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Original Article

The Role of LAVI/a' And E/e' as The Predictors of Major Cardiac Events in ST-Elevation Acute Myocardial Infarction Patients Who Underwent Percutaneous Coronary Intervention

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A R T I C L E I N F O

Keywords:
ST-elevation myocardial infarction;
echocardiography;
LAVI/A';
E/e';
Percutaneous coronary intervention

A B S T R A C T

Background : The risk of adverse cardiovascular events remains substantial and may vary significantly among STEMI patients. Echocardiography is the recommended diagnostic tool in predicting outcomes. This study purposed to assess the prognostic role of the combination of LAVI/a' ratio and E/e' in STEMI patients who received percutaneous coronary intervention (PCI).
Objectives : This study aims to investigated the role of LAVI/a' And E/e'as predictors of major cardiac event in St-Elevation acute myocardial infraction who underwent Percutaneous coronary intervention
Methods : We conducted a retrospective cohort study in Saiful Anwar General Hospital from 2019 to 2020. All STEMI patients who received PCI were registered. Echocardiography examination was conducted within 24-48 hours after admission. The measurements included LVEF, E/A, E/e', LAVI/a', and LV diastolic function according to ASE/EACVI guidelines. All of the patients were given standard medical treatment. Patients who did not comply with the treatment regimen were excluded. The outcome measured was the major adverse cardiovascular events (MACE) within 6-month follow-up period.
Results: This study involved 130 patients with a mean age was 61.48 ± 7 years. About 78% of them were male. The receiver operating characteristics (ROC) curve demonstrated that LAVI/a' ≥4.0 (AUC 0.892, 95% CI 0.819 - 0.965) and E/e' ≥13.4 (AUC 0.874, 95% CI; 0.806 - 0.942) predicted MACE. MACE in 6 months with LAVI/a' ≥ 4.0 was 40%, E/e' ≥13.4 was 20%, and the combination of LAVI/a' ≥4.0 + E/e' ≥ 13.4 was 60%. Prediction of MACE using LAVI/a' ≥4.0 had 92% sensitivity and 88% specificity, while E/e' >13.4 had 80% sensitivity and 74% specificity (CI 95%) and the combination o LAVI/a' ≥4.0 + E/e' ≥13.4 had 92% sensitivity and 88% specificity (CI 95%).
Conclusion: LAVI/A' ratio is a promising supporting parameter in predicting MACE, particularly in STEMI patients who received PCI.

1. Introduction

Coronary artery disease (CAD) is a primary cause of death in almost every part of the world.[1] It is a part of an acute coronary syndrome (ACS).[2] ST-segment-elevation myocardial infarction (STEMI) has a greater mortality rate compared to the other subsets of ACS. STEMI is a condition when ischemia and necrosis occur in the heart muscle because of acute total occlusion in coronary arteries.1 In the United States, approximately 1 million patients per year suffered from acute myocardial infarction (AMI), and more than 1 million patients with suspected AMI were treated in the coronary care unit.[1,2]

There is a strong association between abnormal diastolic function of the left ventricular (LV) and major adverse cardiovascular events (MACE).[1] Several studies showed that the wide myocardial infarction areas and LV dysfunction are strong variables in predicting poor prognosis following AMI.[2] Recently, high LV filling pressure following AMI is well-known as the predictor of poor prognosis following AMI.[3] Patients with restrictive or pseudo-normal physiology suffer from the elevated filling pressure of the left ventricular (LV), poor LV compliance, and worse prognosis than patients with slight diastolic dysfunction.[1-3] But, it is not possible to classify all patients into only four classes in the presence of borderline parameters.

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The ratio of early diastolic trans-mitral velocity (E) to early diastolic mitral annular velocity (e') has a strong association with pulmonary capillary wedge pressure (PCWP) and filling pressure of the left ventricle. LAVI depicts the presence of left ventricular diastolic dysfunction for a long time caused by the reduction of LV compliance.[4,5] Unfortunately, there is no echocardiographic parameter that can depict LV filling pressure and LV compliance accurately and simultaneously. Currently, the left atrium volume index (LAVI) has been recognized as a constant parameter that depicts the severity and duration of abnormal LV diastolic function. Moreover, a high LAVI has been recognized to be a strong post-AMI mortality predictor. A recent study demonstrated that LAVI had the same predictive ability as left ventricular ejection fraction (LVEF) for death in ambulatory adult CAD patients and hospitalization in heart failure (HF) patients. [4,5] The late diastolic mitral annular velocity (a') quantified using tissue doppler imaging (TDI) was known to be a relatively preload-free parameter to assess diastolic function in low LVEF patients. The a' could be used to evaluate LA function, mainly the systolic function of the LA.[6,7] Decreased a' velocity may predict cardiovascular mortality, suggesting a crucial part to compensate the booster pump function of the LA. Park et al.[8] revealed that the LAVI/a' ratio was an important variable to identify the severe diastolic dysfunction of LV and to predict clinical outcomes in dyspnoea patients. The same result was reported by Matsura et al.[9] in patients with ACS, most of which were classified as a non-ST-elevation acute coronary syndrome (NSTE-ACS). That study revealed that the patients have worse outcomes during the 10-year follow-up duration. This study purposed to assess the prognostic role of the LAVI/a' ratio combined with E/e' in STEMI patients who received revascularization through percutaneous coronary intervention (PCI).

2. Method

2.1. Study design

We performed a retrospective cohort study in Saiful Anwar General Hospital, Malang, Indonesia, from January 2019 to June 2020. The research ethics board recognized this study protocol.

2.2. Study Population

The inclusion criteria were: (1) STEMI patients who underwent PCI; (2) Patients got complete revascularization with Thrombolysis in Myocardial Infarction (TIMI) flow 3; (3) got optimal medical therapy for at least six months based on the medical record; (4) patients underwent echocardiography in 24 - 48 hours after STEMI onset. Patients with: (1) atrial flutter; (2) atrial fibrillation; (3) congenital heart disease; (4) severe mitral/aortic stenosis/regurgitation; (5) uncontrolled systemic diseases; (6) autoimmune disease; (7) malignancy; (8) severe liver or renal dysfunction; or (9) idiopathic cardiomyopathy were excluded. The purpose and methods of the study had been informed to all patients before they signed informed consent.

2.3. Data Collection

All patient's information, such as demographic data, payment method, STEMI characteristics, cardiovascular disease (CVD) risk factors, Killip class, and risk stratification using Global Registry of Acute Coronary Events (GRACE) score and TIMI risk score, were obtained using a standardized case report form (CRF). The TIMI score is grouped into 2 groups, TIMI score <5 is considered low risk, while ≥ 5 is classified as high risk. Estimation of 6-month death in STEMI patients was assessed using the GRACE score. According to its severity, the GRACE score is divided into: (1) high risk (GRACE score ≥140); (2) moderate risk (GRACE score 109 to 140); and low risk (GRACE score <109).

2.4. Exposure and Outcome

The exposure variable was echocardiography parameters. Transthoracic echocardiography within 24-48 hours after hospital admission was performed using the commercially available echocardiography machine (Philips CX50 and Philips Affiniti 70). The volume of LV was quantified at both end-diastolic and end-systolic phases using modified biplane Simpson's method by combining apical 2-chamber and apical 4-chamber views. Both left ventricular end-systolic dimensions and end-diastolic dimensions were also quantified. The peak late (A) and early (E) diastolic filling velocities, E-wave deceleration time, and E/A ratio were obtained from pulse wave doppler recording of the mitral inflow. The profile of diastolic function was divided into normal, impaired relaxation, pseudo-normal, or restrictive based on the 2016 American Society of Echocardiography (ASE) guidelines for diastolic dysfunction. The volume of the left atrium (LA) was estimated from an apical 2-chamber and apical 4-chamber views in the end-systolic phase using the biplane Simpson's. LAVI was obtained by dividing the volume of the LA with body surface area (BSA). Peak mitral annular velocities during the late (a') and early (e') diastolic phase were obtained using TDI from the apical 4-chamber view in the septal part of the mitral annulus. After that, the LAVI/a' and E/e' were calculated. All STEMI patients received PCI within the time frames based on the 2017 European Society of Cardiology (ESC) guidelines for STEMI management. The outcome measured was MACE in the 6-month follow-up duration, including hospital readmission and mortality. MACE data were obtained from phone call interviews or medical records.

2.5. Statistical Analysis

The statistical analysis process of this study was completed using IBM SPSS version 22 software. Numbers and percentages were used to show categorical data. Mean and standard deviation (SD) were used to present numeric data. For numeric data that normally distributed, statistical analysis was conducted using analysis of variance (ANOVA). The Kruskal Wallis test was performed for abnormally distributed data. The Chi-square test was applied for the categorical data comparison. A p-value <0.05 was considered significant statistically. Both receiver operating characteristics (ROC) curve and area under the curve (AUC) were applied to determine the cut-off point, specificity, and sensitivity.

3. Result

This study included 130 STEMI patients. We found no significant difference in genders between the MACE and non-MACE groups (p = 0.74). The mean age between both groups (59 ± 11.2 vs. 62 ± 12.2; p = 0.34) was also not different significantly. The prevalence of smoking (20,4% vs 29,6%; p = 0.34), diabetes mellitus (DM) (75.5% vs 80.2%; p = 0.67), hypertension (HT) (73.5% vs 66.7%; p = 0.53), and dyslipidemia (91.8% vs 90.1%; p = 0.98) between the MACE and non-MACE groups were not significantly different. We also found no significant differences between the two groups in Killip class, GRACE, and TIMI scores. Patients with a TIMI score <5 were found mostly in the non-MACE group, while patients with a TIMI score >5 were mostly found in the MACE group (p = 0.32). Patients classified as high risk according to GRACE score experienced more MACE (p = 0.88). Most patients who experienced MACE were categorized as Killip class III (p = 0.09). Table 1. summarizes the baseline characteristics of enrolled patients.

In this study, the cut off point for LAVI/A was 4 (AUC = 0.892; 95% CI = 0.819 - 0.965) (Figure 1). While the cut-off value for E/e' was 13.4 (AUC = 0.874, 95% CI = 0.806 - 0.942) (Figure 2). According to the echocardiography results presented in Table 2, The left ventricular diastolic volume (LVEDV) (130.1 ± 48.4 vs 125.7 ± 46.2; p = 0.46), left ventricular end-systolic volume (LVESV) (72.0 ± 35.3 vs 54.5 ± 27.8; p = 0.69), and grade of diastolic dysfunction (p > 0.05) between MACE and non-MACE groups were relative similar. However, we found the significant differences between both groups in E/e' >13.4 (73.5% vs 19.8%; $p < 0.01$) and LAVI/a' (87.8% vs 12.3%; $p < 0.01$)

Kaplan-Meier curve analysis (Figure 3) for the MACE predictors in STEMI patients within the six months follow-up period revealed that 40%, 20%, and 60% patients experienced rehospitalization when examined using LAVI/a' >4.0, E/e' >13.4, and the combination of LAVI/a' >4.0 & E/e' >3.4, respectively. The grade 2 - 3 diastolic dysfunction did not significantly increase the risk for MACE within six months follow-up (OR = 1.08, 95% CI = 0.56 - 1.46; p 0.46). LAVI/a' and E/e' significantlty increased the occurrence of 6-month MACE following STEMI (OR = 6.25, 95% CI = 3.32 - 11.7; $p < 0.01$ and 4.15, 95% CI 2.4 – 7.0; $p < 0.01$).

In this study, we tried to assess role of the LAVI/a' ratio combined with E/e' in determining the prognosis of STEMI patients who received PCI. LAVI/a' had 82% sensitivity and 81% specificity (AUC = 0,822; $p < 0.01$), E/e' had 80% sensitivity and 73% specificity (AUC = 0,769; p = 0.05), meanwhile combination of LAVI/a' and E/e' revealed 90% sensitivity and 83% specificity (AUC = 0,869; p = < 0.01). Those results suggested that LAVI/a' is a useful variable in predicting MACE (Figure 3).

Table 1. Baseline characteristics of patients included in this study

Charateristics	Group MACE (N=49)	Non-MACE (n=81)	P-Value
Age	59 ±11.2	62 ±12.2	0.34
Gender			
Male	57.1%	61.7%	0.74
Female	42.9%	68.3%	
Risk Factors			
Smoking	20.4%	29.6%	0.34
Anemia	-	-	1.00
Hypertension	73.5%	66.7%	0.53
Diabetes mellitus	75.5%	80.2%	0.67
Dyslipidemia	91.8%	90.1%	0.98
Killip class			
I – II	20.4%	9.9%	0.09
III – IV	79.6%	90.1%	
TIMI score			
<5	77.6%	82.7%	0.47
≥5	22.4%	17.3%	
GRACE score			
<122	53.1%	48.1%	0.85
>123 and <154	22.4%	25.9%	
>155	24.5%	25.9%	
Infarct location			
Anterior	30.6%	23.5%	0.06
Anteroseptal	18.4%	2.5%	
Anterior extensive	14.3%	18.5%	
Inferior	18.4%	22.2%	
Inferoposterior	4.1%	12.3%	
Inferoposterior + right ventricular	8.2%	7.4%	
Inferolateral	0	1.2%	
Posterior	0	2.5%	
Right ventricular	6.1%	9.9%	
Coronary angiographic characteristics - infarct-related artery			
Left main	2.1%	0%	0.55
Left anterior descending	48.9%	50%	
Left circumflex	6.7%	2.1%	
Right coronary artery	44.4%	45.8%	

Note, data were presented in mean ± SD or n(%); GRACE = global registry of acute coronary events; MACE = major adverse cardiovascular events; TIMI = Thrombolysis in Myocardial Infarction.

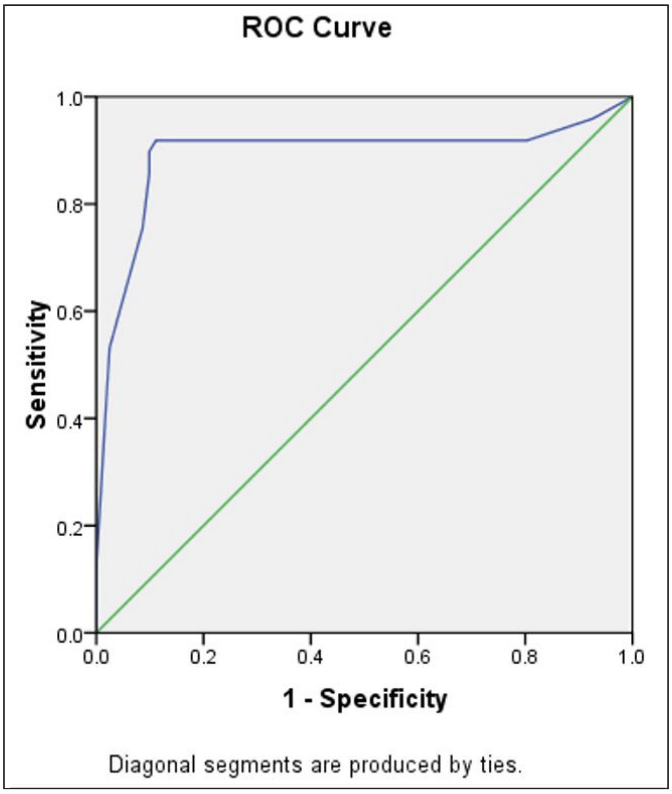

Figure 1. ROC curve to determine the cut-off value of LAVI/A' against MACE.

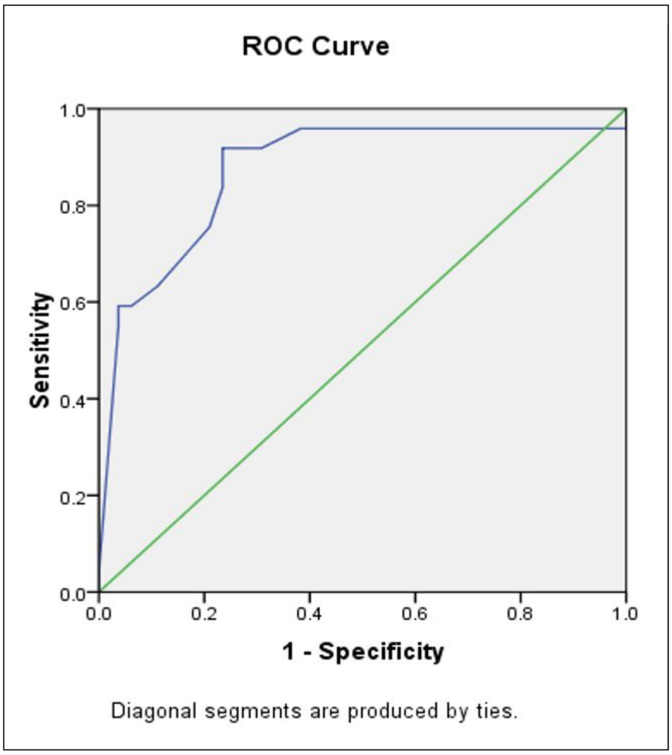

Figure 2. ROC curve to determine the cut-off value of E/e' against MACE.

Table 2. Echocardiography Examination Results

Echocardiography parameters	G. Group MACE (N = 49)	Non-MACE (N = 81)	p - value
E/e' > 13.4	73.5%	19.8%	<0.01
LAVI/A' > 4	87.8%	12.3%	<0.01
EF, %	52.98 ± 8.3	51.7 ± 6.9	0.29
LVEDV, mL/m2	130.1 ± 48.4	125.7± 46.2	0.46
LVESV, mL/m2	72.0 ±35.3	54.5 ± 27.8	0.69
Diastolic function - E/A			
Normal - diastolic dysfunction grade 1	49.0%	40.7%	0.36
Diastolic dysfunction grade 2 – 3	51.0%	59.3%	

Note, data were presented in mean ± SD or n(%); A = late diastolic trans-mitral velocity; a' = late diastolic mitral annular velocity; E = early diastolic trans-mitral velocity; e' = early diastolic mitral annular velocity; EF = ejection fraction; LAVI = left atrial volume index; LVEDV= left ventricular end diastolic volume; LVEDV= left ventricular end systolic volume.

Table 3. Diastolic parameter for predicting MACE within 6 months

Parameter	OR	95% CI	p- value
LAVI/a' > 4	6.25	3.32 – 11.7	0.000
E/e' > 13.4	4.15	2.4 – 7.0	0.000
Diastolic dysfunction grade 2 – 3	1.08	0.56 – 1.46	0.46

Note, a' = late diastolic mitral annular velocity; CI = confidence interval; E = early diastolic trans-mitral velocity; e' = early diastolic mitral annular velocity; LAVI = left atrial volume index; OR = odds ratio.

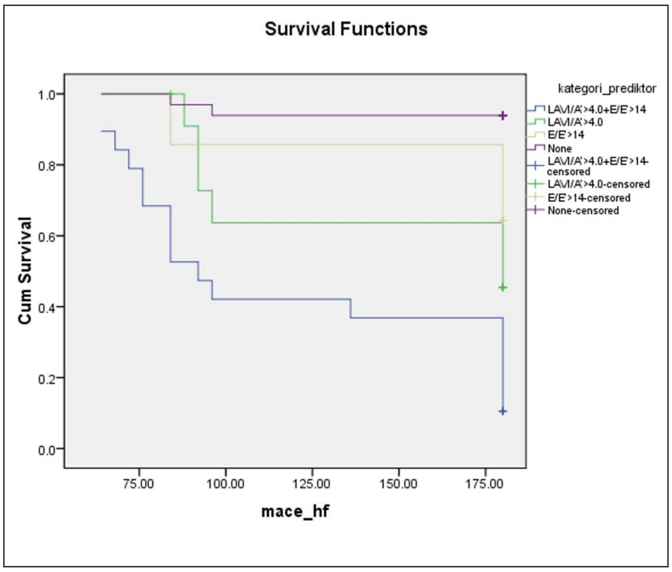

Figure 3. Kaplan-Meier Analysis for MACE MACE during the 6-month follow-up period.

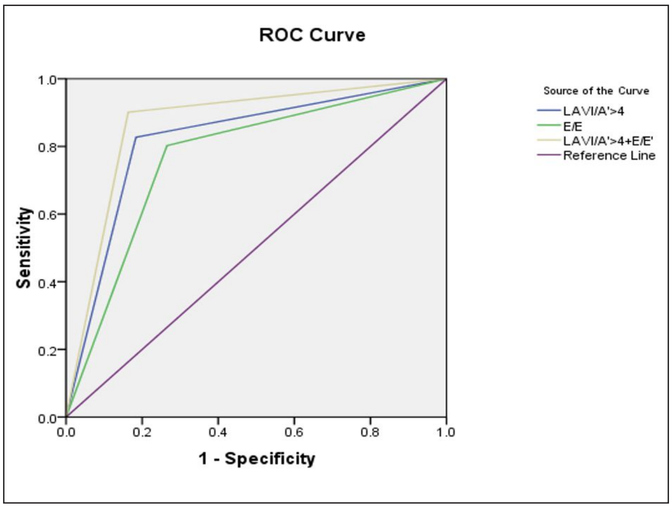

Figure 4. ROC curve to determine the sensitivity and specificity of MACE

4. Discussion

This study has shown that community-based cardiac rehabilitation resThis study demonstrated that the LAVI/a′ ratio was helpful in finding severe diastolic dysfunction of LV and predicting the prognosis in subsets of the hospitalized patient due to dyspnoea and ACS,[10] and this is the first study to our knowledge which demonstrates its clinical use in STEMI patients. In a previous study, the LAVI/a' ratio significantly correlated with B-type natriuretic peptide (BNP) level, showing the higher LAVI/a' ratio related to the greater BNP levels. The ventricles release BNP as the response to the stretch in the myocardium. The high diastolic pressure of LV will increase the plasma BNP levels. [10]

Based on the study from Park et al., a LAVI/a′ ratio of 4.0 was a reasonable cut-off point to identify severe diastolic dysfunction. On the other hand, Matsuura et al. demonstrated a lower cut-off point of 3.0 to predict MACE in CAD patients. This discrepancy may have caused by the fact that the study by Park et al. did not report the data about the cause of dyspnoea. Matsuura et al. took into consideration it to be rational to have a distinct cut-off point for the LAVI/a′ ratio among heart diseases. Matsuura et al. also recommend that the LAVI/a′ ratio of 3.0 in the study be taken in the context of their study population.[9] In our study, the best cut-off is 4.0, since the chest pain onset in our STEMI patients was <12 hours, and primary PCI was performed in all STEMI patients.

LA is encountered to left ventricular filling pressure by opening mitral orifice throughout the diastolic phase. Consequently, its dimension is affected by similar variables that affect the diastolic filling pressure of LV. The pressure in the LA will increase to keep sufficient LV filling if LV diastolic dysfunction becomes prominent,[17] and the higher wall tension of the atrium lead to stretch the atrial myocardium. Finally, the chamber will be dilated. Hence, the volume of LA reflects the chronic LA exposure to the LV diastolic dysfunction and high filling pressure.[12] The LAVI itself is a constant parameter of the diastolic function of the left ventricle. LAVI/a′ ratio provides a useful measure to predict abnormal LV diastolic function by combining functional and structural parameters to identify the smooth alterations in LV diastolic dysfunction, especially in persons who have a diastolic function that is relatively preserved. LAVI/a' is a preferable parameter to assess severe diastolic dysfunction among patients in "the borderline zone" (i.e., 8 ≤ E/e' <15), which posed difficulties in defining and accurately determining clinical status, as such the subjects in this study, whose diastolic dysfunctions were in grade 1 and 2.

PCWP can be estimated using E/e' and those two variables have a strong association. The E/e′ ratio is also a good predictor for survival following AMI. A study demonstrated that the value of >14 could predict survival reduction. Nevertheless, we could not find that the E/e′ ratio was a good predictor. Perhaps it was due to a small number of patients that had a high E/e ratio (E/e′ >15) in this study. Even though the impact of a mild increase in the E/e′ ratio for clinical outcome was unclear,[14] the LAVI/a′ ratio offered a beneficial index for predicting outcomes in patients without high E/e′ ratio or borderline E/e' (i.e., 8≤ E/e' <15). Unfortunately, the invasive hemodynamic data were not available to be compared with LAVI/a' to predict elevated LV filling pressure.

This study has several drawbacks. First, the data in our study were collected from the medical records, and we cannot directly verify the validity of the inputted data. Second, this study was conducted in one center. Consequently, our results did not represent the overall population. Third, our study had a small sample size. Fourth, several confounding factors were difficult to control, such as tachycardia and the fact that the patients in this study were treated in the cardiac intensive care unit. Sometimes we faced difficulties to obtain high-quality images due to postural limitations or the use of ventilators. It was not easy to obtain the accurate LAVI from low-quality images. The last, it is essential to be understood that it was only a cohort study to reveal the LAVI/a′ ratio utilization to predict MACE in STEMI patients who underwent PCI.

5. Conclusion

Our study revealed that LAVI/a' ratio is a promising supporting parameter in predicting MACE, particularly in STEMI patients who underwent revascularization through PCI.

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 involve 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: ADP. Design: ADP. MRF. Control/supervision: BS, AFR, DS, CT. Data collection/processing: ADP, MRF. Extraction/Analysis/interpretation: ADP, MRF. Literature review: BS, AFR, DS, CT. Writing the article: ADP. Critical review: BA, AFR, DS, CT. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

6.7. Acknowledgements
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