

Cardiac Strains for Prediction of Adverse Events and Ventricular Remodeling

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Abstract

Background: Cardiac strains were assumed to accurately predict adverse events after acute ST-segment elevation myocardial infarction (STEMI). There are, however, some debates on it. The aim of the study was to evaluate the effects of cardiac strains obtained from cardiac magnetic resonance (CMR) on cardiac events and adverse LV remodeling.

Methods: A prospective and two-center study included STEMI patients treated with primary PCI with implantation of stents. They underwent CMR before discharge. Major adverse cardiac events and LV remodeling were obtained during 6 months follow-up.

Results: Between February 2015 and September 2016, 76 patients were available for the final analysis. We reported major adverse cardiac events (MACE) rate 23.7% using cardiac death, reinfarction, unplanned revascularization and heart failure as combined events in 6 months follow-up. Global longitudinal strain (GLS) can predict MACE independently, with OR=1.229 (1.087-1.390) and P=0.001. Moreover, GLS can predict LV remodeling independently, with OR=1.943 (1.133-3.334) and P=0.016.

Conclusion: In patients with STEMI treated with primary PCI, CMR-determined GLS before discharge is a good predictor of MACE and adverse LV remodeling in 6 months follow-up.

Introduction

Patients with acute ST-segment elevation myocardial infarction (STEMI) are still at increased risk for adverse outcomes, even after a timely revascularization (1, 2). Hence, early risk stratification for such patients is of clinical importance. The STEMI patients treated with implantation of stents often involves remodeling of the left ventricle (LV). Since LV remodeling is associated with future adverse outcomes, the change of cardiac parameters may be risk factors for prediction of adverse events after revascularization in STEMI patients.

Substantial studies have been reported on the better prognostic power of global longitudinal strain (GLS) not only for predict remodeling but also for adverse events by using the speckle tracking echocardiography technique (3–5). However, cardiac magnetic resonance (CMR) is consider as the gold standard for the assessment of regional myocardial strains. CMR feature tracking (CMR-FT) can acquire steady-state free-precession (SSFP) cine images and predict the transmural infarction, myocardial deformation and wall motion accurately (6, 7). Although CMRFT indices showed independent prognostic implications in dilated and chronic ischemic cardiomyopathy as well as tetralogy of Fallot (8–10), evidence in myocardial infarction had some degrees of controversy (11, 12). Eitel et al suggested an incremental prognostic role of CMR-FT derived GLS over and above classical CMR markers of prognosis in acute myocardial infarction patients (including STEMI and NSTEMI) (11). In contrast, Gavara et al failed to demonstrate prognostic value of GLS over other established CMR parameters in a retrospective study of 323 STEMI patients (12).

The objective of the study is to assess the effects of CMR-determined cardiac strains on cardiac events and adverse LV remodeling. Here, we hypothesized that cardiac GLS measured in patients before discharge is a good predictor of cardiac events and adverse LV remodeling in the follow-up study. To test the hypothesis, a prospective and two-center study was carried out to include STEMI patients treated with primary PCI with implantation of stents. Those patients underwent CMR before discharge. The follow-up data were obtained from hospital records or face-to-face visit in patients 6 months after STEMI. The significance and implication of the study were discussed to enhance the prediction of adverse events after revascularization in STEMI patients.

Materials And Methods

Study Design: This prospective cohort study was performed in two centers, i.e., Peking University First Hospital and Affiliated Hospital of Xuzhou Medical University. The study was approved by the Institutional Review Board (IRB) for each participating center, conforming to the declaration of Helsinki and Good Clinical Practice Guidelines of the China Food and Drug Administration. All patients provided written informed consent.

Participants: The prospective cohort study included 86 STEMI patients treated with primary PCI with implantation of stents in the two centers from February 2015 to September 2016. All patients underwent CMR before discharge.

Exclusive criteria included: 1) complicated with atrial fibrillation, frequent premature contraction, persistent ventricular tachycardia, or other tachyarrhythmia; 2) previous cardiac surgery history or myocardial infarction; 3) severe liver and kidney dysfunction; 4) malignant tumors; 5) life expectancy less than one year; 6) pregnant women; and 7) those who had contraindications for magnetic resonance (e.g. contrast agent allergy, ferromagnetic objects in the body, claustrophobia, etc.).

CMR Measurements: CMR was performed in enrolled patients before discharge (5–7 days after the index event was recommended). All patients were examined with a 1.5 T GE magnetic resonance imaging scanner. Three long-axis views (4-, 3- and 2-chamber orientation) as well as short axis stacks were acquired using a balanced steady state free precession imaging technique for functional cardiac analyses. Native T2, T2 weighted image (T2WI), and post contrast T1 weighted image (T1WI) sequences were used for assessment of edema, infarction size, microvascular obstruction (MVO), and intramyocardial hemorrhage (IMH). T1 weighted images were obtained 15 minutes after administration of Gadolinium-based contrast agents.

CMR Analysis: The analysis was performed offline by two experienced radiologists. Infarct size, edema, MVO and IMH were quantified by using the CVI 42 software (Circle Cardiovascular Imaging Calgary, Canada) (13). CMR feature tracking strains (GLS, GCS and GRS: global longitudinal, circumferential and radial strains), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were determined by using the TomTec Imaging Systems (2D CPA MR, Cardiac Performance Analysis, Version 1.1.2, TomTec Imaging Systems, Germany) (14, 15).

Briefly, LV contours were first drawn semi-automatically at the end of diastole and systole. Subsequently, image features throughout an entire cardiac cycle were determined by the software's automatic border tracking algorithm. Accurate tracking was finally assured by visual review of all borders and manual adjustments with consequent reapplication of the algorithm if necessary.

Follow-up Study: Major adverse cardiac events (MACE), including cardiac death, reinfarction, unplanned revascularization and heart failure, were obtained from hospital records or face-to-face visit in patients 6 months after STEMI. Heart failure manifestations were defined as the exacerbation of exertional dyspnea or pulmonary edema requiring hospital admission, initiation of diuretics, or an increase in an existing diuretic regimen. Follow-up CMR was also performed in patients 6 months after STEMI. Adverse LV remodeling was defined as LVEDV > 15% than that before discharge from the hospital.

Statistical Analysis: Variables are denoted as mean \pm SD (standard deviation), and independent t testing or Fisher exact testing is used to compare differences between groups. Variables that are not normally distributed (as determined by Kolmogorov–Smirnov tests) are expressed as medians with 25th and 75th percentiles and compared using the Mann–Whitney U test. Based on the ratio of infarcted myocardium mass to LV mass (IM%LV), patients are divided into three groups as: group A (IM%LV < 10%), group B ($10\% \leq \text{IM\%LV} < 20\%$), and group C (IM%LV $\geq 20\%$).

A comparison of multiple variables is demonstrated between patients with LV remodeling and patients without LV remodeling as well as between patients who did and did not show MACE during the follow-up study. The logistic backward stepwise regression analysis (two tailed and α of 0.05) was demonstrated to determine which variables are better predictors of MACE as well as LV remodeling. Receiver operating-characteristic (ROC) curve is used to determine the cutoff value of GLS. All statistical analyses were performed with a test significance level of 0.05 using the SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Between February 2015 and September 2016, 86 patients were enrolled in two centers. The follow-up analysis was carried out in 76 patients (55.5 ± 10.7 years and 88% male) treated with primary PCI for STEMI and taken with CMR exams before discharge, as shown in Fig. 1. Baseline patient characteristics are presented in Table 1. The left anterior descending (LAD) artery is the most commonly assessed vessel followed by the right coronary artery (RCA) and left circumflex (LCX) artery. There is no difference of baseline characteristics in patients with different degrees of myocardial infarction except for peak BNP, peak cTNI, and symptom-to-balloon time.

Table 1
Baseline characteristics of the study population

Variables	Total (n = 76)	Group A (n = 29) (IM%LV < 10%)	Group B (n = 33) (10% ≤ IM%LV < 20%)	Group C (n = 14) (IM%LV ≥ 20%)	P
Age (years)	55.5 ± 10.7	53.7 ± 11.3	56.7 ± 9.6	56.3 ± 12.1	0.519
Male (n, %)	67 (88.2)	26 (89.7)	29 (87.9)	12 (85.7)	0.930
BMI (kg/m ²)	24.9 ± 3.1	25.0 ± 3.3	24.4 ± 3.0	25.7 ± 2.7	0.422
Smoking (n, %)	50 (65.8)	17 (58.6)	25 (75.7)	8 (57.1)	0.275
Diabetes mellitus (n, %)	12 (15.8)	3 (10.3)	6 (18.2)	3 (21.4)	0.570
Hypertension (n, %)	38 (50)	16 (55.2)	17 (51.5)	5 (35.7)	0.476
Systolic blood pressure (mmHg)	135 ± 9	140 ± 19	130 ± 18	136 ± 16	0.164
Heart rate (beats/min)	73.5 ± 10.5	75.4 ± 10.2	73.1 ± 11.1	74.4 ± 9.4	0.670
LDL-C (mmol/L)	2.8 ± 0.8	2.8 ± 0.7	2.7 ± 0.7	2.8 ± 1.2	0.787
HDL-C (mmol/L)	1.1 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.1 ± 0.4	0.123
Peak BNP (pg/ml)	1452 ± 1219	626 ± 698	1500 ± 1019	3051 ± 1648	< 0.001
Peak cTNI (ng/ml)	8.53 (3.39, 14.29)	2.6 (1.4, 4.25)	11.4 (8.02, 14.9)	26.4 (13.1, 69.8)	< 0.001
Multivessel coronary disease (n, %)	21 (27.6)	6 (20.7)	10 (30.3)	5 (35.7)	0.529
Culprit lesion on CAG LAD (n, %)	43 (56.6)	16 (55.2)	18 (54.5)	9 (64.3)	0.812
Hospital stay (days)	10 (8, 12)	8 (7, 10)	10 (8, 12)	11 (10, 13)	0.091
TIMI flow frame count (frames)	28 (20, 37)	28 (21.2, 38.9)	26 (18.82, 36.0)	33.0 (25.9, 38.0)	0.476
TIMI Myocardial Perfusion Classification ≤ level 2 (n, %)	4 (5.26)	2 (6.8)	1 (3.03)	1 (7.1)	0.362
Symptom to balloon time (minutes)	346 ± 156	219 ± 115	369 ± 110	535 ± 130	0.002

IM%LV: Infarcted Myocardium Mass/Left ventricular mass; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; BNP: brain natriuretic peptide; cTNI: cardiac troponin I.

Variables	Total (n = 76)	Group A (n = 29) (IM%LV < 10%)	Group B (n = 33) (10% ≤ IM%LV < 20%)	Group C (n = 14) (IM%LV ≥ 20%)	P
With Collateral circulation (n, %)	11 (14.5)	6 (20.9)	4 (12.1)	1 (7.1)	0.436
IM%LV: Infarcted Myocardium Mass/Left ventricular mass; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; BNP: brain natriuretic peptide; cTNI: cardiac troponin I.					

Table 2 lists cardiac characteristics obtained from CMR at baseline. Patients with the highest IM%LV have the lowest absolute values of GLS, GCS and GRS as well as the lowest LVEF while patients with the lowest IM%LV have the highest values despite no statistical difference of other variables. During 6 months follow-up, 18 patients (23.7%) had MACE including a patient with cardiac death, a patient with non-fatal reinfarction, 4 patients with unplanned revascularization, and 12 patients with heart failure. Patients with higher IM%LV have higher MACE ratio. Patients showing MACE had higher peak BNP, higher peak cTNI, longer hospital stay time, longer S-to-B time, and worse CMR parameters than those showing no MACE in Table 3.

Table 2
Cardiac characteristics obtained from CMR at baseline

Variables	Group A (n = 29) (IM%LV < 10%)	Group B (n = 33) (10% ≤ IM%LV < 20%)	Group C (n = 14) (IM%LV ≥ 20%)	P
LVEDV (ml)	123.9 ± 14.8	124.2 ± 12.3	144.6 ± 16.2	0.037
LVESV (ml)	57.1 ± 16.1	66.14 ± 11.6	80.5 ± 12.5	0.021
LVEF (%)	57.5 ± 7.5	47.7 ± 7.6	44.2 ± 4.6	< 0.001
IMH	2 (6.9%)	7 (21.2%)	6 (42.9%)	0.020
MVO	7 (24.1%)	18 (54.5%)	11 (78.5%)	0.002
IMH + MVO	2 (6.9%)	7 (21.2%)	6 (42.9%)	0.020
Edema/LV (%)	23.3 (20.5, 30.2)	32.3 (27.5, 38.0)	36.12 (34.2, 39.1)	0.002
Salvage/LV (%)	18.8 (14.9, 24.6)	17.8 (12.9, 21.9)	12.1 (6.0, 14.4)	0.002
IM%LV (%)	6.2 ± 5.2	14.5 ± 5.8	26.0 ± 7.3	0.002
GLS (%)	-18.8 ± 3.8	-15.6 ± 3.5	-7.3 ± 2.2	P < 0.001
GCS (%)	-28.2 ± 5.16	-22.5 ± 5.6	-18.4 ± 3.25	P < 0.001
GRS (%)	36.87 (33.5, 42.4)	30.24 (23.6, 37.5)	24.58 (20.6, 32.6)	P = 0.005
LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; IMH: intramyocardial hemorrhage; MVO: microvascular obstruction; GLS: global longitudinal strain; GCS: global circumferential strain; and GRS: global radial strain.				

Table 3. A comparison of baseline and cardiac characteristics
(patients with MACE vs patients without MACE in the follow-up study)

Variables	MACE (n=18)	no MACE (n=58)	P
Peak BNP (pg/ml)	2309.5±1610.9	1185.7±1157.6	0.002
Peak cTNI (ng/ml)	12.7 (4.81, 24.51)	7.45 (2.82,13.35)	<0.001
Hospital stay time (days)	12±4	9±3	0.011
Symptom to balloon time (minutes)	442.7±255.7	315.7±298.6	0.022
IM%LV (%)	18.0±9.9	12.0±6.6	0.027
MVO	13 (72.2%)	23 (39.7%)	0.002
IMH	6 (33.3%)	9 (15.5%)	0.020
MVO+IMH	6 (33.3%)	9 (15.5%)	0.020
LVEDV (ml)	141.2±22.5	128.7±26.4	0.034
LVESV (ml)	76.1±15.6	61.9±18.2	0.002
LVEF (%)	46.1±6.9	52.3±9.0	0.009
GLS (%)	-11.44±5.07	-16.48±4.8	<0.001
GCS (%)	-20.6±5.1	-24.9±6.2	0.008
GRS (%)	25.7 (20.2-32.6)	34.7 (25.8-39.4)	0.015

Univariate analysis using logistic regression revealed the variables predicting MACE, i.e., peak BNP, peak cTNI, S-to-B time, IM%LV, MVO, LVEF, GLS, and GCS. These parameters and gender and age were further input to a backward stepwise multivariate analysis, which confirms that GLS can predict MACE independently, with OR = 1.229 (1.087–1.390) and P = 0.001. Figure 2 shows the ROC curve of GLS. The area under the ROC curve was 0.763. The best cutoff value was -14.6% and hence GLS greater than this value can predict MACE with a diagnostic sensitivity of 72.2% and a diagnostic specificity of 74.2%.

On the other hand, CMR were performed at the end of 6 months follow-up in 24 patients (54 ± 11 years and 88% male), as shown in Table 4. Cardiac functions are improved at the end of 6 months follow-up. Table 5 shows a comparison of cardiac characteristics at baseline for patients with LV remodeling vs patients without LV remodeling in the follow-up study. Univariate analysis using logistic regression revealed the variables predicting LV remodeling, i.e., peak BNP, peak cTNI, S-to-B time, LVEF, and GLS. These parameters and gender and age were further input to a backward stepwise multivariate analysis,

which confirms that GLS can predict LV remodeling independently, with OR = 1.943 (1.133–3.334) and P = 0.016.

Table 4. Cardiac characteristics at baseline and follow-up of 6 months

Variables	baseline (n=24)	6 months (n=24)	P
LVEDV (ml)	145.2±21.23	152.6±26.07	<0.001
LVESV (ml)	77.22±16.59	74.41±24.52	<0.001
LVEF (%)	46.85±7.74	52.03±9.90	0.002
IM%LV (%)	17.2 (10.6, 26.7)	12.6 (6.4, 21.7)	<0.001
GLS (%)	-13.22±4.89	-16.16±5.84	0.002
GCS (%)	-22.88±5.74	-23.21±6.92	0.007
GRS (%)	29.91±9.69	33.40±9.14	0.071

Table 5

A comparison of cardiac characteristics at baseline

(patients with LV remodeling vs patients without LV remodeling in the follow-up study)

CMR parameters	LV remodeling (n = 7)	no LV remodeling (n = 17)	P
IM(%LV) (%)	26.8 (22.5, 30.0)	11.9 (9.7, 20.2)	0.004
LVEDV (ml)	141.1 ± 13.7	146.8 ± 23.8	0.564
LVESV (ml)	82.7 ± 11.3	75.0 ± 18.1	0.308
LVEF (%)	41.6 ± 3.4	49.0 ± 8.0	0.004
GLS (%)	-7.9 ± 4.1	-15.4 ± 3.26	< 0.001
GRS (%)	28.7 ± 10.7	30.4 ± 9.6	0.707
GCS (%)	-19.6 ± 3.2	-24.2 ± 6.1	0.071

Discussion

This study showed the use of LV GLS for prediction of MACE and LV remodeling after PCI in patients with STEMI. After adjustment for clinical and morphometric parameters, CMR-determined GLS before

discharge was independently associated with adverse remodeling and outcomes at 6 months follow-up.

Relationship between GLS and MACE

This study reported MACE rate 23.7% using cardiac death, reinfarction, unplanned revascularization and heart failure as combined events; Park et al reported MACE rate 22% using cardiac death and heart failure as combined events (16); Lacalzada et al reported MACE rate 21% using cardiac death, acute myocardial infarction (AMI) and heart failure as combined events (17). These studies showed similar event rates.

When measured acutely after revascularization, LVEF has proven its value as a predictor of poor outcome in patients with MI (18–20). However, LVEF is a global parameter to feature the entire LV function and hence a weak predictor of late myocardial dysfunction (21, 22). Myocardial strains assessment in circumferential, longitudinal, and radial directions (i.e., GLS, GCS, GRS, respectively) have been demonstrated to be sensitive markers of intrinsic myocardial function, allowing an improved analysis of cardiac dysfunctions early after MI in local and global levels (7, 23). Myocardial strains showed accurate prediction of adverse events by using speckle tracking echocardiography technique (24–26). Based on the gold standard CMR measurements (27–29), the present study showed that $|\text{GLS value}| > 14.6\%$ was an independent predictor of MACE. Previous studies also found GLS to be a strong and independent predictor of adverse events (30, 31). In a sample of 659 AMI patients, Antoni et al. demonstrated that $|\text{GLS value}| > 15.1\%$ was an independent predictor of cardiovascular events whether by combining all events or by separating these into mortality, reinfarction, revascularization and hospitalization for heart failure (30), which agrees with the present finding.

Relationship between GLS and LV Remodeling

Even after PCI, adverse LV remodeling occurs in 30–35% STEMI patients (32). It is an important predictor of arrhythmias, heart failure and mortality (33, 34). Here, the rate of adverse LV remodeling at 6 months follow-up was 29%, similar to the rate reported in a previous study (35). Although LVEF was routinely used to assess LV systolic function, it cannot predict the follow-up LV remodeling. GLS was assumed to be an independent predictor of adverse LV remodeling (16, 30, 35). This study showed that GLS can predict adverse LV remodeling independently.

In the prospective study, GLS was identified as a strong predictor of clinical outcomes and an independent predictor of MACE and LV remodeling in the multivariable Cox regression analysis after adjustment for other established prognostic risk factors, e.g., LVEF and infarct size, similar to previous observations (11, 12).

Study Limitations

This study has several limitations. First, the sample size was relatively small and limited to patients with STEMI patients treated with primary PCI with implantation of stents in two centers. Hence, selection bias and low statistical power should be taken into account when interpreting the findings. Second, cardiogenic shock patients and those requiring mechanical ventilation or intra-aortic balloon counter-

pulsation therapy were not included in this study. GLS measurement was not performed in all patients, which resulted in the selection bias. Finally, heart rate and blood pressure, which can influence strain computation, were not available in all patients when undergoing CMR scan.

Conclusions

In patients with STEMI treated with primary PCI, CMR-determined GLS before discharge was a good predictor of MACE and adverse LV remodeling in the follow-up study. Hence, GLS can potentially be a risk factor to quantify ventricular dysfunctions.

Declarations

Ethics approval and consent to participate:

The study was approved by the Institutional Review Board (IRB) for each participating center, conforming to the declaration of Helsinki and Good Clinical Practice Guidelines of the China Food and Drug Administration. All patients provided written informed consent.

Consent for publication:

All authors have read and approved to submit the manuscript to your this journal.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

None.

Funding:

None.

Author contributions:

Yanjun Gong and Yuan Lu made the patients inclusion, data analysis, writing, and editing the manuscript. Jessica C. Huo polished the language of the manuscript. Zhi Wang, Fan Yang and Lin Qiu helped in

follow-up the patients and collected the data. Shu Fang helped editing the manuscript. Jianxing Qiu performed CMR of patients. Yong Huo helped in designing the study ,data analysis and editing the manuscript.

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Figures

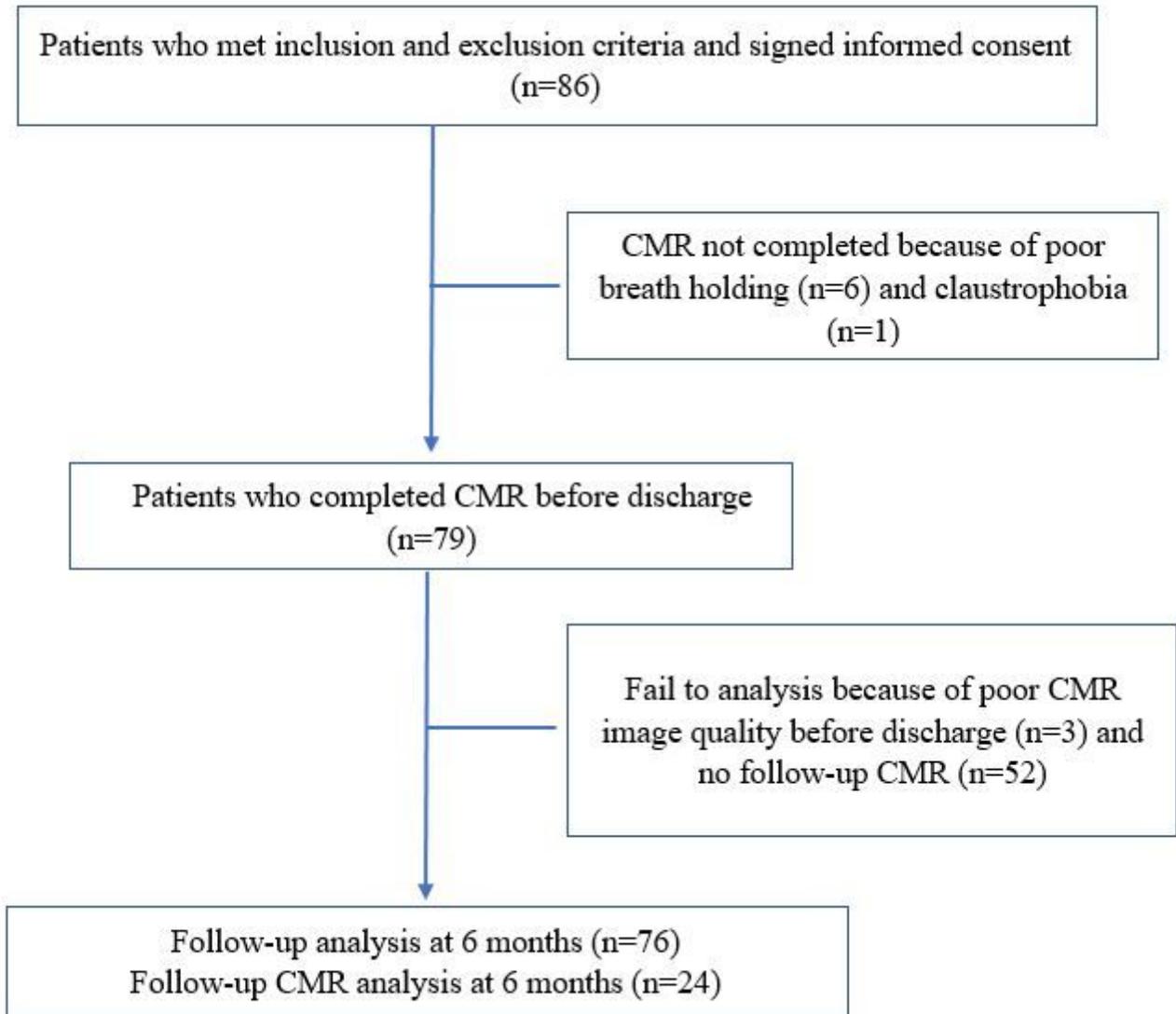


Figure 1

Study Flow.

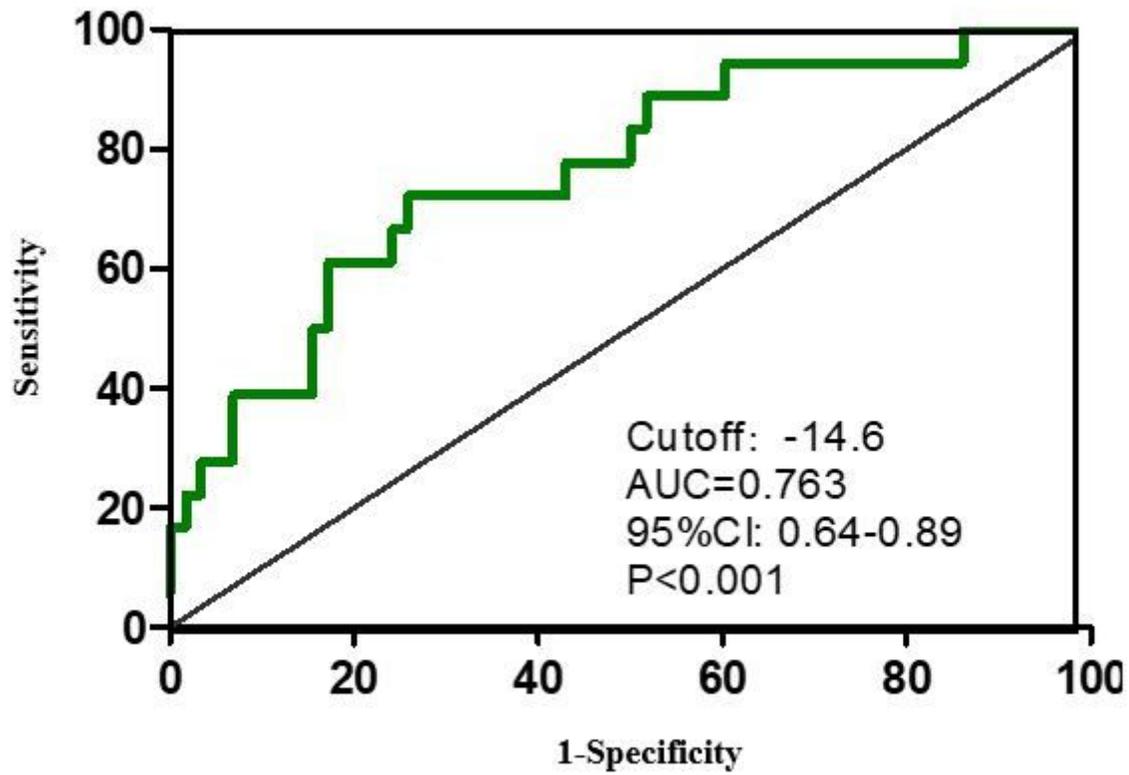


Figure 2

Receiver operating-characteristic curve for the prediction of MACE for 6 months after STEMI using the independent variable LV GLS.