Original Article

Is Indexed Left Atrial Volume (LAVi) in Indian Patients with Acute Coronary Syndrome (ACS) Undergoing Revascularization a Predictor of Cardiovascular Outcomes?

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ABSTRACT

Background: Left atrial volume indexed to body surface area (LAVi) is the recommended method for LA size quantification. Assessing LAVi in Indian patients undergoing coronary interventions for acute coronary syndrome (STEMI, NSTEMI, and UA) is clinically relevant.

Methods and Results: Amongst 190 patients (66.4 yrs, 68.4% males), 29.5%, 40.5%, and 30% respectively had STEMI, NSTEMI and UA. Mean LAVi was 32.29 ± 12.06 ml/m^2 and 111 (58.4%) had LAVi 32 while 79 (41.6%) had LAVi <32. Patients were divided into 2 groups (group 1 LAVi >32 and group 2 LAVi <32). Group 1 patients had higher prevalence of TVD [n = 49 vs *n* = 5, *p* = <0.001] and higher mean Syntax score (24.47 vs 14.64, *p* = <0.001). Despite similar LVEF, those with higher LAVi had had higher incidence of mild MR (50.4 vs 27.8, *P* = 0.0002) and moderate/severe MR was present only in Group 1 patients (27.9% and 5.4%). Grade I, II, and III diastolic dysfunction was present in 71.2, 17.1, and 9.9% patients in Group 1 vs 45.6%, 0%, and 0% in group 2. Diastolic parameters like septal E/e' and lateral E/e'ratio were also higher in Group 1. Major adverse cardiovascular events (MACE) at 30 days was significantly higher in group 1 (20.7 vs 6.3%, *P* = 0.006). On multivariate analysis, triple vessel disease and LAVi were the only predictors of MACE while LVEF was not. 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%. Inter-quartile analysis of LAVi (<26.3, 26.3-33.35, 33.36-36.3, and >36.3 ml/m2) demonstrated that 30 day MACE increased across quartiles (4.16%, 4.25%, 22.44%, and 28.26%, respectively, *P* < 0.001).

Conclusion: Amongst patients with ACS undergoing revascularization, those with higher LAVi had more severe CAD, diastolic dysfunction and higher 30 day MACE. LAVi provides superior prognostic information as compared to conventional LV systolic and diastolic parameters in patients with ACS and should be incorporated in routine echocardiographic analysis. More studies with larger numbers and longer follow up are required to further elucidate on this.

Keywords: Acute coronary syndrome, CV outcomes, left atrial volume indexed

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INTRODUCTION

The atria are cardiac structures that are often overlooked during a routine echocardiographic examination. In past, the measurement of left atrial antero-posterior diameter (LAAPD) with M-mode echocardiography was considered sufficient for evaluation of the left atrium (LA). Although this is simple to perform, its reliability and accuracy in reflecting the exact LA size is variable due to the asymmetric shape of the LA. Estimation of left

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atrial area (LAA), which is another surrogate indicator of LA size, is also limited by the fact that LA enlargement often occurs eccentrically, thus reducing the accuracy of this measurement. 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.[1,2]

Since the LA reflects left ventricular filling pressures, it stands to reason that LA enlargement assessed by echocardiography will be an acceptable surrogate for left ventricular systolic and/or diastolic dysfunction. Increased LA volume has been reported to be a strong predictor of adverse cardiac events including mortality in patients with atrial fibrillation, heart failure, stroke and coronary artery disease and provides superior prognostic information compared with conventional LV systolic and diastolic function measurements and clinical data[3-9]

While clinical studies have reported the usefulness of LAVi in predicting cardiovascular (CV) outcomes in patients with existing coronary artery disease (CAD), most have assessed the prognostic implications in patients following myocardial infarction (MI).[9-14] We assessed LAVi in patients with ACS (STEMI. NSTEMI and US) and studied its role in predicting major adverse cardiac and cerebrovascular (MACCE) outcomes at 30 days.

METHODS

We conducted an observational study for a two years period between January 2018 and January 2020, which included all patients with recent ACS as defined by 4th universal definition of myocardial infarction scheduled to undergo coronary angiography.[15] Patients in the study underwent all coronary interventional procedures aftre obtaining informed consent. Patients withmoderate-severe valvular heart disease, atrial fibrillation, restrictive cardiomyopathy, hypertrophic cardiomyopathy, constrictive pericarditis, chronic renal failure, chronic pulmonary or hepatic disease, cancer and with poor acoustic windows precluding optimal echocardiographic recordings were excluded.

A detailed clinical history, baseline demographics, routine biochemical investigations and echocardiography were preformed in all patients. All echocardiograms were performed by a single operator using a commercially available ultrasound system (Vivid 9Ultrasound, GE Medical Systems, Horten, Norway). Comprehensive TTE was done along with LV and LA measurements of dimentions and volume recorded according to the guidelines of the American Society of Echocardiography.[2] Doppler parameters measured included transmitral flows, (E and A waves) and their ratio (E/A), E wave deceleration time (EDT) of the transmitral diastolic flow, isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and LV myocardial performance index (MPI) was calculated. Tissue Doppler derived early diastolic mitral annular velocity (E') was measured from septal and lateral mitral annulus in apical 4-chamber view and mean E' was calculated for analysis. E/A and E/E' ratios were calculated using the peak E, peak A, and E' values. Measurements were performed over three heart beats and average of the three measurements was taken.

LA volume measurement was done as per ASE gudielines[2]: The maximal LA volume was measured from the apical four-chamber view by using the modified Simpson method (in end-systole before mitral valve opening), biplane area-length method (from apical 4- and 2-chamber views, measurements obtained in end systole from the frame preceding mitral valve opening) and real time 3D echo method (after making zoom function gain adjustments to clarify the endocardial border, a semiautomated tracing of the LA endocardial border was done). The average of LA volume thus measured was then corrected for body surface area to calculate LAV index (LAVi).

Statistical analysis

The study data were analyzed using Statistical Package for the Social Sciences version 20.0. Data were tested for normality with the Shapiro-Wilk test. All normally distributed data were reported as means, and comparison of the means was performed with the Student t test. The rest of the values were reported as median and were analyzed with the Mann-Whitney U statistic. The Fisher exact test was used to analyze associations between categorical variables. We used multivariate analysis to determine the independent predictor of MACEs, with confounding variables entered as covariates. A *P* value of <0.05 was considered statistically significant.

RESULTS

Overall, 286 patients were screened, and 190 were finally included in the study. Ninety-six patients were excluded (AF, $n = 16$, RCM, $n = 8$, HCM, $n = 4$, CKD, $n = 13$, valvular heart disease, $n = 16$, CCP, $n = 1$, COPD, $n = 8$, CLD, $n = 2$, declined to participate in the study, $n = 28$).

Baseline characteristics of the study population

The study included 190 patients with a mean age of 66.4 ± 4.06 (range 29-89 years), 68.4% males ($n = 130$).

Hypertension was present in 138 (72.6%), diabetes in 84 (44.2%), family history of CAD in 44 (23.1%), dyslipidemia in 94 (49.4%) and history of smoking in 86 (45.2%). As per inclusion protocol, all patients had recent (≤2 weeks ACS); STEMI was present in 56 (29.5%), NSTEMI in 77 (40.5%) and UA in 57 (30%). Majority of the patients were in NYHA class I (n = 149, 78.4%), while 9 (4.7%%) were in NYHA Class II, 24 (12.6%) in NYHA Class III and 8 (4.2%) were in Class IV.

The mean LAVi of the study population was 32.29 ± 12.06 ml/m^2 (range 21.0-44.5 ml/m^2), of which 111 (58.4%) had LAVi ≥32 ml/m^2 while 79 patients (41.6%) had LAVi <32 ml/m^2. The mean LAVi was significantly higher in the unstable angina group (34.67 ± 11.88 ml/m^2) as compared to STEMI (31.69 ± 10.14 ml/m^2) and NSTEMI (30.97 ± 12.58 ml/m^2, P < 0.001).

Coronary anatomy: Coronary angiography revealed normal coronary arteries in 13 (6.8%) patients, mild non-obstructive CAD in 10 (5.2%), while single vessel, double vessel, and triple vessel disease was seen in 62 (32.6%), 51 (26.8%) and 54 (28.4%) patients, respectively. The mean syntax score was 20.35 ± 11.25 (range 0-43.0). Overall, 100 patients underwent revascularization (52.6%), of which 82 underwent coronary angioplasty (57/82 (69.5%) underwent single vessel, 20/82 (20.7%) underwent double vessel and 5/82 (6.09%) underwent triple vessel angioplasty]. CABG was performed in 18 patients.

Categorization of patients according to LAVi: Patients were divided into two groups, based on LAVi ≥32 ml/m^2 (Group 1, n = 111) and those with LAVi <32 ml/m^2 (Group 2, n = 79).

- As summarized in Table 1, both groups of patients had a similar prevalence of HT (79.7% vs 67.6%, P = 0.054) as well as DM (44.3% vs 44.1%, P = 0.550). The lipid levels were similar among the 2 groups, as depicted in Table 1.
- The incidence of STEMI was equal in both the groups (30.4% vs 28.8%, P = 0.817), whereas the incidence of NSTEMI (50.6% vs. 33.3%, P = 0.017) and UA (37.8% vs 19%, P = 0.005) was significantly higher in those with LAVi >32 ml/m^2. The mean TnI levels were also significantly higher in the latter group of patients (16.59 ± 21.11 vs 11.07 ± 17.29, P = 0.04.
- **Echo parameters:** as shown in Table 2 the mean LAVi was higher in group 1 as compared to group 2 (36.61 ± 6.36 vs 26.22 ± 6.38 ml/m2 p = <.001). Those with higher LAVi had significantly higher incidence of mild MR [n = 56 (50.45%) vs n = 18 (27.79%), P 0.0002]. Moderate or severe MR was present only in Group 1 patients (moderate MR in 27.9%, severe MR in 5.4%). Only 2 patients in Group 1 had normal diastolic function as compared to 43 in group 2 (p < 0.001). Grade I, II and III diastolic dysfunction was present in 79 (71.17%), 19 (17.11%) and 11 (9.9%) patients as compared to 36 (45.56%), 0 (0%) and 0 (0%) respectively in group 2. Those with higher LAVi had significantly shorter IVRT (62.16 ± 19.77 vs 92.26 ± 24.26, P = 0.003], longer EDT (189.87 ± 31.36 vs 142.25 ± 25.38, P = 0.04), higher septal E/e' 6.2 ± 1.23 vs 5.1 ± 1.09, P = 0.004], higher lateral E/e' [7.2 ± 1.72 vs 6.1 ± 1.64, P = 0.003] while MPI, 0.42 ± 0.09 vs 0.37 ± 0.07 was not significantly different. The mean E/e' ratio (derived by average of septal and lateral E/e'), was also significantly higher in the increased LAVI group (6.9 ± 1.69 vs 5.8 ± 1.56, P = 0.003), reflecting this group's more impaired diastolic function.
- **Coronary anatomy and LAVi:** Group 1 patients had higher prevalence of TVD compared to Group 2 [n = 49 vs n = 5, p = <0.001] and higher mean Syntax score as well (24.47 ± 10.80 vs 14.64 ± 9.22, p = <0.001). CABG was more frequently performed in those with higher LAVI (12.6% vs 5.1%, P = 0.064), while PCI was performed more frequently in those with LAVi <32 ml/m^2 (54.4% vs 35.1%, P = 0.006).

At a follow up of 30 days: 28 patients were categorized as having MACE (n = 16/190, 8.42% had a recurrent ACS/angina event, n = 7/190, 3.68% had CVA/TIA, and 5/190, 2.63% died. The occurrence of 30 days MACE was significantly higher in the group 1 (20.72%) as compared to group 2 (6.32%, P = 0.006)

Predictors of MACE: As shown in Table 3, on univariate analysis, TVD [OR = 4.351 (1.89-9.98), P = 0.001], higher syntax score [OR = 1.093 (1.044-1.143), p = <0.001 and LAVi [OR = 1.08 (1.007-1.162), P = 0.032], were found to be independent predictors of MACE, while successful revascularisation was protective [OR = 0.127 (0.042-0.382), p =<0.001]. Surprisingly, mean LVEF was not found to be a predictor of MACE [OR = 0.996 (0.955-1.039), P = 0.843]

On multivariate analysis the presence of triple vessel disease (OR = 5.338 (1.817-15.683), P = 0.002) and LAVi (OR = 1.139 (1.028-1.261), P = 0.013), were the only significant predictors of MACE, while revascularisation was protective against MACE (OR = 0.207 (.080-.534), P = 0.001). LVEF was not a significant predictor of MACE even on multivariate analysis [OR = 0.984 (0.875-1.543), P = 0.763]

Table 1: Baseline demographics

	Total (*n*=190)	LAVI ≥32 (*n*=111, 58.4%)	LAVI <32 (*n*=79, 41.6%)	*P*
Age	66.42±28.2	67.06±26.28	65.96±29.56	0.685
Males	130 (68.42%)	79 (71.2%)	51 (64.6%)	0.209
BMI (kg/m^2)	29.6±9.08	29.65±9.3	29.52±8.8	0.852
DM	84 (44.2%)	49 (44.1%)	35 (44.3%)	0.550
HT	138 (72.63%)	75 (67.6%)	63 (79.7%)	0.054
Smoking	86 (45.26%)	47 (42.3%)	39 (49.4%)	0.209
Family h/o CAD	44 (23.15%)	24 (21.6%)	20 (25.3%)	0.336
Old CVA	21 (11.05%)	10 (12.7%)	11 (9.9%)	0.356
Previous h/o Revascularization	5 (2.63%)	3 (2.70%)	2 (2.53%)	0.432
eGFR (ml/min/1.73 m^2)	78.55±24.86	78.23±23.54	78.78±26.72	0.762
TC (mg/dl)	173.59±27.01	174.89±28.90	171.76±24.15	0.432
TG (mg/dl)	91.95±16.04	92.85±16.33	90.7±15.65	0.364
LDL (mg/dl)	50.48±27.49	51.20±28.66	49.48±25.91	0.673
HDL (mg/dl)	37.75±11.03	37.83±10.74	37.65±11.5	0.911
VLDL (mg/dl)	18.6±5.33	19.2±5.42	18.1±5.23	0.672
Mean echo LVEF (%)	50.93±18.78	51.78±18.38	49.73±19.22	0.139
STEMI	56 (29.5%)	32 (28.8%)	24 (30.4%)	0.817
NSTEMI	77 (40.5%)	40 (50.6%)	37 (33.3%)	0.017
UA	57 (30%)	42 (37.8%)	15 (19%)	0.005
SVD	62 (32.63%)	31 (27.92%)	31 (39.24%)	0.101
DVD	51 (26.84%)	25 (22.52%)	26 (32.91%)	0.10
TVD	54 (28.42%)	49 (44.14%)	5 (7.59%)	<0.001
Mean Syntax	20.39±11.25	24.47±10.80	14.64±9.22	<0.001
Mean TnI (ng/ml)	13.37±19.11	16.59±21.11	11.07±17.29	0.04
% undergoing PCI	82 (43.15%)	39 (35.1%)	43 (54.4%)	0.006
% undergoing CABG	18 (9.47%)	14 (12.6%)	4 (5.1%)	0.064

Table 2: Echo parameters in those with LAVI≥32 and LAVI<32

	LAVI ≥32 (*n*=111)	LAVI <32 (*n*=79)	*P*
LVESD (mm)	30.18±16.90	31.51±17.96	0.301
LVEDD (mm)	47.35±16.22	47.63±17.21	0.818
No MR	18 (16.21%)	61 (77.21%)	<0.001
MR (Mild)	56 (50.45%)	18 (27.79%)	0.0002
MR (Mod)	31 (27.92%)	0 (0%)	-
MR (Severe)	6 (5.4%)	0 (0%)	-
Normal diastolic function *	2 (1.8%)	43 (54.43%)	<0.001
Grade I Dysfunction	79 (71.17%)	36 (45.56%)	0.009
Grade II Dysfunction	19 (17.11%)	0 (0%)	-
Grade III Dysfunction	11 (9.9%)	0 (0%)	-
IVRT (ms)	62.16±19.77	92.26±24.26	0.003
EDT (ms)	189.87±31.36	142.25±25.38	0.04
E/A	0.70 (.6-1.3)	1.1 (.7-1.3)	0.056
Septal E/e'	6.2±1.23	5.1±1.09	0.004
Lateral E/e'	7.2±1.72	6.1±1.64	0.003
E/e'	6.9±1.69	5.8±1.56	0.003
MPI	0.42±0.09	0.37±0.07	0.872
LA volume index (ml/m2)	36.61±6.36	26.22±6.38	0.001

Table 3: Univariate analysis of predictors of MACE

Parameter	No MACE (*n* = 162)	MACE (*n* = 28)	Odds Ratio	P
LAVi	31.9 +/- 12.18	34.58 +/- 12.004	1.08 (1.007-1.162)	0.032
TVD	38 (124)	16 (12)	4.351 (1.89-9.98)	0.001
Syntax score	19.01 +/- 21.94	28.35 +/- 19.02	1.093 (1.044-1.143)	< 0.001
PCI/CABG	92 (70)	4 (24)	0.127 (0.042-0.382)	< 0.001
LVEF	50.99 +/-18.65	50.61 +/- 19.98	0.996 (0.955-1.039)	0.843

A significant positive correlation of LAVi was found between syntax score ($r = 0.445$, $P < 0.001$) and E/e' ($r = 0.490$, $P < 0.001$)

Analysis of receiver- operating characteristics curve (ROC) As shown in Figure 1; LAVi demonstrated that a cut-off 33.35 ml/m2, predicted 30 day MACE

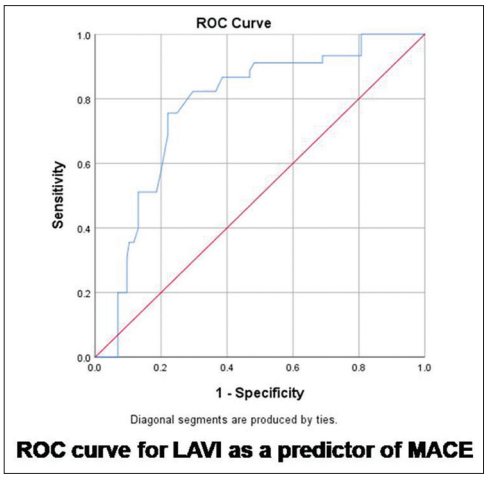

Figure 1: Receiver- operating characteristics curve (ROC) for LAVi

with area under curve (AUC) 0.775 (95% CI 0.700-0.850) with a sensitivity and specificity of 86.7% and 61.4% respectively. **Inter-quartile analysis of LAVi** (<26.3, 26.3-33.35, 33.36-36.3 and >36.3 ml/m2) demonstrated that the incidence of 30 day MACE increased progressively across the quartiles (4.16%, 4.25%, 22.44%, and 28.26%, respectively, $P < 0.001$).

DISCUSSION

In this study of 190 Indian patients with ACS (STEMI, NSTEMI and UA), planned for coronary angiography, mean LAVi was 32.29 ± 12.06 ml/m^2. More than half the patients (58.4%) had LAVi ≥32 ml/m^2 while the rest (41.6%) had LAVi <32 ml/m^2. Coronary angioraphy revealed single, double and triple vessel disease in 32.6%, 26.8% and 28.4% patients respectively, while the rest 12% had either normal coronary arteries or only mild non obstructive CAD with mean syntax score of 20.35 ± 11.25 for the overall patient included in the study. Categorizing patients into these two groups revealed that there was no difference in prevalence of HT, DM or lipid levels amongst the two groups. While the incidence of STEMI was similar (30.4% vs 28.8%), that of NSTEMI (50.6% vs. 33.3%) and UA (37.8% vs 19%) was significantly higher in those with higher LAVi. The mean TnI levels were also significantly higher in this group I patients (16.59 ± 21.11 vs 11.07 ± 17.29).

While we found that ~ 60% of 190 patients with ACS had LAVi >32 ml/m^2, in the Solar registry of patients with ACS (n = 171), 45% had LAVi >32 ml/m^2 while Gunaskeran *et al.* reported high LAVi values in 32/75 (43%) patients with ACS.[16,17] In patients with MI, Moller *et al.*[9] reported that amongst 314 patients with AMI, 45% had LAVi >32 ml/m^2, and Beinart[10] observed a high LAVi in 19% of 395 patients with acute MI. In the VALIANT Echocardiography study, Miser *et al.* observed that 32% patients had LAVi >26 ml/m^2 and 15% had values >32,[11] while data from the Heart and Soul Study of 935 patients with previous MI, revealed LAVI >30 ml/m^2 in 53%.[12]

Although in patients with ACS, clinical heart failure is associated with worse prognosis, even those with subclinical evidence of dysfunction have a worse prognosis, despite being asymptomatic. Hence, having a non-invasive marker of early ventricular dysfunction would be useful in this group of patients. Even though the overall LVEF was normal (mean 53%), 20.5% patients in our study had clinical evidence of heart failure, and the mean LAVi of this group of patients was 35.2 ± 9.7 ml/m^2. While mean LVEF was similar and within normal range (52 and 54% respectively) in those with LAVi >/< 32 ml/m^2, those with higher LAVi had significantly higher prevalence of diastolic dysfunction. Grade I, II and III diastolic dysfunction was present in 71%, 17%, and 9% as compared to 45%, 0%, and 0% in those with/without LAVi ≥32 ml/m^2 respectively. Mild mitral regurgitation was also more common in those with higher LAVi (50% vs 22.7%) while moderate or severe MR was only seen in those with higher LAVi. A greater degree of diastolic dysfunction (higher mitral peak A, DT, E/e' ratio) was also reported by Patel *et al.* in those with higher LAVi, but the degree of MR was not reported in their study.[18]

It is well known that traditional cardiovascular CV risk factors predict adverse cardiac events during follow up. On multivariate analysis only multivessel coronary artery disease (p = 0.002), LAVi (0.001) and successful revascularization (p = 0.01) were significant predictors of 30 day MACE. None of the other echocardiographic parameters including LVEF or filling velocities and E/E' ratio predicted outcomes. Moreover, Doppler echocardiographic variables that are traditionally used to assess LV systolic and diastolic function reflect beat-to-beat changes and the dynamic relationship between LV filling pressures and ventricular compliance. In contrast, LA volume assessment is an indicator of increased LV filling pressure over a longer period of time, reflecting three-dimensional changes and asymmetrical alterations in LA size.[19,20] Our study therefore adds to the existent literature that apart from LVEF, LAVi estimated by echocardiography may also be used as an additional predictor of CV outcomes, especially in patients with baseline normal LV function.

ROC analysis showed that a cut-off value for LAVi (33.35 ml/m^2), predicted 30 day MACE with a sensitivity

and specificity of 86.7% and 61.4% respectively. Amongst different quartiles of LAVi (<26.3, 26.3-33.35, 33.36-36.3 and >36.3 ml/m^2), the incidence of 30 day MACE increased progressively across the quartiles (4.16%, 4.25%, 22.44%, and 28.26%, respectively, $P < 0.001$) highlighting the robustness of LAVi as a marker of adverse CV outcomes. Higher short-term and long-term adverse CV event rate has been reported to be associated with moderate or severe LA enlargement in previous studies as well.[13,18,21,22]

Limitations

The major limitations of the study are that it is a single center study and involves only a short term follow up of 30 days. Multi-center studies with larger patient numbers and longer follow up will help add more insights into this subject, especially in patients undergoing surgical revascularization. Interpreting a single point analysis of LAVi also represents a limitation and multiple echocardiographic analysis during follow up can also help assess if changes in LAVi (delta LAVi: baseline minus follow up values) also add to the predictive value and throw more light on the natural remodeling of the left atrium. Lack of a comparative arm (controls or chronic stable angina) also represents a limitation, that should be addressed in future studies.

CONCLUSIONS

In this study of 190 Indian patients with ACS we observed that ~60% had LAVi >32 ml/m^2. Those with higher LAVi presented more often with NSTEMI and unstable angina and had more severe CAD on coronary angiography, with higher Syntax score. These patients also had higher prevalence of diastolic dysfunction, with grade II and III diastolic dysfunction observed in 26% as compared to none in those with LAVi <32 ml/m^2. Multivessel coronary artery disease and LAVi were significant predictors of 30 day MACE while none of the other echocardiographic parameters including LVEF or trans-mitral velocities and E/E' ratio predicted CV outcomes. A cut-off value for LAVi (33.35 ml/m^2), predicted 30-day MACE with a sensitivity and specificity of 86.7% and 61.4%, respectively. Amongst different quartiles of LAVi (<26.3, 26.3-33.35,), the incidence of 30 day MACE was higher in those in the higher quartiles.

We conclude that LAVi provides good prognostic information apart from traditional CV risk factors and conventional LV systolic and diastolic parameters in patients with acute coronary syndrome and needs to be incorporated in routine echocardiographic analysis. More studies with larger patient numbers and longer follow up are required to clearly understand the temporal profile of LA remodeling.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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