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Original Article

Left Atrial Emptying Fraction as Predictor Parameter of Major Adverse Cardiovascular Events (MACE) and Decrease of Functional Capacity in Patients with STEMI Treated by Primary Percutaneous Coronary Intervention

Harris Kristanto[1*], Budi Satrijo[2],Anna Fuji Rahimah[2]

[1] *Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.*
[2] *Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.*

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ABSTRACT

Background: HF is associated following ST-elevated myocardial infarction (STEMI) and aasociated with morbidity and mortality. Echocardiography is routine examination and commonly utilized for risk stratification. In current guideline. In current guideline, enlarged LA volume, doppler parameter, and tissue doppler imaging were used for diastolic dysfunction. However, they have several limitations. LAEF may be superior to LAVI, doppler parameter, or TDI as markers of cardiac function in acute phase after AMI. This study conducted to assess the LAEF in predicting death, rehospitalization of heart failure (HF), and decrease functional capacity after STEMI.

Methods and Results: Between January 2018 and January 2021, 391 patients with STEMI who got primary percutaneous coronary intervention were included. After STEMI, patients had echocardiography within 48 hours. All of the patients were subjected to standardized 2-dimensional echocardiography procedures. The LAEF was determined by dividing the maximal LA volume by the minimal LA volume. The primary endpoint of this study was a Major Adverse Cardiovascular Events that consisting of all-cause death and rehospitalization due to decompensation of heart failure within 12 months. The secondary end point was decline of functional capacity within 12 months. During the 12-month follow-up period, 162 individuals developed MACE. Only LAEF remained an independent predictor of MACE after adjusting for clinical, biochemical, and echocardiographic factors. (P = 0.000, Odds Ratio 15,46 (CI 95%: 9,264 – 26,409)). For secondary end point, there was a significant difference in the number of patients experiencing decreased functional capacity between the groups with LAEF ≥37.5% and LAEF <37.5% (based on cut off value) in the 6-month range (p=0.000) and was consistent within 12 months (p=0.000).

Conclusion: LAEF can be a predictor of MACE and decline functional capacity of STEMI patients who have undergone primary PCI within 12 months.

1. Introduction

ST-elevated myocardial infarction (STEMI) is a spectrum of acute myocardial infarction marked by unstable angina pectoris with ST segment elevation on the electrocardiogram.[1] In STEMI, regional myocardial injury can cause decreased systolic and diastolic function, resulting in systemic neurohormonal activation, LV remodeling, and heart failure (HF). HF after an AMI is prevalent and complicates up to 45 percent of patient and it affect patient's morbidity and mortality.[2] Hence, risk stratification is important thing for optimalization management after STEMI. Echocardiography is routine examination and commonly utilized for risk stratification. In current guideline, Parameter LV ejection fraction (LVEF) is playing a major role for risk stratification after STEMI.1 However, diastolic function after AMI has gotten few attention, perhaps due to a concern with LV systolic performance following AMI 3 But, diastolic dysfuntion occurred earlier compared to systolic dysfunction after AMI.

Several parameters are suggested by the 2016 ASE/EACVI recommendations for diagnosing diastolic dysfunction, including transmitral flow, tissue velocity, maximum left atrial volume (LAV), and estimated pulmonary artery pressure.[4] Several study showed that LAV can predict morbidity after STEMI.[5] In response to high filling pressure after AMI, the LAV dilates. But, LAVI assesses the average effect of persistently high filling pressure over time, it may be unable to detect the sudden decrease in cardiac function that happens after AMI.[6]

*Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
E-mail address: harkristanto@gmail.com (A. S. Santoso).

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Doppler parameter had limitation such as affected by patient's age and loading condition. Tissue Doppler Imaging (TDI) also affected by angle and translation from the neighbouring myocardium.[7] It has been found that the left atrial emptying fraction (LAEF) correlates more significantly with left ventricular filling pressure than the left atrial volume index when assessed by echocardiography (LAVI).[8] As a result, it's possible that LAEF parameters are better than LAVI, doppler parameter, or TDI as markers of cardiac function in the short-term after an AMI.

The loss of functional capability is one of the hallmarks of heart failure patients. Several cardiac and peripheral mechanisms affect the decrease in functional capacity in patients with heart failure, most notably is an increase of PCWP. Left atrial and left ventricular function are related to each other in regulating pulmonary capillary vascular hemodynamics.[9] Role of left atrial function as predictor of decrease functional capacity after STEMI has not been studied previously. As a result, the goal of this study was to investigate if measures of LA function (LAEF) could be beneficial in predicting MACE and decreased functional capacity in STEMI patients who got pPCI.

2. Materials and Method

2.1 Study Sample

Patients with STEMI treated with pPCI at Saiful Anwar Hospital in Malang, Indonesia, between January 2018 and January 2021 are included in this retrospective cohort analysis. The STEMI diagnosis criteria were as follows: 1) chest discomfort lasting more than 30 minutes; and 2) electrocardiography revealing ST elevation in two or more contiguous leads, bundle branch blocks, or a newly developed bundle branch block. Inclusion criteria were all patient with STEMI got primary PCI and had echocardiography examination within 48 hours after PCI. The exclusion criteria were patient with atrial fibrilation, idiopathic cardiomyopathy, moderate to severe valve stenosis or regurgitation, malignancy, severe renal and liver failure, intrahospital mortality, psychiatric problem, or patient refuse to be included in the study. Hypertension was defined as SBP 140 mmHg or DBP 90 mmH in admission or history blood pressure lowering medication consumption. Diabetes was defined as fasting plasma glucose levels ≥126 mg/dL, HbA1c ≥ 6.5% or the history antidiabetes medications consumption. Smoker as risk factor divided to current smoker, past smoker, or not smoker. Troponin was measured at baseline and 6 hours following admission. Functional capacity defined as NYHA classification. Decrease functional capacity defined if there is decrease ≥ 1 class after 6 month and 1 years compared to baseline.

2.3 Ethics

For inclusion in the trial, all patients signed a consent form. The study was accepted by Saiful Anwarn Hospital ethics committee (No 400/191/K.3/302/2021) and follows the second Declaration of Helsinki's ethical policies.

2.4 Treatment

All of the patients were treated in accordance with the European Society of Cardiology's (ESC) recommendations. Patients were given antiplatelets and anticoagulant (unfractioned heparin or low molecular weight heparin) before pPCI. After pPCI, all patients were given antiplatelet, ACEinhibitor, beta-blocker, and statin medication as ESC guidelines recommendation.[1]

2.5 Echocardiograpyhic Examination

All of the patients had echocardiography examination using Phillips Affinity machines with a 3.5 MHz probe. The procedure were done within 48 hours of the pPCI. All of the patients were subjected to standardized 2-dimensional echocardiography procedures. One investigator was blinded to evaluate all data and analyzed the echocardiograms off line. The dimensions of the left ventricle end-diastole were determined at the level of the mitral leaflet tips using parasternal long axis images. The modified biplane Simpson equation was used to calculate the LVEF. The left ventricular mass index (LVMI) was determined with end-diastolic dimensions of the LV and indexing it to the body surface area.[10]

Mitral inflow patterns were determined with pulsed-wave Doppler in apical four-chamber view. The peak early-inflow velocity (E), the peak late-inflow velocity (A), and the E/A ratio were determined from these inflow patterns. The early diastolic tissue velocity (e') in the septal and lateral positions in the four-chamber view was determined using pulsed-wave Doppler tissue imaging. The E/e' ratio was calculated as the average of these two measurements. For left atrial volume index (LAVI), biplane area-length method was used to determine the maximal LA volume. The Left Atrial Emptying Fraction (LAEF) was determined by dividing the (maximal LA volume – minimal LA volume) divided by the maximal LA volume, in biplane area-length method.

2.6 Follow Up

The primary endpoint of this study was major adverse cardiovascular events that consisting of all-cause death and rehospitalization because decompensation of heart failure within 1 year. The criteria for heart failure rehospitalization was the presence of symptoms consistent with HF in conjunction with echocardiographic evidence of decreased LVEF, or a HFpEF score ≥ 6 in patients with preserved EF. During follow-up, data on all-cause death were gathered via interview and questionaire. Functional capacity based on NYHA classification was assessed with questionnaire. All MACE and functional capacity outcomes were thoroughly adjudicated by a single cardiologist using hospital-source data and interview.

2.7 Statistical Analysis

All data were analyzed using SPSS version 22. P-value < 0.05 was considered statistically significant. Categorical variables were compared using the x2 or Fisher's exact test, while continuous variables were compared using the Student's t-test or the Mann–Whitney test. Logistic regression analyses were used to identify variables with a P-value 0.25 in the univariate study as independent predictors of MACE. Receiver operating characteristic (ROC) curves were developed to determine the cutoff threshold for LAEF as MACE predictors. Survival analysis were analyzed using the Kaplan–Meier technique and the log-rank test. Decrease of functional capacity in 6 month and 12 month compared between 2 groups (base of cut off point of LAEF) and analyzed using x2.

3. Results

3.1 Baseline Charateristics

After going through the selection based on inclusion and exclusion criteria, a total of 391 STEMI patients were involved in this study. The characteristics of the research subjects are shown in table 1.

Table 1 displays the baseline characteristics of the patients. During a follow-up of 12 months, 162 (41.4%) patients reached the composite end-point consisting of MACE. Troponin I, LVEF, LAVI, and LAEF was different significantly between MACE dan no MACE group.

Table 1. Baseline Characteristics of the Study Sample

Parameter	N = 391		p value
	MACE n=162 (41.4%)	No MACE n=229 (58.6%)	
Age (year old)	**55.70±9.6**	**57.31±11.11**	**0.137**
Body Mass Index (kg/m2)	**25.03±1.96**	**25.28±3.08**	**0.298**
Gender			
Male	**141 (36.1%)**	**198 (50.6%)**	**0.869**
Female	**21 (5.4%)**	**31 (7.9%)**	
Onset (minutes)	**416.36±544.62**	**312.95±212.18**	**0.270**
Risk Factor			
Smoker			
Not smoker	**49 (12.5%)**	**66 (16.9%)**	**0.864**
Previous smoker	**29 (7.4%)**	**38 (9.7%)**	
Current smoker	**84 (21.5%)**	**125 (32.0%)**	
Hypertension	**79 (20.2%)**	**100 (25.6%)**	**0.372**
Diabetes Mellitus	**47 (12.0%)**	**50 (12.8%)**	**0.105**
Dyslipidemia	**24 (6.1%)**	**30 (7.7%)**	**0.628**
TIMI risk score			
<5	**124 (31.7%)**	**185 (47.3%)**	**0.310**
≥5	**38 (9.7%)**	**44 (11.3%)**	
GRACE score			
<109	**72 (18.4%)**	**119 (30.4%)**	**0.196**
109-140	**55 (14.1%)**	**75 (19.2%)**	
>140	**35 (9.0%)**	**35 (9.0%)**	
SBP (mmHg)	**131.87±22.38**	**128.38±19.8**	**0.159**
MAP (mmHg)	**96.56±14.04**	**94.51±11.80**	**0.119**
Heart Rate (beats per minute)	**81.15±16.72**	**80.75±15.03**	**0.297**
Haemoglobin (g/dL)	**13.5±1.92**	**13.51±2.26**	**0.338**
WBC (/μL)	**12389.03±3651.94**	**12233.54±3639.3**	**0.582**
Creatinin (mg/dL)	**1.16±0.29**	**1.13±0.27**	**0.370**
Troponin I (ng/mL)	**19.42±16.49**	**15.29±12.14**	**0.000**
Angiography			
SVD	**15 (3.8%)**	**34 (8.7%)**	**0.100**
MVD	**147 (37.6%)**	**195 (49.9%)**	
Culprit lession			
LAD	**69 (17.6%)**	**108 (27.6%)**	**0.289**
LCx	**33 (8.4%)**	**33 (8.4%)**	
RCA	**60 (15.3%)**	**88 (22.5%)**	
Medical Treatment			
DAPT	**162 (41.4%)**	**229 (58.6%)**	**n/a**
ACEi/ARB	**159 (40.7%)**	**223 (57.0%)**	**0.618**
Beta blocker	**150 (38.4%)**	**209 (53.5%)**	**0.637**
Statin	**162 (41.4%)**	**229 (58.6%)**	**n/a**
Echocardiography			
LVEF	**53,23±9.37**	**55,69±49,02**	**0,008**
LVMI	**98,5±19.5**	**95,9±17,6**	**0,183**
IVSd	**1,06±0.27**	**1,04±0,20**	**0,542**
LVIDd	**4,82±0.69**	**4,77±0,65**	**0,484**
LVPWd	**1,12±0.23**	**1,10±0,22**	**0,333**
E/A	**1,14±0.50**	**1,17±0,57**	**0,750**
E/e'	**11,97±5.14**	**11,11±4,21**	**0,172**
LAVI	**31,1±5.08**	**26,82±5,94**	**0,000**
LAEF	**36,31±2.49**	**41,73±3,56**	**0,000**

Note. MACE = Major Adverse Cardiovascular Events; ; TIMI = Thrombolysis in Myocardial Infarction; GRACE = The Global Registry of Acute Coronary Events, SBP = Systolic Blood Pressure, MAP = Mean Arterial Pressure, WBC = White Blood Count, SVD = Single Vessel Disease, MVD = Multi Vessel Disease, LAD = Left Anterior Descending , LCx = Left Circumflex; RCA = Right Coronary Artery, DAPT = Dual Antiplatelet Therapy, ACEi = Angiotensin Converting Enzyme Inhibitors, ARB = Angiotensin Receptor Blocker

3.2 Multivariate Analysis

The multivariate analysis in this study was to determine the relationship between several risk factors, patient physical examination data, angiography, and echocardiographic examination results on the incidence of MACE. Variables with p<0.25 in bivariate analysis were tested in multivariate analysis, it includes age, risk factor diabetes mellitus, GRACE score, SBP, MAP, troponin I, number of coronary arteries involved angiographically, LVEF, LVMI, E/e', LAVI, and LAEF. The logistic regression analysis will be carried out using the Backward LR method, which is to include all independent variables into the model, but then one by one the independent variables are removed from the model based on certain statistical significance criteria. The variable selection stage runs up to 10 stages, where in the 10th stage the final results are obtained as follows.The results of the multivariate analysis are shown in table 2.

Table 2. Multivariate analysis

				95,0% C.I.for EXP(B)	
	B	Sig.	Exp(B)	Lower	Upper
LAEF	2.750	0.000	15,461	9,264	26,409
LAVI	0.514	0,063	1,672	0,972	2,873
Trop I	0,017	0,079	1,018	0,998	1.037
Constant	-14,513	0,000	0,000		

Note. PPCI = primary percutaneous coronary intervention; 95% CI = 95% confidence interval

The LAEF parameter was the only parameter that is still consistent with MACE at the last stage, with a p value of 0.000, and Odds Ratio 15,46 (CI 95%: 9,264 – 26,409).

3.3 Roc Curve LAEF As Predictor Mace

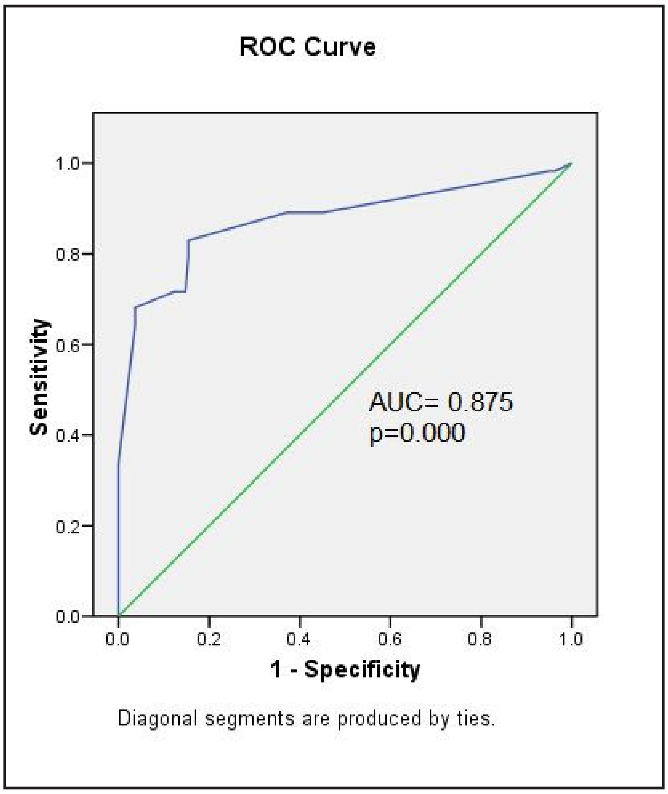

Figure 1. ROC curve to determine cut off LAEF against MACE.

The AUC value for LAEF was 87.5% (95% CI: 84.0%-91.2%, with p=0.000). AUC value of 87.5% for LAEF is quite strong to predict the incidence of MACE in STEMI patients. Additionally, the ROC analysis provides values for sensitivity and 1-specificity at several cutoff points, which then calculates the cut off point limits, with the following results. From the calculation results above, it can be seen that the cut off point for LAEF is 37.5, so LAEF can be divided into 2 categories, LAEF < 37.5 and LAEF ≥37.5 category.

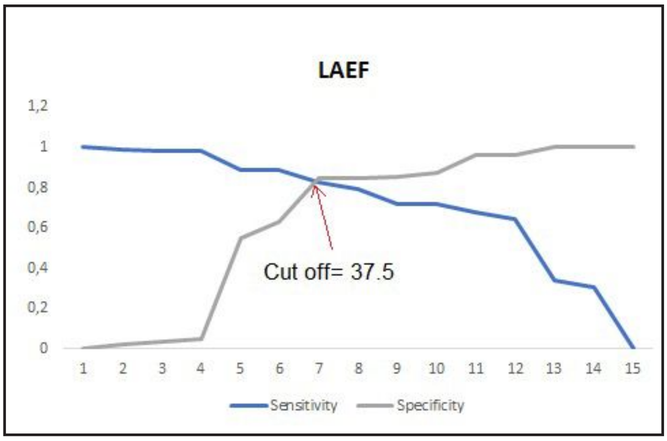

Figure 2. The graph of the intersection of sensitivity and specificity in determining the cut off of LAEF to MACE

From the calculation results above, it can be seen that the cut off point for LAEF is 37.5, so LAEF can be divided into 2 categories, LAEF < 37.5 and LAEF ≥37.5 category.

3.4 Survival Analysis

Based on the cut off value that we got previously, Kaplan-Meier analysis was performed (Figure 2). Kaplan-Meier showed that patients with LAEF ≥ 37.5 had a higher survival rate than patients with LAEF <37.5.

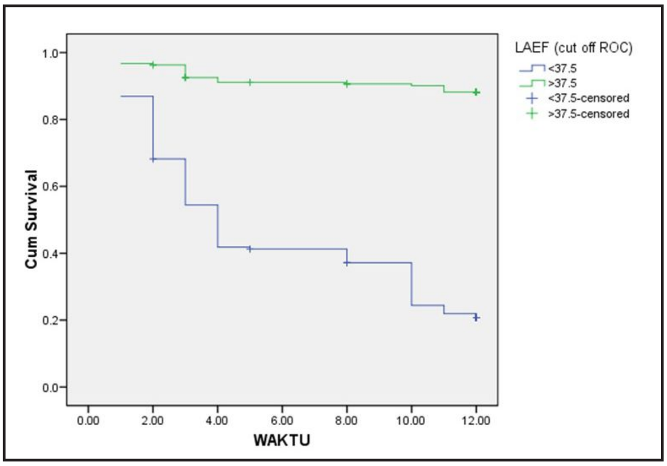

Figure 3. Kaplan-Meier predictor of MACE at 12 months

We compared the decline in functional capacity of patients based on LAEF cutoff values at 6 months (table 3) and 12 months (table 4). From the two tables, we got the results that there was a significant difference in the number of patients experiencing decreased functional capacity between the groups with LAEF ≥37.5% and LAEF <37.5% in the 6-month range (p=0.000) and was consistent within 12 months (p=0.000).

3.5 LAEF as Predictor Of Decrease Functional Capacity

Tabel 3. Decreased functional capacity 6 months based on LAEF

Group	N = 391			P value
	Decreased functional capacity (+)	Decreased functional capacity (-)	Can not be evaluate (mortality)	0.000
LAEF ≥37.5%	66	135	5	
LAEF <37.5%	82	76	14	

Tabel 4. Decreased functional capacity 12 months based on LAEF

Group	N = 391			P value
	Decreased functional capacity (+)	Decreased functional capacity (-)	Can not be evaluate (mortality)	0.000
LAEF ≥37.5%	92	108	10	
LAEF <37.5%	109	30	42	

4. Discussion

4.1 LAEF As Predictor Mace

In our study, we found that LAEF was superior than other echocardiography parameter in predicting 12-month MACE. This is in accordance with the research of Modin et al. Modin et al conducted a study on left atrial function parameters based on echocardiography of MACE in 369 AMI-EST patients. The LA function parameters assessed were LAEF, LAi, and minLAVI. Echocardiography examination is done in 2 days (1-3 days). The outcome studied was MACE (rehospitalization of worsening heart failure and death from any cause). The results showed that the measurement of left atrial function with LAEF parameters was superior to LAVI in predicting MACE.[11]

This study is also in accordance with the research of Lonborg et al. Lonbork et al studied left atrial function using MRI modalities in 199 patients with AMI-EST undergoing IKP. Several LA parameters were evaluated, including LA maximal colume, LA passive fraction, LA minimal volume, and LAEF. MRI examination was performed within 1 – 3 days after admission. The patient outcomes studied were the incidence of death, reinfarction, stroke, or hospitalization due to heart failure within 2 years. The study indicate that LAEF is an predictor of death, reinfarction, stroke, and heart failure.[12]

In STEMI, myocardial necrosis causes an acute decreased in cardiac output. The heart will compensate by increasing the pulse rate and stroke volume. In addition, there is also an increase in sympathetic nervous system activity and neurohormonal activity which increases left ventricular filling pressure and pulse rate. LAVI, on the other hand, represents a long-term increase in left atrial pressure, so it is less likely to represent a short-term hemodynamic decline after STEMI. After multivariate analyses, only LAEF was consistent with MACE, not with others parameter.

4.2 LAEF As Predictor Decline of Functional Capacity

Our study showed a significant difference in the proportion of decreased functional capacity of patients in the LAEF < 37.5% compared to LAEF ≥ 37.5%. Several researchers have analyzed the role of echocardiographic parameters as predictor patient's physical capacity. The study of Wong et al showed that LA volume was an independent predictor of exercise capacity in patients with diastolic dysfunction. The study was conducted retrospectively by looking at the patient data center regarding echocardiographic data and treadmill testing. Study result showed that patients with normal diastolic function had the best physical capacity based on higher levels of the Bruce protocol and longer exercise time on the treadmill stress test. Meanwhile, patients with increased LA volume had the lowest exercise capacity.[13]

Carvalho et al investigated the role of echocardiographic parameters in 225 acute myocardial infarction patients as predictors of exercise capacity at 1 month post AMI. Several echocardiographic parameters were analyzed, including e' septal, e' lateral, E/e septal, E/e lateral, E/e mean, E/A, DT, IVRT, LAVI, LVEF, s' septal, and s'lateral . Exercise capacity was measured using the cardiopulmonary exercise test (CPET) modality. This study indicate that measurement of diastolic function at rest can be a predictor of physical capacity in AMI patients, where septal E/e' is the strongest predictor. However, as with other Doppler techniques, TDI is affected by the angle of retrieval, translation of the surrounding myocardium, and the loading condition.[14]

Bytyci et al investigated the role of LAEF parameters by echocardiography in predicting exercise performance based on the 6 minutes walk test (6MWT) in heart failure patients. The 6MWT examination was performed within 24 hours after the echocardiography examination. The results showed that a decrease in LAEF (LAEF < 60%) could predict a decrease in exercise capacity.[15]

To the best of our knowledge, there has been no research on the prognostic role of LAEF in predicting a decrease in functional capacity in 1 year after STEMI who undergo primary PCI. However, our study also has limitations such as the use of the NYHA scale based on patient interviews as a parameter of the patient's functional capacity where recall bias may occur.

5. Conclusion

This study shows that LAEF can be a predictor of MACE and decline functional capacity of STEMI patients who have undergone primary PCI within 12 months. This research also has several limitations. First, our research was conducted at dr. Saiful Anwar Hospital Malang so that it cannot represent the whole STEMI population. Second, our study only involved a small sample, so further research with a large sample and multicenter is needed so that it can represent the STEMI population in the community.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: HK. Design: HK. Control/supervision: BS, AFR. Literature search: HK. Study quality assessment: BS, AFR. Data extraction: HK. Statistical analysis: HK. Results interpretation: HK. Critical review/discussion: BS, AFR. Writing the article: HK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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