# Left atrial volume index as a predictor of events in acute coronary

# Le volume de l'oreillette gauche indexé comme prédicteur d'événements dans le syndrome coronarien aigu

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## Summary

**Introduction :** According to some international studies, patients with acute coronary syndrome (ACS) and increased left atrial volume index (LAVI) have worse long-term prognosis. The aim of our study is to assess the role of LAVi as a predictor of major adverse clinical events (MACE) after ACS.

**Methods:** This was a prospective mono-centric observational study conducted between January 2019 and September 2022, and included patients with ACS. The maximal LA volume was measured from the apical four and two chambers views by using the biplane area length method. The primary clinical endpoint was the occurrence of MACE.

**Results:** The study included 139 patients with a mean age 59.8 years. Our population was predominantly male, with 117 men (84.2%). Mean LAVi was 34.76 ±10 ml/m².

With an average follow-up time of 25 months, MACE was noted in 34.5% of cases. On multivariate analysis, a higher LAVi [OR = 1.139 (1.028 1.261), P = 0.047], was a predictor of MACE. A cut off of LAVi≥ 33.15 ml/m2, predicted MACE with area under curve (AUC) 0.600 (95% CI 0.490 0.701) with a sensitivity and specificity of 60.4% and 53.8% respectively in ROC curve analysis.

**Conclusion:** Increased LAVi is an independent predictor of outcome in patients with ACS. Thus, LAVi measurement should be incorporated as routine to the assessment of patients diagnosed with ACS.

## Mots-clés

Acute coronary syndrome, major adverse cardiac events, echocardiography, left atrium volume

## Résumé

**Introduction :** Selon certaines études internationales, les patients se présentant pour syndrome coronarien aigu (SCA) et ayant une augmentation du volume de l'oreillette gauche (VOGi) ont un pronostic à long terme plus péjoratif. L'objectif de notre étude est d'évaluer le rôle du VOGi comme prédicteur d'événements cliniques indésirables majeurs (MACE) après un SCA.

**Méthodes :** Il s'agit d'une étude longitudinale monocentrique prospective réalisée entre janvier 2019 et septembre 2022, incluant des patients atteints de SCA. Le VOGi a été mesuré à partir des incidences apicales quatre et deux chambres en utilisant la méthode de la longueur de la surface biplan. Le critère d'évaluation clinique principal était la survenue de MACE.

**Résultats :** L'étude a inclus 139 patients avec une moyenne d'âge de 59,8 ans. Notre population était majoritairement masculine, avec 117 hommes (84,2%). Le VOGi moyen était de 34,76 ±10 ml/m². Des MACE ont été notés dans 34,5 % des cas au cours d'un suivi moyen de 25 mois. En analyse multivariée, un VOGi élevé [OR = 1,139 (1,028 1,261), P = 0,047] était prédicteur significatif de MACE. Un seuil de VOGi ≥ 33,15 ml/m² prédisait les MACE avec une aire sous la courbe (AUC) de 0,600 (IC à 95 % 0,490-0,701) avec une sensibilité et une spécificité de 60,4 % et 53,8 % respectivement.

**Conclusion :** L'augmentation du VOGi est un prédicteur indépendant de l'issue chez les patients atteints de SCA. Ainsi, la mesure du VOGi devrait être intégrée systématiquement.

## Keywords

Syndrome coronarien aigu, événements cardiaques indésirables majeurs, échocardiographie, volume de l'oreillette gauche

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## Background

Left atrial (LA) measurements have emerged, in recent years, as the focus of cardiovascular research. LA volume and size have close association with left ventricular (LV) systolic and diastolic function. After acute coronary syndrome (ACS) diastolic function assessed by Doppler echocardiography provides important prognostic information. However, Doppler variables are affected by multiple factors and may change rapidly. In contrast, left atrial volume is less influenced by acute changes and reflects subacute or chronic diastolic function.

The aim of our study is to assess the role of Left atrial volume index (LAVi) as a predictor of major adverse clinical events (MACE) after acute coronary syndrome.

## METHODS

### *Study population*

This was a prospective mono-centric observational study conducted between January 2019 and September 2022, in the Cardiology Department of the Internal Security Forces Hospital of Marsa, Tunisia and included 139 patients with acute coronary syndrome.

### *Inclusion criteria*

We included all patients hospitalized for ST segment elevation myocardial infraction (STEMI), no ST segment elevation myocardial infraction (NSTEMI) or unstable angina with an age ≥ 18 years, stable hemodynamic state and Left ventricular ejection fraction (LVEF) ≥ 40%.

### *Exclusion criteria*

We excluded all patients with atrial fibrillation (AF), infiltrative or hypertrophic, constrictive pericarditis, and significant valvular heart disease.

### *Data collection*

Baseline clinical characteristics, comorbidities, previous cardiovascular disease, diagnosis, ECG, biological data, echocardiographic data, coronary angiography results and treatment were collected.

All patients underwent transthoracic echocardiography (TTE) using a Philips EPIQ 7C with assessment of systolic function by measuring Simpson LVEF and global longitudinal strain. Diastolic function was assessed according to the American society of echocardiography (ASE) 2015 and 2016 guidelines (1,2).

The maximal LA volume was measured from the apical four chamber view by using the biplane area length method (from apical 4 and 2 chamber views, measurements obtained in end systole from the frame preceding mitral valve opening) (Figure 1). The average of LA volume thus measured was then corrected for body surface area to calculate LAV index (LAVi).

Normal LA size was defined as LAVi ≤34 ml/m$^2$, mild dilatation as 35-41 ml/m$^2$, moderate dilatation as 42-48 ml/m$^2$ and severe dilatation as >48 ml/m$^2$ (2).

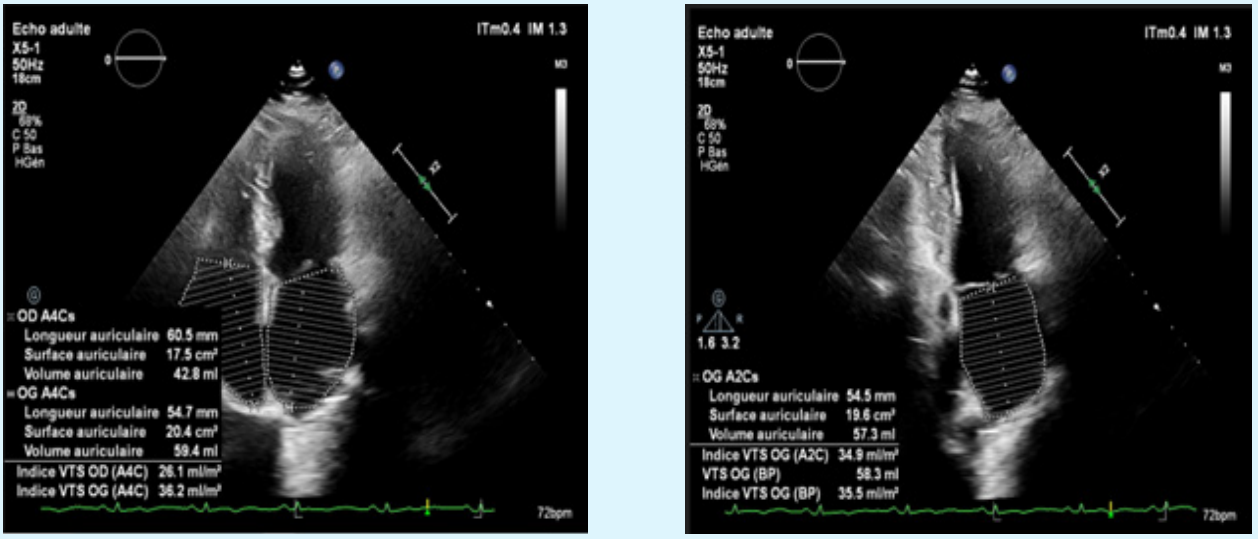


**Figure 1.** Measuring LAVi using the biplane area length method

### Primary clinical endpoint

The primary clinical endpoint was the occurrence of MACE (myocardial infarction, hospitalization for heart failure, stroke and death).

### Statistical analysis

The study data were analyzed using SPSS 22.0 software.

Simple frequencies and relative frequencies (percentages) were calculated for the qualitative variables.

For comparisons of qualitative variables between two or more groups, we used Pearson's Chi 2 test or Fisher's exact test, where the number of participants was less than 5.

For comparisons of quantitative variables, we used Student's t-test and analysis of variance (ANOVA) to compare means in case of a normal distribution, and the Mann Whitney and Kruskal Wallis tests in if it is a non-Gaussian distribution.

The determination of predictive factors of MACE after ACS was carried out in two stages. The first step was to perform a univariate analysis to test the significance of each variable, independently of the other variables. The second step was to perform a multivariate analysis to look for independent predictive factors of MACE after ACS. This was carried out by Cox regression using the stepwise method, with the inclusion of all factors for which the p values were < 0.1 in the univariate analysis. In all statistical tests, a P value of <0, 05 was considered statistically significant.

## RESULTS

### Baseline characteristics of the study population

The study included 139 patients with a mean age 59.8 years (range 28 - 92 years). Our population was predominantly male, with 117 men (84.2%) and 22 women (15.8%), giving a sex ratio of 5.3.

Cardiovascular risk factors were dominated by smoking in 70.5% of cases, followed by type II diabetes in 56.8% and arterial hypertension in 53%. As regards previous history, peripheral artery disease (PAD) was noted in 10.8% of patients. 5% of patients had chronic kidney disease (CKD), 24.5% of the population had an acute coronary syndrome (ACS) history and 2.9% had an episode of heart failure (HF).

Unstable angina was diagnosed in 55.4% of cases, NSTEMI in 35.3% and STEMI in 9.4%. The mean GRACE score was 120±32 with a mean troponin peak of 3540.52.

Echocardiographic parameters are shown in table 1.

**Table 1**. Echocardiographic characteristics of the population

| | Mean | Standard deviation | Minimum | Maximum |
|---|---|---|---|---|
| LVEF % | 60,5 | 7 | 40 | 78 |
| GLS % | -19,7 | 3,3 | -8 | -28 |
| LVEDD mm | 51 | 5 | 39,2 | 63,8 |
| LV EDV mL | 96,3 | 27,5 | 44 | 162 |
| LV ESV mL | 41,2 | 20 | 12 | 127 |
| LVMI g/m$^2$ | 99,4 | 26,5 | 49 | 234 |
| Mitral E wave cm/s | 67,8 | 17,5 | 36 | 122 |
| E/A | 1 | 0,35 | 0,4 | 2,4 |
| E/E' | 7,5 | 2,7 | 4 | 13,4 |
| sPAP mmHg | 29,8 | 8,9 | 15 | 70 |
| Vmax TR m/s | 2,4 | 0,39 | 1,19 | 3,6 |
| LAVi mL/m$^2$ | 34,7 | 10 | 14 | 81 |

LAVI: Left atrial volume index; LV EDV: Left ventricular end diastolic volume; LVEDD: left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LV ESV: Left ventricular end systolic volume; LVMI: left ventricular mass index; LVEF: Left ventricular ejection fraction; LVMI: Left ventricular mass index; GLS: Global longitudinal strain; sPAP: systolic pulmonary artery pressure; V max TR: peak velocity (Vmax) of the tricuspid regurgitation

Angiography showed a single vessel disease in 43.9% of cases, a double vessel coronary artery disease in 20.9% of cases and multivessel disease in 26.6% of patients. A stenosis of the left main was noted in 5.8% of cases. A tight stenosis of the LAD was found in 71% of patients and a lesion of the circumflex in 51% of cases. The right coronary artery was involved in 42.4% of cases. 71.9% of patients received percutaneous treatment and 6.5% underwent coronary artery bypass grafting.

With an average follow-up time of 25 months, MACE was noted in 34.5% of cases, with non-fatal MI in 26.6% and death from any cause in 2.2% of patients.

### Baseline and echocardiographic characteristics according to left atrial enlargement by volume index

Hypertension, PAD and CKD in dialysis were associated with moderate to severe enlargement of the left atrium. Patients with greater LA enlargement had higher LV mass index, mitral E wave velocity, E/E' ratio and systolic pulmonary artery pressure (sPAP). Worse LV diastolic dysfunction was associated with greater LA enlargement (Table 2).

**Table 2**. Different types of AVSD and Patient demographic data in our study

| | Normal and Mild LA size enlargement n=113 | Moderate to severe LA size enlargement n=26 | P |
|---|---|---|---|
| **Baseline characteristics** | | | |
| Age, years | 59±10 | 63 ±9 | 0,064 |
| Male gender | 85% | 76,9% | 0,261 |
| Hypertension | 47,8% | 76,9% | 0,007 |
| Diabetes | 54,8% | 65,3% | 0,329 |
| Current smoker | 72,5% | 61,5% | 0,266 |
| PAD | 7,9% | 23% | 0,O25 |
| CKD | 4,6% | 7,6% | 0,492 |
| Dialysis | 0% | 3,8% | 0,036 |
| ACS history | 24,7% | 23% | 0,856 |
| HF | 1,7% | 7,6% | 0,103 |
| **Diagnosis** | | | |
| STEMI | 10,6% | 3,2% | 0,250 |
| NSTEMI | 37,1% | 26% | 0,250 |
| Unstable angina | 52,2% | 62% | 0,250 |
| **Culprit vessel** | | | |
| Left main | 5% | 7,6% | 0,638 |
| LAD | 69,6% | 80,7 | 0,256 |
| Circumflex | 54,4% | 38,4% | 0,141 |
| Right coronary | 46,4% | 26,9% | 0,07 |
| Multivessel disease | 30,6% | 11,5% | 0,06 |
| Grace score | 121±32 | 116±31 | 0,557 |
| **Biomarkers** | | | |
| Troponines (pg/ml) | 4255±11971 | 335±969 | 0,105 |
| **Echocardiographic characteristics** | | | |
| **LVEDD, mm** | 51±5 | 52±5 | 0,192 |
| **LVMI, g/m2** | 96,5±23,8 | 112±33 | 0,006 |
| **LVEF, %** | 60,6±7 | 60,2±7,5 | 0,79 |
| **Mitral E wave, cm/s** | 66,6±17,5 | 75±16 | 0,021 |
| **Mitral E/A** | 0,96±0,3 | 1,17±0,4 | 0,007 |
| **Mean mitral E/E'** | 7,6±2 | 9,1±2,7 | 0,092 |
| **PAPs** | 28±6 | 35±11 | 0,0001 |
| **GLS,%** | 19,5±3,3 | 20,8±3 | 0,08 |
| **LV diastolic function** | | | |
| Grade I | 89,1% | 47,6% | 0,0001 |
| Grade II | 6% | 23% | 0,0001 |
| Grade III | 0% | 9,5% | 0,0001 |

Data shown as numbers (%) or mean and standard deviation (SD). ACS history: acute coronary syndrome history; CKD: chronic kidney disease; GLS: global longitudinal strain; HF: Heart failure; LAD: Left anterior descending artery; LVEDD: left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; LVMI: left ventricular mass index; NSTEMI: no ST segment elevation acute myocardial infraction PAD: peripheral artery disease; PAPs: systolic pulmonary artery pressure; STEMI: ST elevation acute myocardial infarction; LV: left ventricular

## *Predictive factors for MACE*

As shown in Table 3, on univariate analysis, CKD [OR = 5.1 (0.96 27.7), P = 0.035], acute coronary syndrome history [OR = 3.32 (1.49 7.3), p =0.003], LAD stenosis [OR = 2.62(1.09-6.3), P = 0.027] and higher LAVi [P = 0.014] were significantly associated with the occurrence of MACE.

**Table 3**. Predictive factors for MACE in in univariate analysis

| | No MACE | MACE | Odds ratio | P |
|---|---|---|---|---|
| Age, years | 59,5±10,2 | 60,4±11,4 | - | 0,64 |
| Male gender | 64,9% | 35% | 0,86(0,32-1,29) | 0,77 |
| Hypertension | 51,6% | 56,2% | 0,60(0,59-2,43) | 0,605 |
| Diabetes | 52,7% | 64,5% | 1,63(0,79-3,35) | 0,180 |
| Current smoker | 73,6% | 64,5% | 0,65(0,3-1,38) | 0,266 |
| PAD | 7,7% | 16,6% | 2,4(0,81-7,08) | 0,105 |
| CKD | 2,2% | 10,4% | 5,17(0,96-27,7) | 0,035 |
| Dialysis | 0% | 2,1% | - | 0,340 |
| ACS history | 16,5% | 39,6% | 3,32(1,49-7,3) | 0,003 |
| HF history | 1,1% | 6,2% | 6(0,60-59,3) | 0,084 |
| **Diagnosis** | | | | |
| STEMI | 9,8%% | 8,3% | - | 0,092 |
| NSTEMI | 35,1% | 35,4% | - | 0,092 |
| Unstable angina | 54,9% | 56,2% | - | 0,092 |
| **Culprit vessel** | | | | |
| Left main | 4,4% | 8,3% | 1,97(0,47-8,2) | 0,343 |
| LAD | 65,5% | 83,3% | 2,62(1,09-6,3) | 0,027 |
| Circumflex | 47,7% | 58,3% | 1,53(0,75-3,1) | 0,237 |
| Right coronary | 40% | 47,9% | 1,38(0,68-2,79) | 0,371 |
| Multivessel disease | 28,1% | 30% | 1,77(0,81-3,83) | 0,146 |
| **Biomarkers** | | | | |
| Troponines (pg/ml) | 4255±11971 | 335±969 | - | 0,266 |
| **Echocardiographic characteristics** | | | | |
| **LVEF, %** | 60,8±7 | 60±7 | - | 0,484 |
| **GLS,%** | 19,9±3 | 19,4±4 | - | 0,374 |
| **LAVi, ml/m²** | 33,1±8,7 | 37,8±13,1 | - | 0,014 |

Data shown as numbers (%) or mean and standard deviation (SD). ACS history: acute coronary syndrome history; CKD: chronic kidney disease; GLS: global longitudinal strain; HF: Heart failure; LAD: Left anterior descending artery; LVEF: Left ventricular ejection fraction; NSTEMI: no ST segment elevation acute myocardial infraction; PAD: peripheral artery disease; STEMI: ST elevation acute myocardial infarction; LAVi : left atrial volume index.

On multivariate analysis, the presence of CKD [OR = 5.338 (1.817 15.683), P = 0.045], acute coronary syndrome history [OR = 3.32 (1.49 7.3), P=0.002)] and higher LAVi [OR = 1.139 (1.028 1.261), P = 0.047], were the only significant predictors of MACE (Table 4).

**Table 4**. Multivariate analysis with confounding variables

| | | | | | 95% CI for EXP(B) | |
|---|---|---|---|---|---|---|
| | B | E.S | P value | | Lower | Upper |
| **CKD** | -1,833 | ,912 | ,045 | ,160 | ,027 | ,956 |
| **ACS history** | -1,346 | ,430 | ,002 | ,260 | ,112 | ,604 |
| **LAVi** | ,038 | ,019 | ,047 | 1,039 | 1,000 | 1,079 |

ACS history: acute coronary syndrome history; CKD: chronic kidney disease; LAVi: left atrial volume index.

***Analysis of receiver operating characteristics curve (ROC)*** as shown in Figure 2; LAVi demonstrated that a cut off 33.15 ml/m$^2$, predicted MACE with area under curve (AUC) 0.600 (95% CI 0.490 0.701) with a sensitivity and specificity of 60.4% and 53.8% respectively.

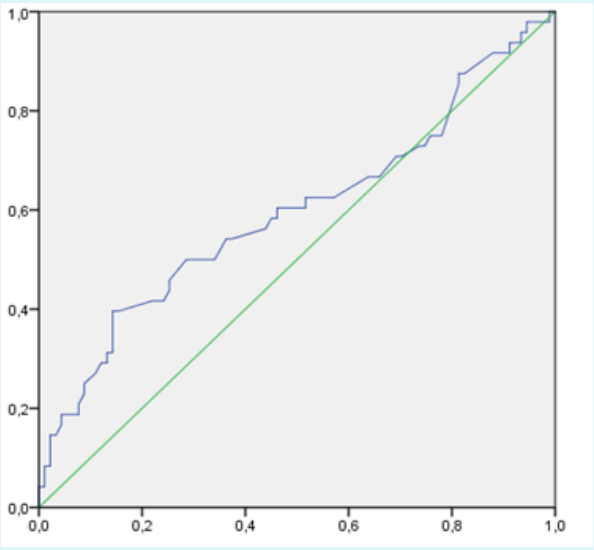


**Figure 2.** Receiver- operating characteristics curve (ROC) for LAVi

## DISCUSSION

In this study, patients with greater LA enlargement had higher LV mass index, mitral E wave velocity, E/E' ratio and sPAP. Worse LV diastolic dysfunction was associated with greater LA enlargement. Likewise, Hypertension, PAD and CKD in dialysis were associated with moderate to severe enlargement of the left atrium. Increased LAVi is an independent predictor of outcome in patients with ACS. A cut-off of LAVi ≥ 33,15 ml/m$^2$, predicted MACE. A Tunisian study included 50 hypertensive patients compared to 50 healthy controls, Antit et al. concluded that hypertension was associated with an increase of LAVi, ventricular hypertrophy and the degree of diastolic dysfunction (3).

Hence the interest in assessing LAVi as an index of long-term diastolic dysfunction. In fact, during ventricular diastole, the left atrium is directly exposed to LV pressures through the open mitral valve. Doppler indices of diastolic function have been shown to predict morbidity and mortality in patients with acute myocardial infarction (AMI) but it provides an instantaneous assessment of diastolic function, therefore LA volume is less sensitive to acute variations, reflecting subacute or chronic changes in diastolic function, would predict long-term outcome after AMI and might be superior in this respect to conventional Doppler (4–6).

In a study including 1128 patients, Shih et al. showed that LA volume parameters can identify LVFP >15 mm Hg and differentiate among patterns of ventricular diastolic dysfunction and offer better performance than even tissue Doppler(7).

Tsang et al. showed , in a study including 140 patients, that LA volume was found to correlate positively with LV end-diastolic and end-systolic dimensions, LV mass, diastolic function grade, tissue Doppler E/E' tricuspid regurgitation velocity.LA volume expressed the severity of diastolic dysfunction and provided an index of cardiovascular risk and disease burden. In addition, an indexed OG volume >28 ml/m$^2$ was superior to the E/E' ratio for identifying diastolic dysfunction (8).

Assessment of the left atrium is based on a number of parameters, including the anteroposterior diameter of the left atrium obtained in the left parasternal long axis view, which remains limited due to the eccentric enlargement of the left atrium, which reduces its accuracy. Similarly, LA planimetry, which is widely used in daily practice, underestimates LA dilatation in the majority of cases (9).

Calculating the LA volume therefore represents a more consistent determination of LA size as compared to diameter or area measurements and LA volume indexed to body surface area (LAVi) is the recommended method for LA size quantification (9). In our study, indexed LA volume was the reference method for detecting LA dilatation using the formula area-length 0.8 x A1 x A2/L in apical 4-chamber and 2 chamber.

In the present study, with an average follow-up time of 25 months, MACE was noted in 34.5% of cases, with non-fatal AMI in 26.6% and death from any cause in 2.2% of patients.

The presence of CKD [OR = 5.338 (1.817 15.683), P = 0.045], acute coronary syndrome history [OR = 3.32 (1.49 7.3), P=0.002)] and higher LAVi [OR = 1.139 (1.028 1.261), P = 0.047], were the only significant predictors of MACE.

The impact of CKD and ACS history on MACE in patients hospitalized for ACS is well defined (10). In a study including 3281 patients with CKD, Hashimoto et al.

showed that three-year MACE significantly deteriorated from 15.8% in no CKD through 38.2% in moderate CKD to 57.9% in severe CKD, respectively (P<0.0001) (11).

The left atrium is a major prognostic parameter not only in the general population but also in coronary patients.

Several studies has shown that increased LAVi is a powerful predictor of mortality after AMI and provides prognostic information. In a series including 314 patients, Moller et al. showed that LA volume index was associated with a hazard ratio of 1.05 for a 1 mL/m² increase (95% CI 1.03 to 1.06, P=0.0001) (12). These results were found in our study with an HR of 1.039 for 1ml/m² increase in LAVi.

In a Malaysian study, including 75 patients who were admitted with ACS stratified into 2 arms: normal LAVi and increased LAVi, with a cut off value of 28 ml/m², Gunasekaran et al. showed that Patients with increased LAVI had significantly more MACEs , p=0,021(13).

A portuguese study including 299 patients with STEMI, Cordeiro et al. demonstrated that severe LA enlargement by LAVI was an independent predictor of all-cause mortality (HR: 11.153; 95% CI: 1.924-64.642, p=0.007) and cardiaovascular endpoints during follow-up [ (HR: 4.351; 95% CI: 1.919-9.862, p<0,001](14)

In prospective cohort of the "Solar Registry" carried out at Hospital Sao Lucas, Brazil, including 171 patients distrupt into two groups according to LAVI values : normal LAVi ≤32m² and increased LAVi > 32 mL/m²,Secondo Junior et al. showed the increase in the relative risk (RR) for combined outcome in 365 days in patients with increased LAVi (RR = 3.459; 95% CI = 1.54-7.73) as compared with the group of patients with normal LAVi(15). Similarly, Salehi et al. , in a cohort conducted on 100 patients admitted with ACS, demonstrated that mortality (27.3%) in patients with atrium index > 32 mL /m² is more than cases with lower atrium index (1.3%) (p = 0.001) (16).

A Meta-analysis included a total of 2,705 patients from 11 cohort studies with a mean follow-up 18.7 ± 9.8 months.Ahmeti et al. concluded that patients with low LAVi (<32ml/m²) had low risk for MACE (15.9% vs. 33.7%; p < 0.01), long-term all-cause mortality (9.14% vs. 18.1%; p < 0.01), short-term mortality (3.31% vs. 9.38%; p = 0.02) and lower hospitalization rate (11.6% vs. 25.5%; p < 0.01) compared to patients with increased LAVi (17).

Saklecha et al. showed in an indian study that 190 patients hospitalized for ACS and divided in two groups s (group 1 LAVi ≥32 ml/m² and group 2 LAVi <32 ml/m²), major adverse cardiovascular events(MACE) at 30 days was significantly higher in group 1 (20.7 vs 6.3%, P = 0.006) .ROC curve analysis for LAVi demonstrated that a cut off 33.35 ml/m², predicted 30 day MACE with Area under curve (AUC) 0.775 (95% CI 0.700 0.850); sensitivity and specificity of 86.7% and 61.4%(18).

This same cut-off was found in our study but with low sensibility and specificity. In fact, ROC curve analysis for LAVi found that a cut off 33.15 ml/m², predicted MACE with area under curve (AUC) 0.600 (95% CI 0.490 0.701) with a sensitivity and specificity of 60.4% and 53.8% respectively.

## CONCLUSION

Increased LAVi is an independent predictor of outcome in patients with ACS. A cut-off of LAVi ≥ 33,15 ml/m², predicted MACE with a sensitivity and specificity of 60.4% and 53.8% respectively.

LA volume was associated with LV hypertrophy, diastolic function and filling pressures in patients with ACS. It provides additional information to other prognostic marker such as LVEF and it is easily obtained in echocardiography. Thus, LAVI measurement should be incorporated as routine to the assessment of patients diagnosed with ACS.

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