Prognostic Value of Left Ventricular Global Strain Analysis by Two-Dimensional Speckle-Tracking Echocardiography in Non-Hemodynamically Significant Intermediate Coronary Lesions

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Abstract: Intermediate coronary lesions represent a major challenge for the invasive and noninvasive cardiologist. Left ventricular strain calculation by speckle tracking echocardiography has the capacity to analyze the motion of the cardiac tissue. This study aimed to evaluate its usefulness and prognostic significance in nonhemodynamically significant intermediate coronary lesions. We studied 247 patients who underwent a clinically indicated coronary angiogram. Each of the patients had a single nonrevascularized nonhemodynamically significant intermediate severity coronary lesion (ISCL) with a fractional flow reserve greater than 0.80. The left

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ventricular global longitudinal strain (GLS) was calculated using speckle-tracking echocardiography with TomTec 2D Cardiac Performance Analysis (Unterschleissheim, Germany). An abnormal GLS was defined as less than -20%. The primary endpoints were revascularization of the target lesion, admissions for major adverse cardiac events (MACE), and cardiac-related mortality, all within 2 years. On multivariate logistic regression data analysis, we found that patients with an ISCL and abnormal GLS had an increased risk for admissions due to MACE (odds ratio [OR] 1.06, *P* < 0.05, confidence interval [CI] 95%, 1.005-1.120], and an increased risk of cardiac-related death (OR 1.12, *P* < 0.05, CI 95% 1.012-1.275). There was no difference in the need for target lesion revascularization among individuals with normal and abnormal GLS (1.00, *P* 0.88, CI 95% .950-1.061). Left ventricular strain analysis by speckle-tracking echocardiography showed an independent prognostic value in patients with nonrevascularized nonhemodynamically significant coronary lesions. (Curr Probl Cardiol 2021;46:100787.)

Introduction

Intermediate severity coronary lesions (ISCL) can be found in up to 50% of subjects undergoing a coronary angiography. Such lesions are defined as having more than 40% but less than 70% in diameter narrowing of the coronary artery assessed by visual inspection during coronary angiography.[1] The development of fractional flow reserve (FFR) has helped identify the hemodynamically significant lesions requiring intervention, thus avoiding unnecessary procedures and stent implantations.[2] Multimodality coronary imaging tools such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) provide a more thorough anatomic assessment of the coronary plaque and are of invaluable help for the interventional cardiologist.[3,4] However, these are all invasive diagnostic tools, and as such, always represent a higher risk to the patient.

Two-dimensional speckle-tracking echocardiography (2D-STE), is able to analyze the motion of the cardiac tissue and measure the myocardial deformation or strain.[5-8] There are several FDA-approved 2D-STE

processing software from different vendors making the standardization of the reference values more challenging, given the inter-vendor variability.[9,10] However, recent studies have found a good reproducibility of the global longitudinal strain (GLS) measurements among the most widely-used software.[9] The recommendations from the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) state that a global longitudinal strain (GLS) around -20% is normal in a healthy person, with lower (less negative) absolute values being considered abnormal.[11-13]

Several studies have found clinical utilities for left ventricular (LV) strain, such as the prediction of outcomes in subjects with heart failure, stress-induced cardiomyopathy, aortic stenosis, or the correlation with the infarct size in chronic ischemic heart disease, among others.[5,14-16]

However, its usefulness as a risk stratification tool in ISCL has not been assessed. The purpose of our study is to evaluate the prognostic value and usefulness of LV strain measurement by 2DSTE in nonhemodynamically significant ISCL.

Material and Methods

Study Population and Procedures

The study was conducted at Einstein Medical Center, Philadelphia, PA, USA; where institutional review board approval was obtained. We included subjects with a coronary arteriography between 2013 and 2015 demonstrating a single intermediate coronary lesion, with an FFR greater than 0.80 that was not revascularized at the time of the procedure or planned for a future revascularization; and who had a transthoracic echocardiogram within 1 month before or after the coronary arteriography. We excluded subjects with systolic and diastolic heart failure, atrial fibrillation, subjects who had revascularization of the target lesion at the time of the procedure, subjects who were lost follow up, and subjects with poor quality transthoracic echocardiograms or without an echocardiogram.

A total of 247 subjects were included in the study. The subject distribution included: 109 (44%) males and 138 females (56%), with a mean age of 64 years. The majority of subjects were African-American (65%, n = 160), followed by Caucasian, Hispanic, Asian, and other ethnicities (Table 1).

TABLE 1. Baseline demographic and comorbid characteristics by race/ethnicity

Characteristic	Total (%) (n = 247)	Race/Ethnicity, %					*P* value
		African-American (n = 160)	Caucasian (n = 41)	Asian (n = 10)	Hispanic (n = 32)	Other (n = 4)	
Gender							< 0.05
Male	109 (44.1)	38.1	51.2	80	53.1	50	
Female	138 (55.9)	61.9	48.8	20	46.9	50	
Comorbidities							
Hypertension	243 (98.4)	98.1	100	100	100	75	< 0.05
Dyslipidemia	220 (89.1)	90.6	82.9	90	96.9	25	< 0.05
Diabetes	119 (48.2)	49.4	31.7	70	59.4	25	0.594
Chronic kidney disease*	67 (27.1)	33.1	14.6	30	15.6	0	< 0.05

*Stages 2 to 5, including end-stage kidney disease.

Fractional Flow Reserve Calculation

Fractional flow reserve was measured using PressureWire Aeris (St Jude Medical, St Paul, MN) by 4 experienced interventional cardiologists. This was done using the standard protocol and quality control measures established in our catheterization laboratory. This included an Adenosine infusion at 140mcg/kg/min for 2 minutes to measure the FFR at peak hyperemia.

Strain Analysis

Each patient underwent a 2-dimensional transthoracic echocardiogram within one month after the FFR measurement. Every study was acquired using the same Philips EPIQ cardiac ultrasound system (Andover, MA), and standard views obtained by a certified cardiac sonographer.

The LV GLS was calculated retrospectively in 4-chamber raw images by 2 experienced cardiologists using 2D-STE with 2D Cardiac Performance Analysis (TOMTEC, Unterschleissheim, Germany), a vendor-independent software (Fig 1).

Statistical Analysis

Data analysis was performed with IBM SPSS Statistics for Mac, Version 22.0. (Armonk, NY: IBM Corp.). Descriptive statistics were used to analyze the baseline characteristics of the subjects in the study, as well as cross-tabbing for the different variables. The analysis of the categorical variables was done using Pearson's X^2 and Fisher's exact test for

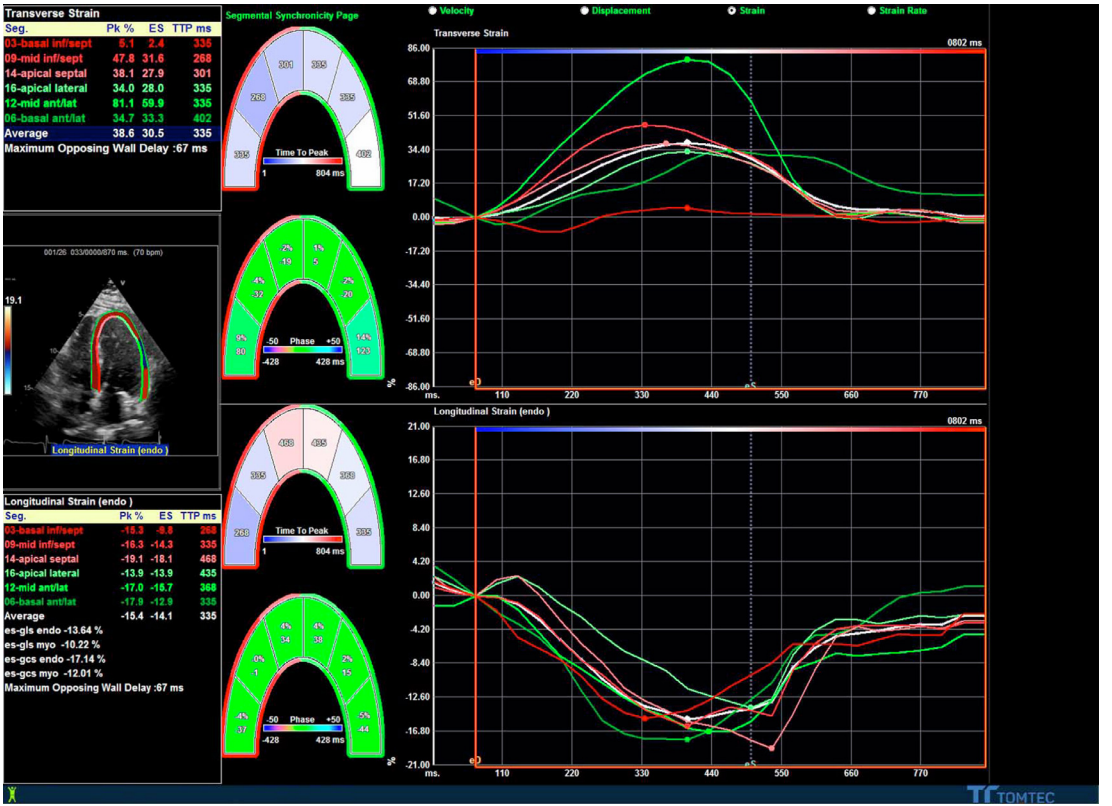

FIG. 1. Left ventricular strain calculation with TomTec 2D CPA. (Color version of figure is available online.)

frequencies less than 7, and student *t* test was used for other variables. We defined statistical significance as a *P* value less than 0.05. Logistic regression was used for univariable and multivariate analysis of the continuous and categorical variables, in order to calculate the odds ratios and relationships between them.

Results

The primary endpoints of this study were admissions for major adverse cardiac events (MACE) which included myocardial infarction, ventricular arrhythmias, sudden cardiac death and acute heart failure, also the need for percutaneous coronary intervention (PCI) of the target lesion, and 2-year mortality due to cardiac events.

The patient distribution included: 44% (n = 109) males and 56% (n = 138) females, with a mean age of 63.03 years in males and 65.13 years in females. Of those, 65% (n = 160) were African-American, followed by 17% (n = 41) Caucasian, 13% (n = 32) Hispanic, 4% (n = 10) Asian, and 2% (n = 4) from other ethnicities (Table 1).

The comorbidities with the highest prevalence were hypertension (HTN) (98%, n = 243), and dyslipidemia (DLD) (90%, n = 220). Diabetes (DM) was present in 48% (n = 119) of the subjects, followed by chronic kidney disease including stages 2 to 5 (CKD) in 27% (n = 67) of them (Table 1).

The most prevalent coronary lesions were found in the left anterior descending artery (LAD) 55% (n = 137), followed by 21% (n = 51) in the right coronary artery (RCA), and 13% (n = 33) in the left circumflex artery (LCX). Lesions in the left main artery (LM), other sub-branches and internal mammary grafts were less prevalent (Table 5).

An abnormal LV GLS was defined as greater than negative 20%, this is consistent with the ASE and ESCI recommendations.[11,12,17]

We found an abnormal LV GLS in 90% (n = 221) of the studied subjects. Among the lesions, we found an abnormal LV GLS in 91% (n = 124) of the lesions in the left anterior descending artery, 90% (n = 9) of the left main artery lesions, followed by 88% (n = 45) in the right coronary artery, and 85% (n = 28) in the left circumflex artery. Other branches including grafts had a variable prevalence of an abnormal LV GLS (Table 6).

We categorized the lesions in quartiles for both, the FFR and the LV GLS.

The distribution of lesions among the FFR quartiles was as followed: 31% (n = 77) from 0.80 to 0.84, 35% (n = 86) from 0.85 to 0.89, 27%

(n = 67), from 0.90 to 0.94, and 7% (n = 17) greater than 0.94. The first and second quartile had the greatest prevalence of lesions (Table 2).

Of the 221 subjects with an abnormal LV GLS, 33.0% (n = 73) were in the first quartile, 35.7% (n = 79) in the second, 25.3% (n = 56) in the third, and 5.9% (n = 13) in the fourth quartile (Table 2).

Among the subjects requiring revascularization of the target lesion within 24 months, 44.8% (n = 39) were in the first quartile, 35.6% in the second, followed by 14.9% (n = 13) and 4.6% (n = 4) in the third and fourth respectively. The rate of readmission for MACE within 24 months was 40% (n = 48) in the first quartile, 29.2% (n = 35) in the second quartile, 26.7% (n = 32) in the third and 4.2% (n = 5) in the fourth quartile. Thirteen subjects died due to cardiac events; of those 38.5% (n = 5) had lesions within the first quartile, 23.1% (n = 3) in the second, 38.5% (n = 5) in the third, and none within the fourth quartile (Table 2).

In the LV GLS quartile categorization, the prevalence of the lesions among the quartiles was as follows: 5% (n = 14) from -27.71 to -21.58, 38% (n = 93) from -21.59 to -15.45, 39% (n = 96) from -15.46 to -9.33, and 18% (n = 44) greater than -9.33 (Table 3); with a significantly higher prevalence of lesions in the second and third quartiles.

Forty eight percent of the subjects were readmitted for MACE within 24 months. Of those, 93.3% (n = 112) of them had an abnormal LV GLS. Thirty 5 percent (n = 87) of the subjects required revascularization of the target lesion within 24 months, with 37% (n = 82) of them having an abnormal LV GLS. Among the 15% (n = 13) of the subjects who died within 2 years due to cardiac reasons (including myocardial infarction, ventricular arrhythmias, sudden cardiac death and acute heart failure), 92.3% (n = 12) had an abnormal LV GLS (Table 7).

On multivariate logistic regression data analysis, we found a statistically significant increase in the risk of admissions for MACE within 2 years in subjects with an abnormal LV GLS (OR 1.06, $P < 0.05$, CI 95% 1.005-1.120). We also found an increased risk for mortality due to cardiac events within 2 years in subjects with an abnormal LV GLS (OR 1.12, $P < 0.05$, CI 95% 1.012-1.275). The likelihood for needing target lesion revascularization within 2 years was not increased in subjects with an abnormal LV GLS compared with those with a normal LV GLS (1.00, p 0.88 CI 95% .950-1.061) (Table 4).

Discussion

We found a significant prevalence of abnormal GLS among patients with intermediate LAD and RCA lesions. Also, the greatest prevalence of

TABLE 2. Target lesion, cardiac events and abnormal GLS stratified by FFR quartiles

		% (n) within characteristic				
	Total (%)	**0.80 to 0.84 (31%, n = 77)**	**0.85 to 0.89 (35%, n = 86)**	**0.90 to 0.94 (27%, n = 67)**	**Greater than 0.94 (7%, n = 17)**	***P* value**
Abnormal LV GLS	221 (90)	33.0 (73)	35.7 (79)	25.3 (56)	5.9 (13)	< 0.05
*Target lesion**						0.142
LAD	137 (55.5)	33.6 (46)	38.7 (53)	22.6 (31)	5.1 (7)	
RCA	51 (20.6)	23.5 (12)	33.3 (17)	39.2 (20)	3.9 (2)	
LCX	33 (13.4)	21.2 (7)	27.3 (9)	30.3 (10)	21.2 (7)	
OM	5 (2.0)	20.0 (1)	60.0 (3)	20.0 (1)	0 (0)	
Diagonal	4 (1.6)	25.0 (1)	25.0 (1)	25.0 (1)	25.0 (1)	
Ramus	3 (1.2)	33.3 (1)	33.3 (1)	33.3 (1)	0 (0)	
LM	10 (4.0)	7.8 (6)	2.3 (2)	3.0 (2)	0 (0)	
PDA	1 (0.4)	100 (1)	0 (0)	0 (0)	0 (0)	
Internal mammary graft**	3 (1.2)	66.7 (2)	0 (0)	33.3 (1)	0 (0)	
Event within 24 months						
Revascularization of target lesion	87 (35.2)	44.8 (39)	35.6 (31)	14.9 (13)	4.6 (4)	< 0.001
Readmission for MACE	120 (48.6)	40.0 (48)	29.2 (35)	26.7 (32)	4.2 (5)	< 0.05
Cardiac-related death	13 (5.3)	38.5 (5)	23.1 (3)	38.5 (5)	0 (0)	0.499

*LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; OM, obtuse marginal; LM, left main; PDA, posterior descending artery.
**Graft to the LAD.

TABLE 3. Target lesion and cardiac events stratified by GLS quartiles

		% (n) within characteristic				
	Total (%)	**-27-71 to -21.58 (5%, n = 14)**	**-21.59 to -15.45 (38%, n = 93)**	**-15.46 to -9.33 (39%, n = 96)**	**Greater than -9.33 (18%, n = 44)**	***P* value**
*Target lesion**						0.468
LAD	137 (55.5)	5.8 (8)	33.6 (46)	41.6 (57)	19.0 (26)	
RCA	51 (20.6)	2.0 (1)	45.1 (23)	31.4 (16)	21.6 (11)	
LCX	33 (13.4)	9.1 (3)	42.4 (14)	36.4 (12)	12.1 (4)	
OM	5 (2.0)	0 (0)	60.0 (3)	40.0 (2)	0 (0)	
Diagonal	4 (1.6)	0 (0)	0 (0)	75.0 (3)	25.0 (1)	
Ramus	3 (1.2)	33.3 (1)	33.3 (1)	0 (0)	33.3 (1)	
LM	10 (4.0)	10.0 (1)	50.0 (5)	30.0 (3)	10.0 (1)	
PDA	1 (0.4)	0 (0)	100 (1)	0 (0)	0 (0)	
Internal mammary graft**	3 (1.2)	0 (0)	0 (0)	100 (3)	0 (0)	
Event within 24 months						
Revascularization of target lesion	87 (35.2)	2.3 (2)	40.2 (35)	39.1 (34)	18.4 (16)	0.392
Readmission for MACE	120 (48.6)	4.2 (5)	34.2 (41)	39.2 (47)	22.5 (27)	< 0.05
Cardiac-related death	13 (5.3)	7.7 (1)	15.4 (2)	30.8 (4)	46.2 (6)	< 0.05

*LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; OM, obtuse marginal; LM, left main; PDA, posterior descending artery.
**Graft to the LAD.

TABLE 4. Odds Ratios for cardiac events in subjects with an abnormal LV GLS

	Odds Ratio (95% CI)	*P* value
*Readmission due to MACE**	1.06 (1.005 to 1.120)	< 0.05
Need for target lesion revascularization	1.00 (.950 to 1.061)	0.884
Cardiac-related death	1.12 (1.012 to 1.275)	< 0.05

*MACE, major adverse cardiac events.

an abnormal GLS was in the FFR range between 0.80 and 0.89. Similarly, the majority of subjects who experienced significant cardiac events (including myocardial infarction, ventricular arrhythmias, sudden cardiac death and acute heart failure) fell under that same FFR range with the exception of cardiac death, which occurred across the FFR value quartiles except for the group greater than 0.94. It is likely that the amount of myocardium at risk from the lesion and supplied by the vessel being tested contributes significantly to the GLS result and affects patient outcomes.

We found the greatest prevalence of significant cardiac events in subjects with GLS values between -21.59 and -9.33, with the majority being below the value recommended (an absolute value close to -20%).[16] Also, the majority of the lesions in the proximal vessels covering larger territories revealed GLS values in the abnormal range.

Although other conditions such as heart failure, hypertension, chronic kidney disease, or age itself[14,18-21] may impair GLS, on multivariate logistic regression data analysis, an abnormal LV GLS was associated with a significant increase in the risk of admissions for MACE within 2 years (OR 1.06, $P < 0.05$, CI 95% 1.005-1.120) as well as cardiac mortality (OR 1.12, $P < 0.05$, CI 95% (Table 4; Figs 2 and 3). An explanation to these findings could be that a "low-grade" ischemia may be causing early "silent" systolic dysfunction.

The limitations of our study include a relatively small sample size, although ours is the only study to date that have addressed the utility of GLS in this patient subset. Also, we did not compare GLS with other cardiac imaging modalities such as myocardial perfusion imaging; this would be important to investigate in future studies, considering that FFR was validated by the later.[22] Nevertheless, we believe that GLS by 2D STE is a cost-effective noninvasive tool that could help identify subjects at risk for future adverse events.

Conclusions

The increased prevalence of major adverse cardiac events in abnormal GLS ranges, is in line with higher prevalence of MACE in subjects

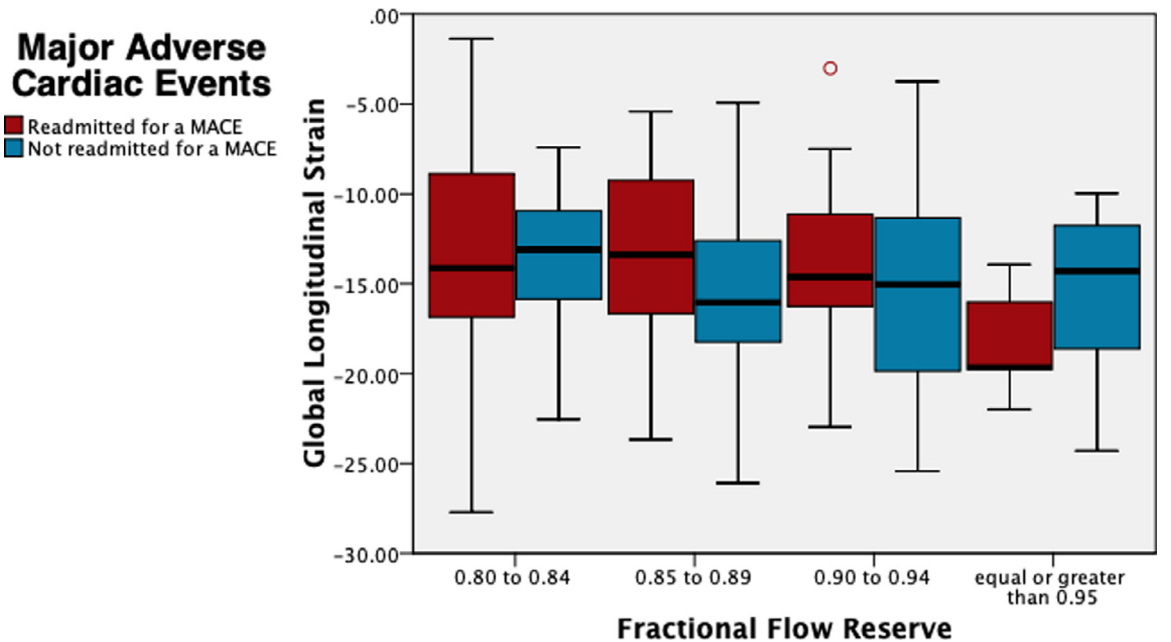

FIG. 2. Admissions for major adverse cardiac events by FFR and GLS. (Color version of figure is available online.)

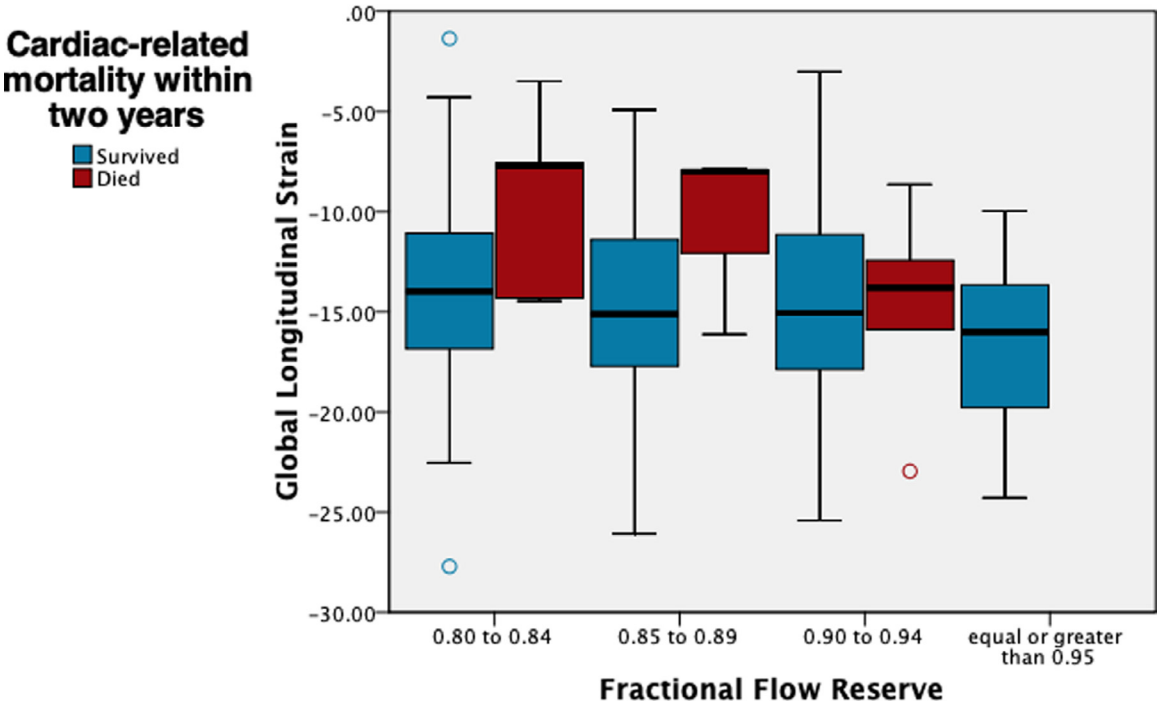

FIG. 3. Distribution of cardiac-related mortality by FFR and GLS. (Color version of figure is available online.)

TABLE 5. Prevalence of lesions by vessel

	No.	%
Left anterior descending	137	55
Right coronary	51	21
Left circumflex	33	13
Obtuse marginal branch	5	2
Diagonal branch	4	2
Ramus intermedius	3	1
Left coronary	10	4
Posterior descending	1	1
Internal mammary graft	3	1

with lower FFR values demonstrates that GLS can be used to further risk-stratify noninvasively patients with nonrevascularized nonhemodynamically significant ICLs, identifying such patients at higher risk for significant cardiac events. This may justify closer follow up, with subsequent GLS analyses and its response to guideline-directed medical therapy for CAD.

Author Contributions

Rubio MD, Manolo: Concept, design of the study, data collection, statistics, analysis and interpretation, drafting article.

Lo MD, Kevin B: Data collection, approval of article.

Ram MD, Pradhum: Data collection, approval of article.

Rubio MD, Cindy S: Critical revision of article, drafting article, approval of article.

Co MD, Michael L: Critical revision of article, statistics.

Varadarajan MD, Padmini: Critical revision of article, approval of article, Concept, design of the study.

Amanullah MD, Aman M: Critical revision of article, approval of article, Concept, design of the study.

Truong MD, Huu T: Critical revision of article, approval of article, Concept, design of the study.

Khouzam MD, Rami N: Critical revision of article, approval of article, Concept, design of the study.

Abudayyeh MD, Islam A: Critical revision of article, approval of article, Concept, design of the study.

TABLE 6. Prevalence of abnormal LV GLS by target lesion

Target lesion, % (n)									
	Total (%)	Left anterior descending (n = 137)	Right coronary (n = 51)	Left circumflex (n = 33)	Obtuse marginal (n = 5)	Diagonal (n = 4)	Ramus (n = 3)	Left main (n = 10)	Posterior descending (n = 1)	Internal mammary graft* (n = 3)
LV GLS less than -20%	221 (90)	91 (124)	88 (45)	85 (28)	100 (5)	100 (4)	67 (2)	90 (9)	100 (1)	100 (3)

*Graft to the LAD.

TABLE 7. GLS and cardiac events

Event within 24 months	Total (%)	% within event		*P* value
		Abnormal GLS (< -20) (90%, n = 221)	Normal GLS (> -20) (10%, n = 26)	
Revascularization of target lesion	87 (35.2)	94.3 (82)	5.7 (5)	0.714
Readmission for MACE	120 (48.6)	93.3 (112)	6.7 (8)	0.556
Cardiac-related death	13 (5.3)	92.3 (12)	7.7 (1)	0.731

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