthoracic Echocardiography

Comprehensive transthoracic echocardiography was performed by experienced echocardiographers using existing 2D echocardiography (Vivid S6, GE Medical Systems, Chicago, IL, USA). Two-dimensional and color Doppler echocardiography was performed on standard parasternal and apical views. LVEF was measured using a modified Simpson method. All images were stored online and then measured with an offline software by independent researchers who were blinded to the clinical data.

LV Strain Measurements

LV strain parameters were obtained by examining the recordings. The endocardial border was monitored manually in the end-diastolic frame. The software automatically tracked the myocardium throughout the cardiac cycle. Peak values of segmental longitudinal stretch were obtained from grayscale recorded images in apical four-chamber, two-chamber, and long-axis views with a frame rate of 50 to 70 frames per second. GLS was obtained by averaging the peak values. The two-observer coefficients of variation for the GLS were 11%. The mean of the results of the two observers was taken as the GLS value for the same patient.

Coronary Angiography Assessment

All angiograms were retrospectively analyzed by two operators blinded to clinical outcomes to evaluate the angiographic variables required for the calculation of Syntax Score 1 (SS1). SS1 was calculated using the online calculator. After calculating Syntax Score 1 (SS1) manually, some clinical parameters (age, gender, presence of chronic obstructive pulmonary disease, creatinine clearance, left ventricular ejection fraction, and presence of peripheral artery disease) are added online and Syntax Score 2 [SS2 and CABGO for PCI) for SS2)] values was calculated. The two-observer coefficients of variation for the Syntax scores were 7%. The averages of the results of the two operators were taken as SS1 and SS2 values.

Statistical Analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median, according to the first and second percentiles (Q1-Q3) and distribution patterns of the data. Categorical variables were expressed as frequency (n) and percentage (%). The normal distribution of data was analyzed using Kolmogorov-Smirnov's or Shapiro-Wilk's tests. Survival rates in groups formed according to all-cause mortality were analyzed using the Kaplan-Meier's method. Continuous variables were compared using the *t*-test or Mann-Whitney U test as appropriate. Univariate analysis was used for continuous variables, Chi-square test, or Fisher's exact test were used for categorical variables. Independent predictors of in-hospital mortality were determined using Cox regression analysis with appropriate univariate and multivariate models, and results were expressed as odds ratio (OR) and 95% confidence interval (CI). A p-value < 0.05 was considered significant.

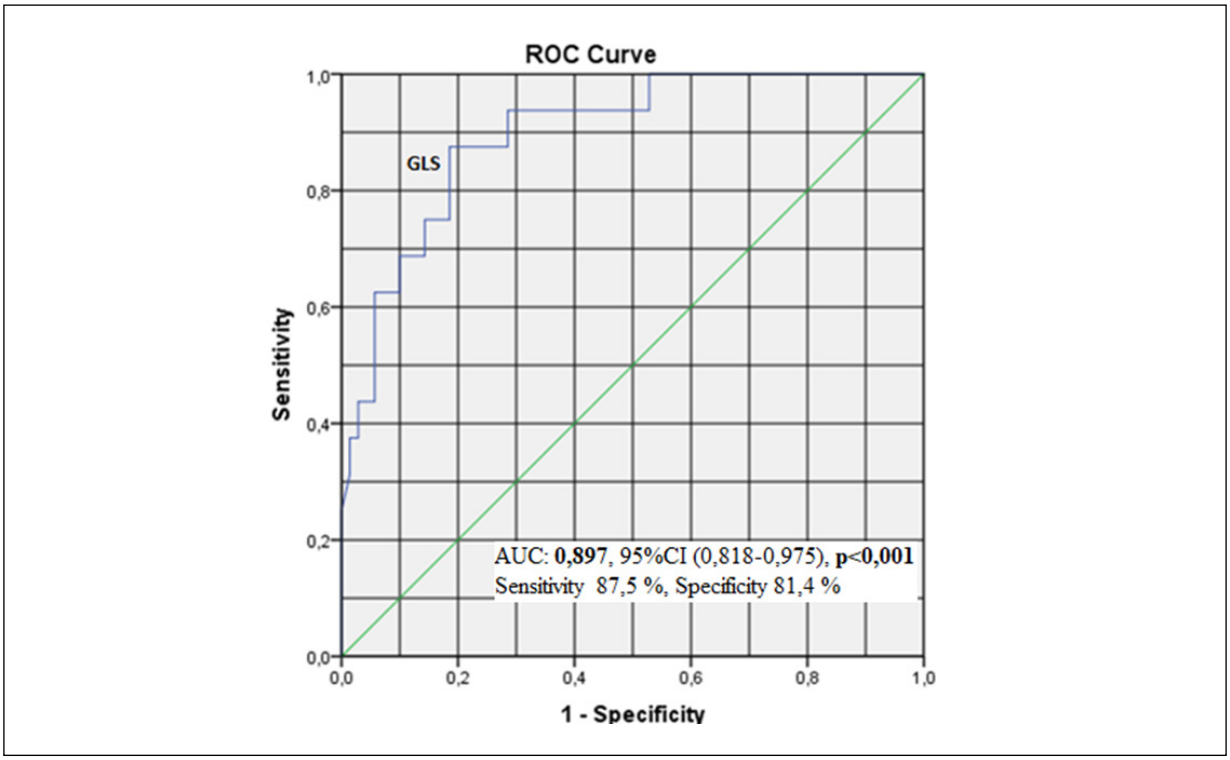

Figure 1. Receiver-operating characteristic (ROC) curve to predict mortality in patients with thrombectomy. AUC: Area under the curve, CI: Confident interval.

Results

A total of 86 consecutive patients were reviewed in the study.

Baseline Demographic Characteristics and Admission Biochemical Variables

All-cause death occurred in 16 (18.6%) of the 86 patients included in the study at a mean follow-up of 49 months. The optimum GLS score cut-off value (≥ 14.18) to predict mortality was determined using receiver operating characteristic (ROC) curve analysis (AUC: 0.897, sensitivity 87.5%, specificity 81.5%, $p < 0.001$) (Figure 1).

When the groups were separated according to the cut-off value of the GLS value in the ROC curve in Table I, no significant difference was observed between the groups in terms of age and gender. There was no significant difference between the two groups in terms of the way of admission and treatment of patients after coronary angiography.

At follow-up, a significant difference was found between the two groups in all-cause mortality as determined by the GLS score [2 (3.4%) and 14 (51.9%) ($p < 0.001$)].

It was determined that the platelet count (226±69 *vs.* 267±85) and blood glucose level (125±61 *vs.* 149±62) were higher in the group with a low GLS score (p-values 0.035 and 0.034, respectively).

While the mean SS1 score was 19.53±8.10 in the group with low GLS score, it was calculated as 13.83±5.00 in the other group and it was found that there was a significant difference ($p < 0.001$). While the mean SS2 score was 29.5±5.4 in the group with a low GLS score, it was 24.8±6.1 in the group with a high GLS score and a significant difference ($p < 0.001$) was found.

Correlations Between GLS Score and Other Variables

In Table II, the relationship between the GLS score and other parameters is examined. A negative and strong correlation was observed between GLS score and all-cause mortality, SS1 and SS2.

The Effect of LV GLS on All-Cause Mortality in Patients with CTO

As seen in Figure 2, a significant difference in mortality was observed between the group with a low LV GLS score and the group with a high

Table I. Comparison of basic demographic and angiographic characteristics and acceptance biochemical variables according to GLS score.

	GLS > -14.18 (n:59)	GLS ≥ -14.18 (n:27)	*p*-value
Age (year)	62.01±8.72	63.51±8.29	0.454
Gender (male) (%)	40 (67.8)	13 (48.1)	0.134
Follow-up period (months) IQR	50 (24)	48 (27)	0.621
Mortality, n (%)	2 (3.4)	14 (51.9)	**<0.001**
Age of death	70.00±8.5	69.4±7.5	0.912
Hypertension, n (%)	18 (30.5)	11 (40.7)	0.493
Diabetes mellitus, n (%)	13 (22.0)	9 (33.3)	0.396
Smoking, n (%)	19 (32.2)	3 (11.1)	0.070
Symptomatology, n (%)			
Stable coronary artery disease	24 (40.7)	16 (59.3)	0.171
Acute coronary syndrome	35 (59.3)	11 (40.7)	
Culprit lesion n (%)			
LAD	16 (27.1)	13 (48.1)	0.095
LCX	11 (18.6)	3 (11.1)	0.534
RCA	32 (54.2)	11 (40.7)	0.353
Treatment n (%)			
PCI	32 (54.2)	14 (51.9)	
Medical	17 (28.89	9 (33.3)	0.906
CABGO	10 (16.9)	4 (14.8)	
Left Atrium Diameter (cm)	3.72±0.44	3.80±0.35	0.389
Leukocyte (K/μL)	7,804±1,751	8,306±1,638	0.228
Hemoglobin (HgB) (g/dL)	13.61±1.64	13.33±1.50	0.465
Hematocrit (%)	41.52±5.05	39.50±4.13	0.074
Platelet (Null)	226±69	267±85	**0.035**
Lymphocyte (Null)	2,254±792	2,348±736	0.613
Neutrophil (Null)	4,846±2,130	4,939±1,372	0.837
GFR (mg/dL)	87.7±20.6	82.8±21	0.214
Glucose (mg/dL)	125±61	149±62	**0.034**
Albumin (g/dl)	3.62±0.46	3.60±0.38	0.887
Total cholesterol (mg/dL)	179±45	182±59	0792
Triglyceride(mg/dL)	165±88	212±239	0.524
LDL (mg/dL)	108±37	102±42	0.389
HDL (mg/dL)	37.9±8.6	37.1±8.7	0.710
Syntax-1 score	13.8±5.0	19.5±8.1	**0.001**
Syntax-2 (PCI)	24.8±6.1	29.5±5.4	**0.001**
Syntax-2 (CABG)	21.4±7.9	22.4±7.1	0.577
LV Global Longitudinal Strain (LV-GLS)	-17.24±1.74	-11.88±1.58	**<0.001**
LV Global Longitudinal Strain Rate (LV-GLSRI)	-1.07±0.21	-0.87±0.14	**<0.001**

Abbreviations: CABGO - Coronary Artery Bypass Grefting operation, CX - Circumflex koroner arter, GLS - Global Longitudinal Strain, GLSRI - Global Longitudinal Strain Rate Index, GFR - Glomerular filtration rate, Hct - hematocrit, HDL - High Density Lipoprotein, Hgb - Hemoglobulin, LAD - Left Anterior Desendan artery, LDL - Low Density Lipoprotein, LVDD - Left Ventricular Diastolic Disfunction, LVH - Left Ventrcular Hypertrophy, PCI - Percutaneus Coronary Intervention, RCA - Right Coronary Artery
Continuous variables are presented as mean ± SD. Nominal variables are presented as frequencies (%).

GLS score, according to Kaplan-Meier analysis (log rank: 27, $p < 0.001$). It is noteworthy that this difference has started from the early follow-up period and became more pronounced.

Discriminative Power

In Table III, predictors of all-cause mortality were evaluated in univariate and multivariate regression analysis. In the univariate analysis, it was determined that female gender, high SS2, high glucose level, high platelet count, high total cholesterol value, high triglyceride value, and low GLS score were predictors of mortality. Even after making necessary adjustments in Cox regression multivariate analysis, the effect of GLS score in predicting mortality is observed [Low GLS score; OR: 6.368 95% CI (1.039-39.013), $p = 0.045$, Table III].

Discussion

We found the following important results in our study: 1) GLS was an independent predictor of all-cause mortality in patients with CTO with preserved EF, regardless of treatment. 2) There was a weak to moderate correlation between GLS score and angiographic Syntax scores in patients with CTO. 3) Although there was no difference in age and gender between the group with a high GLS score and the group with a low GLS score, a significant difference was observed in survival times.

GLS is accepted as an indicator of mortality in many heart diseases[8]. GLS has many advantages, such as being simple to measure within the framework of certain rules, not being operator dependent, and is considered more objective than EF[9]. It has been shown[10] that GLS is an independent predictor of cardiac events and all-cause mortality compared to EF in the general population and patients with heart failure. Recently, the GLS score has been shown to be a strong prognostic finding in patients with cardiac surgery, non-ischemic cardiomyopathy, and aortic stenosis[11]. Evaluation of the LV with strain echocardiography may allow non-invasive evaluation of patients undergoing CTO-PCI to evaluate pre-procedural indication and treatment effects in follow-up[12]. Our findings showed a de-

Table II. Spearman correlation analysis.

	GLS Score	
	r	*p*-value
Age (year)	-0.092	0.397
Gender (male)	0.188	0.084
All-cause mortality	**-0.578**	**<0.001**
Smoking, n (%)	0.224	**0.038**
Hct (%)	0.219	**0.043**
Glucose (mg/dL)	-0.230	**0.033**
Platelet (mg/dL)	0.225	**0.038**
Syntax 1	**-0.350**	**0.001**
Syntax 2 (PCI)	**-0.362**	**0.001**
Syntax 2 (CABG)	-0.093	0.393

Abbreviations: Hct - Hematocrit, PCI - Percutan Coronary Intervention, SYNTAX score - Synergy between PCI with TAXUS and Cardiac Surgery.

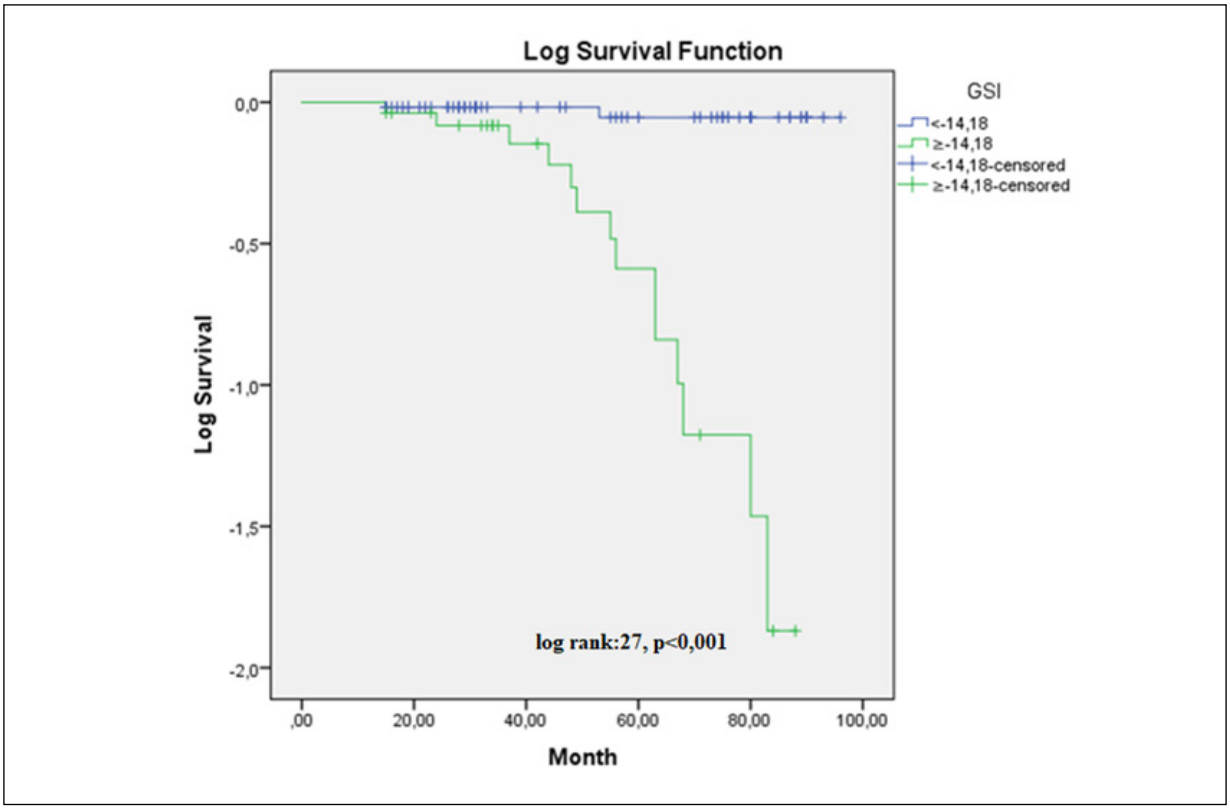

Figure 2. Kaplan-Meier survival analysis for mortality. During follow-up period, patients' group with low GLS score had significantly worse survival than patients group with high GLS score (p<0.001).

Table III. Predictors of all-cause mortality in univariate and multivariate regression analysis.

All-cause mortality	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Gender	0.259 (0.095-701)	**0.008**	1.924 (0.298-12.436)	0.492
Age	1.038 (0.972-1.108)	0.267		
Syntax-2(PCI)	1.143 (1.060-1.233)	**0.001**	1.095 (0.941-1.274)	0.242
Platelet	1.010 (1.004-1.016)	**0.002**	1.005 (0.997-1.014)	0.227
Glucose	1.009 (1.001-1.016)	**0.025**	1.004 (0.993-1.016)	0.469
Total cholesterol	1.013 (1.002-1.023)	**0.017**	1.010 (0.995-1.026)	0.175
Trigliserit	1.003 (1.001-1.004)	**0.002**	1.000 (0.996-1.003)	0.843
GLS (≥-14.18)	17.822 (4.039-78.649)	**<0.001**	6.368 (1.039-39.013)	**0.045**

OR: Odds ratio. CI: Confident Interval.

crease in GLS in pa tients with poor prognosis in CTO patients, even with preserved EF. This finding highlights the importance of GLS assessment as an indicator of cardiovascular disease in CTO patients. Based on the results of this retrospective determination, we can say that the GLS score can be a diagnostic method that will enable the identification and follow-up of the invasive group in patients with preserved EF, based on the previously demonstrated benefits of invasive intervention.

It has been shown in previous studies[13] that the platelet count was significantly higher in patients with CTO with poor collateral development than in patients with CTO with good collateral development. Non-HDL-Cholesterol/HDL was negatively correlated with coronary collateral circulation (CCC) development and was shown to be an independent predictor of CCC development[14]. Increased triglyceride glucose index (TyG) was strongly associated with less improved collateralization in CAD patients with CTO lesions[15]. Significant correlations between platelet count, cholesterol parameters and mortality in our study clearly show the importance of collateral development in terms of prognosis. When considered from this point of view, we think that necessary lifestyle changes and medical treatment changes that increase collateral circulation in CTO patients will have positive effects in terms of prognosis.

Hyperglycemia induced by acute MI was associated with MI size, area at risk, and increased mortality in patients with and without DM[16]. High glucose levels were associated with mortality in our CTO patients regardless of diabetes. Whatever the patient's complaints and history, we think that tight regulation of blood sugar should be one of the main goals for a positive prognostic effect.

In a recent study[17], the SS1 score predicted procedural failure in patients undergoing CTO-PCI. In addition, it was observed that high SS1 scores were strongly associated with an increased risk of 30-day MACE. The SS1 score was shown to be an independent negative predictor for LVEF and an independent positive predictor for LVEDV at 4-months follow-up[18]. In our study, SS1 and SS2 scores were closely related to the strain score and were found to be effective variables on mortality. We suggest that the previously determined SS1 score and SS2 score should be used as effective parameters in the follow-up of CTO patients and in determining the treatment modality.

Limitations

This study has several limitations, including the small number of cases that may affect the results. First, it was a single-center, observational study. Second, because it was a retrospective scan, some patients could not be automatically analyzed by echocardiography due to poor image quality. Therefore, several prospective studies with larger numbers of patients are needed to elucidate whether non-invasive assessment using GLS contributes to better outcomes in CTO patients.

Conclusions

As a predictor, GLS may be a valuable marker of cardiac subclinical dysfunction in CTO patients. More prospective studies with larger sample sizes are needed to confirm the outcome of this study. GLS assessment can provide appropriate patient selection in a non-invasive manner in CTO patients, sensitive and objective information about the clinical benefits of successful outcomes, and wider use of the treatment procedure in clinical practice.

Conflict of Interest

There is no conflict of interest to declare.

Funding

The authors declare that there is not any financial disclosure.

Informed Consent

The study was conducted with the informed consent of the patients.

Ethics Approval

This study was approved by the local ethics committee and was performed according to approved guidelines.

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