Role of growth differentiation factor-15 and left ventricular global longitudinal strain in predicting major adverse cardiovascular events following acute myocardial infarction

Trisulo Wasyanto[1,2], Annisa Tridamayanti[1], Suwondo Ariyanto[1], Ahmad Yasa[1,2], Niniek Purwaningtyas[1,2], Habibie Arifianto[1]

Abstract

***Background*: Acute myocardial infarction (AMI) remains the leading cause of death worldwide. High serum levels of growth differentiation factor-15 (GDF-15) are associated with apoptosis and post-AMI inflammation. Increased left ventricular global longitudinal strain (GLS) is correlated with a worse prognosis and reflects the extent of the post-AMI ventricular injury. We compared the abilities of GDF-15 and GLS in predicting major adverse cardiovascular events (MACEs) during hospitalization.**

***Methods*: This cross-sectional study included 40 patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) who were admitted to Dr. Moewardi Hospital, Indonesia. Serum GDF-15 levels were estimated in the Emergency Department, and GLS was assessed on the third day of hospitalization.**

***Results*: Of the 40 patients (mean age 58±12 years), 29 (72.5%) had STEMI, and 11 (27.5%) had NSTEMI. Among patients with MACEs, the mean GDF-15 level was 4013.48±1979.09 pg/ml, and the mean GLS was -8.45%±3.53%. In-hospital MACEs in 22 (55%) patients included acute heart failure (n=12, 30%), stroke (n=2, 5%), major bleeding (n=1, 2.5%), and in-hospital death (n=7, 17. 5%). The area under the receiver operating characteristic curve (AUC) for GDF-15 level and MACEs was 0.744, and the optimal cut-off GDF-15 level was 2830.50 pg/ml. The AUC for GLS was 0.672 with an optimal cut-off of 8.65%.**

***Conclusions*: GDF-15 can be used as a predictor of short-term MACEs during hospitalization in patients with AMI and is a better predictor than left ventricular GLS.**

Key words: GDF-15, global longitudinal strain, acute myocardial infarction, STEMI, NSTEMI.

Introduction

Acute myocardial infarction (AMI) is the leading cause of death worldwide, and the incidence of AMI, both acute ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), has continued to increase in developing countries. (1) Data from Dr. Moewardi Hospital, Surakarta, Indonesia, showed that the death rate due to acute coronary syndrome (ACS) during 2014-2018 reached 15.9%. (2) In patients with AMI, both STEMI and NSTEMI are cardiac emergencies associated with high morbidity and mortality rates. (3) Several studies have reported that left ventricular (LV) systolic dysfunction is a major determinant of the long-term outcomes of AMI. Patients with AMI with LV ejection fraction (LVEF) <40% showed higher mortality and hospitalization rates in the first year. (4)

Newer AMI biomarkers have proven to be very useful as diagnostic and prognostic tools. (5) Of these, growth differentiation factor-15 (GDF-15) has emerged as a promising biomarker since an increase in the serum levels of GDF-15 can predict the incidence of ACS. (6) GDF-15 is a consistent biomarker in patients with ACS and stable coronary artery dis-

[1.] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[2.] Department of Cardiology and Vascular Medicine, Dr. Moewardi Hospital, Surakarta, Indonesia

Address for correspondence:
Trisulo Wasyanto, MD, PhD, FIHA, FAPSC, FAsCC
Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital
Jl. Kol. Sutarto 132, Surakarta 57126, Indonesia
Tel: +62-271-611129
Fax: +62-271-663188
Email: trisulo.wasyanto@gmail.com

ease. (7) Under normal circumstances, GDF-15 is slightly expressed by endothelial cells and macrophages; however, GDF-15 production is increased in damaged and inflamed tissues (5) It increases within hours of AMI, remains elevated for several days, and is associated with cardiometabolic risk. (7) In patients with cardiovascular disease, high levels of GDF-15 indicate a poor prognosis and disease progression. (5) A recent prospective study reported that assessment of GDF-15 levels within the first 24 h in patients with AMI is useful in predicting short- and long-term outcomes and may facilitate risk stratification. (8) GDF-15 is a superfamily of transforming growth factor-β (TGF-β), which is synthesized as a 40-kDa propeptide with an N-terminal propeptide and GDF-15 mature C-terminal domain. The human GDF-15 gene is located on chromosome 19p13.1-13.2. Normally, GDF-15 is expressed in small amounts in several tissues and organs. (9) However, its secretion by cardiomyocytes increases rapidly during myocardial ischemia. Experimental evidence has demonstrated the important role of GDF-15 in the regulation of cardiomyocyte survival, post-infarction inflammation, and remodeling of infarcted hearts. (10)

In patients with AMI, assessment of LV dysfunction is important to determine the appropriate therapy and disease; these assessments are usually performed by measurement of the LV ejection fraction (LVEF). However, LVEF measurements in some patients may not accurately indicate myocardial damage because of the presence of frequent regional hyperkinetic compensation despite extensive myocardial damage. (11) Moreover, LVEF assessments cannot detect minimal changes or early pathological conditions in the myocardium. (12) Alternatively, the wall motion score index (WMSI) can be used to measure post-AMI systolic function. (11) WMSI is a semi-quantitative assessment of LV function. (13) However, WMSI shows limitations because it requires considerable examiner expertise. (14) Currently, a myocardial function can be quantitatively evaluated by assessing the global longitudinal strain (GLS) using a strain imaging technique. GLS is more sensitive than LVEF in determining LV systolic function (15) and is also better for diagnosing myocardial death post-AMI. (16) GLS is the strain assessed using echocardiography, which represents the degree of deformity of a segment analyzed in relation to its initial dimensions. It is calculated as the mean of all segments and is a measure of global LV function. (13) GLS is evaluated using an automated functional imaging technique based on two-dimensional (2D) longitudinal strain imaging in the echocardiography machine software. Longitudinal strain is defined as the physiological change in the length of the region of interest (ROI) between the end of diastole and the end of systole. During this period, the longitudinal strain is negative because of the shortening of the ROI. The GLS results are expressed as the averaged global peak systolic strain (GLPSS-Avg), which reflects the overall systolic peak of each LV segment. (17)

Based on these data, this study aimed to investigate the value of GDF-15 and LV GLS as predictors of short-term major adverse cardiovascular events (MACEs) during hospitalization in patients with AMI.

Methods

This cross-sectional study was conducted between September and October 2020 in patients with AMI, both STEMI and NSTEMI, who visited Dr. Moewardi Hospital, Surakarta, Indonesia. The exclusion criteria were as follows: malignancy, chronic renal failure, stroke, and severe sepsis. GDF-15 levels were measured in the Emergency Department (ED), and GLS was evaluated on the third day of hospitalization in all patients. Venous blood samples (6 ml) were obtained using the closed suction method and placed in ethylenediaminetetraacetic acid (EDTA) tubes. Blood was centrifuged for 15 min at 5000 rpm to obtain the serum. The blood serum was stored in a special tube and frozen at -80 °C until further examination. The definition of AMI was based on the fourth universal definition of myocardial infarction (2018) ESC/ACC/AHA/WHF Expert Consensus Document. (18)

GLS was assessed using the apical four-chamber, two-chamber, and apical long-axis views. (19) Normal GLS values on echocardiography are between -18% and -25% in healthy individuals. (13) Meanwhile, the normal value of GLS according to the American Society of Echocardiography is greater than -20%±2%. (20)

MACEs during the hospitalization period were defined as the presence of at least one of the following events: death, cardiopulmonary resuscitation (CPR), cardiogenic shock (Killip class IV), acute heart failure (Killip class II-III), stroke, major bleeding, and arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, and new atrial fibrillation). The study protocol, including informed consent, identity confidentiality, and ethical clearance, was approved by the research ethics committee of Dr. Moewardi Hospital, Surakarta.

Statistical analyses were performed using SPSS v22 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±standard deviation,

while categorical variables were described as percentages. Comparisons between groups were performed using unpaired Student's t-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Only the first event was included in the analyses of patients who experienced more than one event. The optimal cut-off values of GDF-15 and LV GLS in predicting the occurrence of MACEs during hospitalization were calculated and analyzed using receiver operating characteristic (ROC) curves. A p-value<0.05 was considered to indicate a significant difference.

Results

Clinical characteristics

This study included 40 patients (33 [82.5%] men and 7 [17.5%] women) with AMI, with a mean age of 58±12 years (range 32-82 years). Of these, 29 (72.50%) had STEMI and 11 (27.5%) had NSTEMI. Baseline clinical characteristics of the patients are summarized in **Table 1**.

Tests for GDF-15 and LV GLS as predictors of MACE

The patients were divided into two groups based on the occurrence of MACEs. The mean age of the patients in the groups without and with MACEs was 57.33±11.13 (range 32-77) years and 58.24±12.47 (range 39-82) years, respectively. Hypertension was the most dominant risk factor in this study: 26 (65%) patients had hypertension. Echocardiography revealed that LVEF ranged from 15% to 60%, with a mean of 41.90%±9.80%. In the group without MACEs, LVEF ranged from 15% to 60% with a mean of 48.00%±9.59%. In the group with MACEs, LVEF ranged from 24% to 59% with a mean of 38.14%±8.58%. The characteristics of the two groups are summarized in **Table 2**.

In-hospital MACEs

Of the 40 patients, 22 (55.0%) developed in-hospital MACEs, which included acute heart failure (n=12, 30%), stroke (n=2, 5%), major bleeding (n=1, 2.5%), and death (n=7, 17.5%). Seven patients died in the hospital. The causes of in-hospital mortality were cardiogenic shock (n=2, 28.57%), ventricular arrhythmias (n=2, 28.57%), septic shock (n=2, 28.57%), and respiratory failure (n=1, 14.29%). The serum GDF-15 levels in these 40 patients ranged from 855 pg/ml to 6000 pg/ml (mean 3247.03±1910.73 pg/ml). In the group without MACEs, serum GDF-15 level ranged from 855.00 pg/ml to 6000 pg/ml with a mean value of 2399.99±1454.45 pg/ml. In the group with MACEs, it ranged from 1109.00 pg/ml to 6000 pg/ml with a mean value of 3013.48±1979.09 pg/ml.

The overall LV GLS in STEMI ranged between -19.30% and -2.52%, with a mean value of -9.96%±3.30%. The mean LV GLS value was -9.92%±3.06% in the group without MACEs and -9.45%±3.53% in the group with MACEs. The differences in the means of serum GDF-15 and LV GLS are summarized in **Table 3**.

The ROC curve for MACEs with GDF-15 as a predictor showed an AUC of 0.744, which suggests that serum GDF-15 levels can predict MACEs well. Based on the ROC curve, the optimal cut-off value of GDF-15 was 2830.50 pg/ml (**Figure 1**), with a sensitivity of 66.67%, specificity of 73.68%, and odds ratio of 5.60 (95% confidence interval [CI] 1.43-21.95). The ROC curve for the occurrence of MACEs with LV GLS as a predictor resulted in an AUC of 0.672, suggesting that LV GLS is a relatively weak predictor of MACEs in patients with AMI. Based on the ROC curve, the cut-off level of LV GLS was -8.65% (**Figure 2**). Comparisons of sensitivity, specificity, and odds ratios of serum GDF-15 and LV GLS as predictors of MACEs are summarized in **Table 4**. A combination of the ROC curves of serum GDF-15 level and LV GLS resulted in an AUC of 0.744 (**Figure 3**). Therefore, the combination of GDF-15 level and LV GLS did not improve the detection of MACEs. The combined power of serum GDF-15 level and LV GLS in detecting MACEs was the same as that of GDF-15 alone. However, the GDF-15 level was a better predictor of MACE than LV GLS. Thus, GDF-15 evaluation has sufficient power to predict MACEs in patients with AMI during hospitalization.

Discussion

This study aimed to determine a better predictor of short-term MACEs, between GDF-15 and LV GLS, in patients hospitalized for AMI. Most studies have used serum GDF-15 or GLS as predictors of long-term MACEs in post-AMI patients. Therefore, we investigated whether GDF-15 or GLS can be used as a predictor of short-term MACEs during hospitalization and determined which marker is better. LV GLS is an excellent predictor of post-AMI remodeling. (19) Over the past decade, studies have found that GLS demonstrated higher sensitivity in describing LV dysfunction than LVEF and that it can provide additional prognostic information. (20,21) The mechanism of decreasing LV GLS following AMI is related to cell necrosis and damage to the matrix, which triggers the release of GDF-15. (22,23) GDF-15 functions as a pro-apoptotic and anti-hypertrophic molecule via the p-38 signaling pathway and reduces the cardioprotective effect.

(16,24)
Li et al conducted a cohort study with a median follow-up period of 6.4 years to determine the prognostic value of GDF-15 levels in the occurrence of MACEs and all-cause death in patients with coronary artery disease by performing coronary angiography. Of the 3884 patients who were evaluated, the MACE rate was significantly higher in patients with serum GDF-15 levels >1800 ng/l than in those with lower levels. Additionally, GDF-15 level >1800 ng/l was significantly associated with the incidence of all-cause death, with an AUC of 0.766 (95% CI 0.735-0.798). (25) In our study, the cut-off serum GDF-15 level was 2830.50 pg/ml (2830.50 pg/ml = 2830.50 ng/l) for the occurrence of short-term MACE during hospitalization, and the AUC was 0.744 for MACEs and all-cause mortality. Our study adds new evidence for the short-term predictive value of serum GDF-15 levels in patients with AMI. Higher levels of GDF-15 in the management of AMI have been consistently associated with increased MACE prevalence and cardiovascular mortality.
Lindholm et al reported that high serum levels of GDF-15 at baseline and within 1 month after treatment of ACS with dual antiplatelet therapy provided information about the risk of major bleeding. Patients with elevated baseline levels of GDF-15 that did not increase at 1 month had the same risk as patients with elevated levels on both measurements. Among patients with GDF-15 level >1800 ng/l at 1 month, 3.9% experienced non-coronary artery bypass grafting-related major bleeding from 1 month up to 300 days thereafter, in comparison with 1.2% of the patients with non-elevated levels of GDF-15 at 1 month. (26) In our study, the cut-off GDF-15 value was 2830.50 pg/ml for the occurrence of MACEs during hospitalization, and major bleeding was observed in 2.5% of the patients.
Reindl et al conducted a prospective observational study of 451 patients who underwent revascularization for STEMI and were followed up for 24 months (range 11-48 months); of these, 46 (10%) patients developed MACEs. GLS was the strongest MACE predictor among strain parameters (AUC 0.73 [95% CI 0.69-0.77]) and was significantly better than LVEF (AUC 0.64 [95% CI 0.59-0.68]) (p=0.005). A GLS value of -11.3% was the best cut-off point for predicting MACEs in post-STEMI. (27) Our study found that the mean GLS in patients with MACEs was -8.45%±3.53% and the AUC was 0.672 with an optimal cut-off point of -8.65%.
Shetye et al conducted a systematic review of myocardial strain assessments using imaging modalities to predict the prognosis following STEMI. Seven studies that matched the search criteria used speckle-tracking echocardiography to evaluate strain parameters. Of these, four assessed GLS in predicting MACE progression, which resulted in an overall hazard ratio between 1.1 (95% CI 1-1.1, p=0.006) and 2.34 (95% CI 1.10-4.97, p<0.05). GLS <-13% can predict the incidence of MACE with a sensitivity and specificity of 100% and 89%, respectively. High GLS immediately after STEMI is a poor predictor of prognosis. (28) Our study found that the optimal cut-off for LV GLS was -8.65%, with a sensitivity of 66.67%, specificity of 78.95%, AUC of 0.672 (95% CI 0.496-0.848), and odds ratio of 7.50 (95% CI 1.80-31.28).
Therefore, serum GDF-15 levels can be used as a short-term prognostic biomarker in patients with AMI (including STEMI and NSTEMI) caused by the rupture or erosion of susceptible atherosclerotic plaques, which can lead to death and recurrent MI at any time after the first episode. GDF-15 was a better predictor of MACEs and short-term mortality during hospitalization (AUC 0.744 [95% CI 0.592-0.897]) than LV GLS (AUC 0.672 [95% CI 0.496-0.848]). The AUC for the combined use of GDF-15 and LV GLS as predictors of MACE and death was 0.744.
This study had several limitations. First, MACE was observed only in the short term during hospitalization. Second, primary percutaneous coronary intervention for STEMI and invasive (<24 h) or immediate (<2 h) strategies in high-risk patients with NSTEMI have not yet been fully implemented in our hospital because of financial factors (i.e., lack of health insurance coverage), and high creatinine levels will affect the incidence of MACE. Third, serum GDF-15 levels were only assessed at admission in the ED, and serial measurements were not performed; therefore, we were unable to evaluate the changes in GDF-15 levels in relation to the treatment.

Conclusions

Serum GDF-15 can be used as a predictor of MACEs during hospitalization in patients with AMI and is a better predictor than LV GLS. The combination of GDF-15 and LV GLS as predictors of MACE in patients with AMI during hospitalization was as effective as GDF-15 alone.

Acknowledgments

We would like to thank Dr. Moewardi Hospital, Surakarta, who permitted us to collect the data.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests
The authors declare that there is no conflict of interest.

Table 1. Baseline clinical characteristics

Variable	STEMI (n=29) Mean±SD (min-max)	NSTEMI (n=11) Mean±SD (min-max)	p-value
Age (years)	62±12.47 (32-78)	54.55±2.80 (44-82)	0.105
Sex - Male, n (%) - Female, n (%)	 24 (82.8%) 5 (17.2%)	 9 (81.8%) 2 (18.2%)	1.000
LOS (days)	4.5±3.19 (1-11)	4.73±0.33 (2-15)	0.988
Onset (hours)	17±37.67 (1-72)	85.73±60.71 (6-168)	0.031
SBP (mmHg)	134.82±27.87 (78-198)	135.36±23.81 (108-184)	0.990
DBP (mmHg)	84.18±20.20 (45-128)	82.09±10.78 (67-109)	0.744
HR (beat/min)	76.61±21.74 (40-124)	84.00±18.836 (64-129)	0.297
GDF-15 (pg/ml)	2470.00±1874.28 (1100-6000)	3837.64±491.88 (855-5000)	0.094
LVEF (%)	43.21±9.96 (15-60)	37.36±7.86 (24-50)	0.071
GLS (%)	-9.96±3.30 (-19.30-[-2.52])	-7.46±0.08 (-12.12-[-2.80])	0.034
In-hospital MACE, n (%)	15 (51.7%)	7 (63.6%)	0.650
Acute HF, n (%)	12 (41.4%)	6 (54.5%)	0.498
Stroke (n, %)	2 (6.9%)	0 (0.0%)	1.000
Major bleeding, n (%)	0 (0.0%)	1 (9.1%)	0.275
All-cause mortality, n (%)	6 (20.7%)	1 (9.1%)	0.650

Legend: STEMI=ST-segment elevation myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; SD=standard deviation; LOS=length of stay; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; GDF-15=growth differentiation factor-15; LVEF=left ventricular ejection fraction; GLS=global longitudinal strain; MACE=major adverse cardiovascular event; HF=heart failure.

Table 2. Characteristics of patients with and without MACEs

Variables	MACE (-)	MACE (+)	p-value
Demographics			
- Sex			0.105
Male, n (%)	17 (94.40%)	16 (72.70%)	
Female, n (%)	1 (5.60%)	6 (27.30%)	
- Age, mean±SD (years)	57.33±11.13	58.24±12.47	0.673
Risk factors			
- Hypertension, n (%)	13 (72.20%)	13 (59.10%)	0.510
- Diabetes, n (%)	4 (22.20%)	10 (45.50%)	0.186
- Smoking, n, (%)	11 (61.10%)	11 (50.00%)	0.537
- Dyslipidemia, n (%)	1 (4.50%)	0 (0.0%)	0.928
- History of CAD, n (%)	5 (27.80%)	6 (27.30%)	1.000
Clinical conditions			
- BMI, mean±SD (kg/m^2)	23.98±3.19	23.508±2.742	0.693
- Onset, mean±SD (hours)	20.50±41.998	50.00±54.094	0.050
- Killip class			0.001
Killlip I, n (%)	18 (100%)	5 (22.70%)	
Killip II-IV, n (%)	0 (0%)	17 (77.30%)	
- Type of AMI			0.723
STEMI, n (%)	14 (77.80%)	15 (68.20%)	
NSTEMI, n (%)	4 (22.20%)	7 (31.80%)	
- Length of stay, mean±SD (days)	4.53±1.31	5.81±3.49	0.265
Therapy			
- Fibrinolytic, n (%)	5 (27.80%)	3 (13.60%)	0.342
- ACEI/ARB, n (%)	17 (94.40%)	19 (86.40%)	0.673
- B-blocker, n (%)	18 (100.0%)	22 (100.0%)	1.000
Laboratory (mean±SD)			
- Hemoglobin (g/dl)	13.46±1.86	13.68±1.68	0.664
- Leukocytes (10^3/µl)	13.11±3.76	12.10±6.78	0.586
- Platelets (10^3/µl)	238.33±69.01	242.98±88.89	0.916
- Urea (mg/dl)	26.60±15.56	44.00±35.36	0.002
- Creatinine (mg/dl)	2.40±4.26	1.20±0.83	0.354
- eGFR (ml/min /1.73 m^2)	67.00±31.04	66.88±40.93	0.993
- FBS (mg/dl)	106.11±25.573	84.00±55.18	0.216
- BS 2-h postprandial (mg/dl)	130.22±34.60	115.00±42.73	0.448
- HbA1c (%)	6.14±1.01	7.17±1.99	0.107
- Uric acid (mg/dl)	6.20±2.29	7.70±3.55	0.059
- Total cholesterol (mg/dl)	152.11±29.71	164.16±45.38	0.339
- LDL cholesterol (mg/dl)	115.32±30.77	135.84±64.80	0.220
- HDL cholesterol (mg/dl)	34.17±10.78	33.20±17.50	0.759
- Triglycerides (mg/dl)	135.42±71.32	114.16±43.42	0.274
Echocardiography (mean±SD)			
- LVEF (%)	48.00±9.59	38.14±8.58	0.009
- TAPSE (cm)	2.09±0.46	1.88±0.54	0.175

Legend: MACE=major adverse cardiovascular event; SD=standard deviation; CAD=coronary artery disease; BMI=body mass index; AMI=acute myocardial infarction; STEMI=ST-segment elevation myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; eGFR=estimated glomerular filtration rate; FBS=fasting blood sugar; BS=blood sugar; HbA1c=hemoglobin A1c; LDL=low-density lipoprotein; HDL=high-density lipoprotein; LVEF=left ventricular ejection fraction; TAPSE=tricuspid annular plane systolic excursion.

Table 3. Differences in the means of serum GDF-15 and left ventricular GLS

Variable	MACE (-)		MACE (+)	
	Mean	SD	Mean	SD
GDF-15	2399.99	1454.45	3013.48	1979.09
GLS	-9.92	3.06	-9.45	3.53

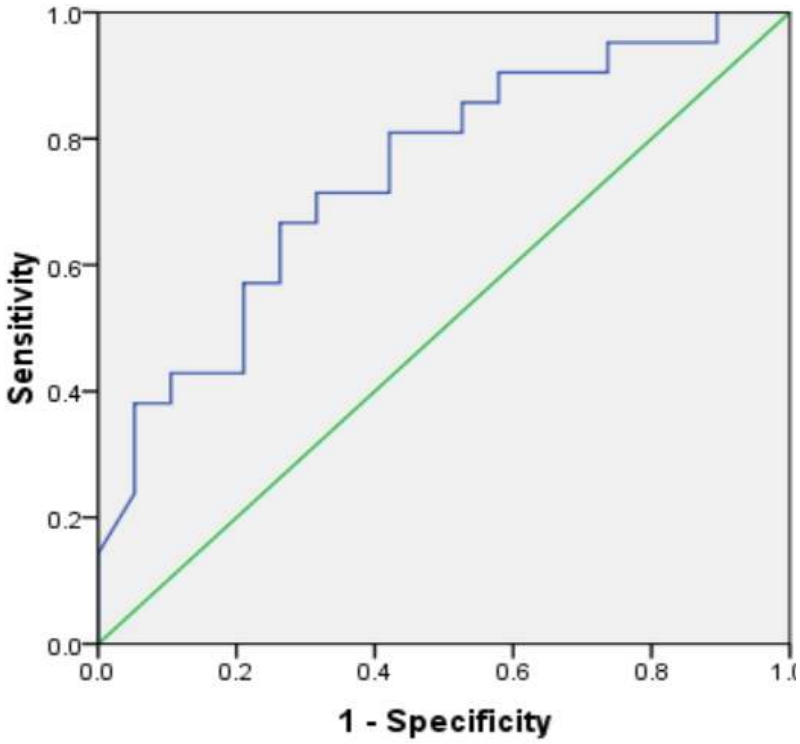
Legend: GDF-15=growth differentiation factor-15; GLS=global longitudinal strain; MACE=major adverse cardiovascular event; SD=standard deviation.

Table 4. Comparisons of sensitivity, specificity, and odds ratio of serum GDF-15 and left ventricular GLS as predictors of MACE

Size	GDF-15	Left ventricular GLS
Sensitivity (%)	66.67	66.67
Specificity (%)	73.68	78.95
AUC	0.744	0.672
Odd ratio (95% CI)	5.60 (1.43-21.95)	7.50 (1.80-31.28)

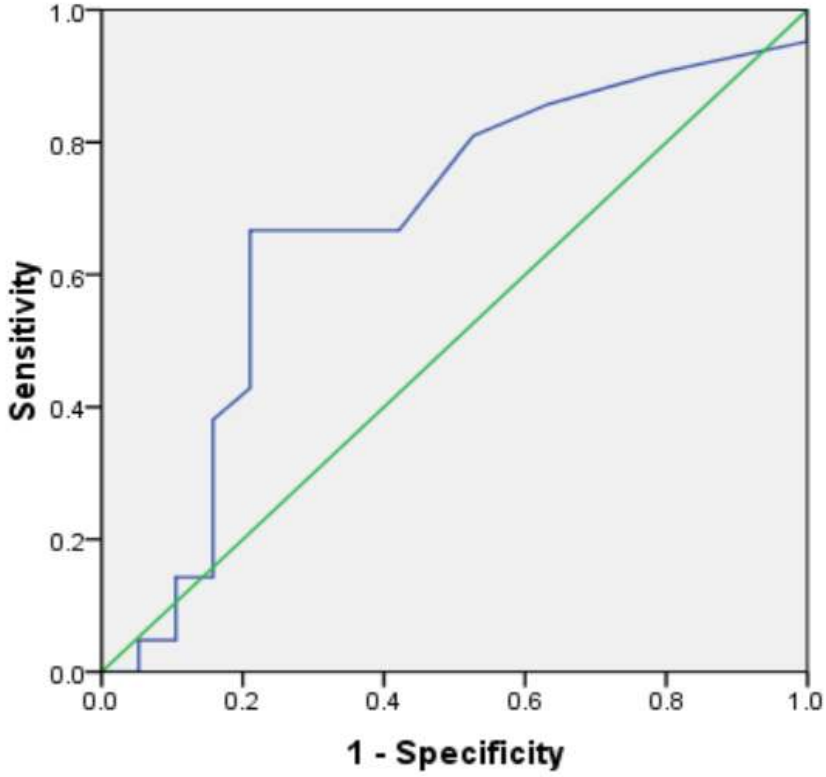
Legend: GDF-15=growth differentiation factor-15; GLS=global longitudinal strain; MACE=major adverse cardiovascular event; AUC=area under the curve; CI=confidence interval.

Figure 1. ROC curve for determining the GDF-15 cut-off against MACE incidence



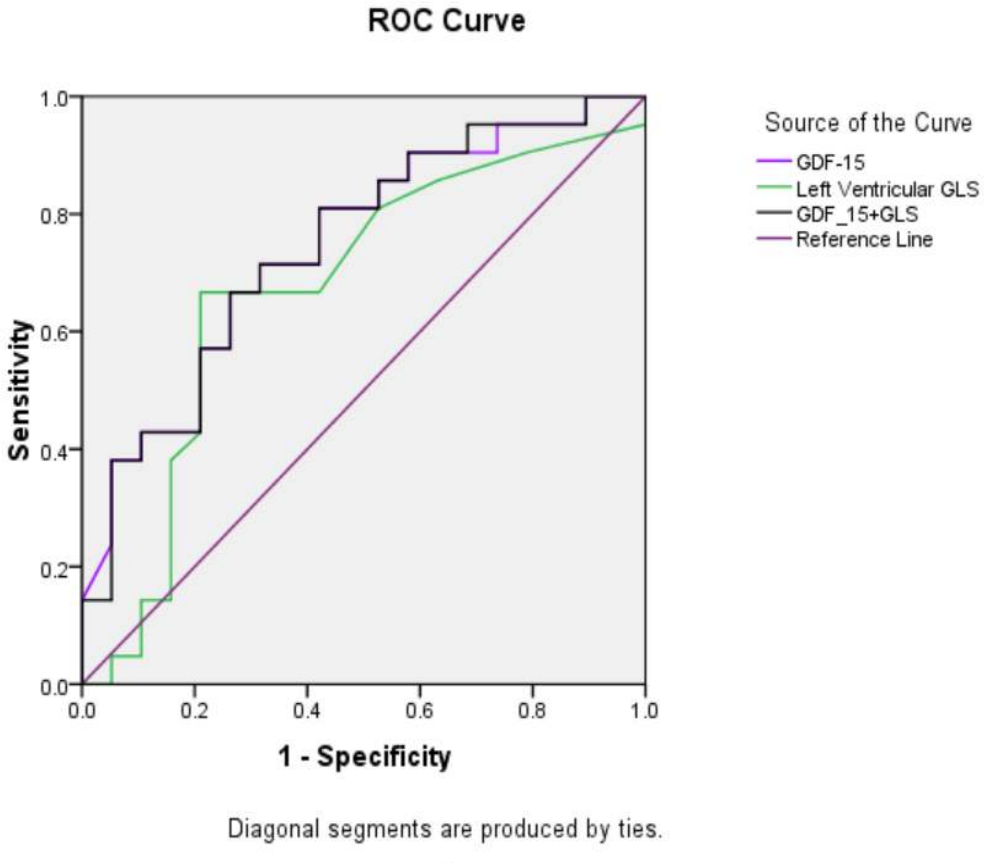
Legend: The cut-off point was 2830.50 pg/ml. ROC=receiver operating characteristic; GDF-15=growth differentiation factor-15; MACE=major adverse cardiovascular events.

Figure 2. ROC curve for determining the cut-off of left ventricle GLS against MACE incidence



Legend: The cut-off was -8.65%. ROC=receiver operating characteristic; GLS=global longitudinal strain; MACE=major adverse cardiovascular events.

Figure 3. Combined ROC curve of GDF-15 and left ventricular GLS as a predictor of MACE



Legend: ROC=receiver operating characteristic; GDF-15=growth differentiation factor-15; GLS=global longitudinal strain; MACE=major adverse cardiovascular events.

References

1. Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. Eur Heart J 2017;38:774-84.
2. Wasyanto T, Tridamayanti A. Blood urea nitrogen as a predictor of in-hospital mortality in acute coronary syndrome patients. Indonesian Journal of Medicine 2019;4:241-51.
3. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017;376:2053-64.
4. Khaled S, Matahen R. Cardiovascular risk factors profile in patients with acute coronary syndrome with particular reference to left ventricular ejection fraction. Indian Heart J 2018;70:45-9.
5. Tzikas S, Palapies L, Bakogiannis C, Zeller T, Sinning C, Baldus S, et al. GDF-15 predicts cardiovascular events in acute chest pain patients. PLoS One 2017;12:e0182314.
6. Buljubasic N, Vroegindewey MM, Oemrawsingh RM, Asselbergs FW, Cramer E, Liem A, et al. Temporal pattern of growth differentiation factor-15 protein after acute coronary syndrome (from the BIOMArCS Study). Am J Cardiol 2019;124:8-13.
7. Wang X, Chen L-L, Zhang Q. Increased serum level of growth differentiation factor 15 (GDF-15) is associated with coronary artery disease. Cardiovasc Ther 2016;34:138-43.
8. Rueda F, Lupón J, García-García C, Cediel G, Nevado MCA, Gregori JS, et al. Acute-phase dynamics and prognostic value of growth differentiation factor-15 in ST-elevation myocardial infarction. Clin Chem Lab Med 2019;57: 1093-101.
9. Xu X, Li Z, Gao W. Growth differentiation factor 15 in cardiovascular diseases: from bench to bedside. Biomarkers 2011;16:466-75.
10. Hanna A, Frangogiannis NG. The role of the TGF-β superfamily in myocardial infarction. Front Cardiovasc Med 2019;6:140.
11. Jurado-Román A, Agudo-Quílez P, Rubio-Alonso B, Molina J, Díaz B, García-Tejada J, et al. Superiority of wall motion score index over left ventricle ejection fraction in predicting cardiovascular events after an acute myocardial infarction. Eur Heart J Acute Cardiovasc Care 2019;8:78-85.
12. Diao K-Y, Yang Z-G, Ma M, He Y, Zhao Q, Liu X, et al. The diagnostic value of global longitudinal strain (GLS) on myocardial infarction size by echocardiography: A systematic review and meta-analysis. Sci Rep 2017;7:10082.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande R, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.
14. Joyce E, Hoogslag GE, Leong DP, Debonnaire P, Katsanos S, Boden H, et al. Association between left ventricular global longitudinal strain and adverse left ventricular dilatation after ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging 2014;7:74-81.
15. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37:1196-207.
16. Karlsen S, Dahlslett T, Grenne B, Sjøli B, Smiseth O, Edvardsen T, et al. Global longitudinal strain is a more reproducible measure of left ventricular function than ejection fraction regardless of echocardiographic training. Cardiovasc Ultrasound 2019;17:18.
17. Ismail AM, Samy W, Aly R, Fawzy S, Hussein K. Longitudinal strain in patients with STEMI using speckle tracking echocardiography. Correlation with peak infarction mass and ejection fraction. Egypt J Crit Care Med 2015;3:45-53.
18. Thygesen K. What's new in the Fourth Universal Definition of Myocardial infarction. Eur Heart J 2018;39:3757-8.
19. Mondillo S, Galderisi M, Mele D, Cameli M, Lomoriello VS, Zaca V, et al. Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med 2011;30:71-83.
20. Collier P, Phelan D, Klein A. A test in context: Myocardial strain measured by speckle-tracking echocardiography. J Am Coll Cardiol 2017; 69:1043-56.
21. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: The case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging 2018;11:260-74.
22. Ago T, Sadoshima J. GDF15, a cardioprotective TGF-beta superfamily protein. Circ Res 2006; 98:294-7.
23. Bonaterra GA, Zügel S, Thogersen J, Walter SA, Haberkorn U, Strelau J, et al. Growth differentiation factor-15 deficiency inhibits atherosclerosis progression by regulating interleukin-6-dependent inflammatory response to vas-

vascular injury. J Am Heart Assoc 2012;1: e002550.
24. Adela R, Banerjee SK. GDF-15 as a target and biomarker for diabetes and cardiovascular diseases: A translational prospective. J Diabetes Res 2015;2015:490842.
25. Li M, Duan L, Cai Y-L, Li H-Y, Hao B-C, Chen J-Q, et al. Growth differentiation factor-15 is associated with cardiovascular outcomes in patients with coronary artery disease. Cardiovasc Diabetol 2020;19:120.
26. Lindholm D, Hagström E, James SK, Becker RC, Cannon CP, Himmelmann A, et al. Growth differentiation factor 15 at 1 month after an acute coronary syndrome is associated with increased risk of major bleeding. J Am Heart Assoc 2017;6:e005580.
27. Reindl M, Tiller C, Holzknecht M, Lechner I, Beck A, Plappert D, et al. Prognostic implications of global longitudinal strain by feature-tracking cardiac magnetic resonance in ST-elevation myocardial infarction. Circ Cardiovasc Imaging 2019;12:e009404.
28. Shetye A, Nazir SA, Squire IB, McCann GP. Global myocardial strain assessment by different imaging modalities to predict outcomes after ST-elevation myocardial infarction: A systematic review. World J Cardiol 2015;7:948-60.