Prevalence and Predictors of Left Atrial Appendage Inactivity in patients of Rheumatic Mitral Stenosis in Sinus Rhythm- An observational study.

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Abstract

BACKGROUND: Systemic thromboembolism is a known complication of rheumatic mitral stenosis (RMS) in sinus rhythm (SR). Left atrial appendage (LAA), the commonest site of thrombus formation is usually hypocontractile (inactive) in such patients. We aimed to study the prevalence of LAA inactivity (LAAI) in severe RMS and assess its independent predictors. METHODS: The study population consisted of 100 patients of severe RMS in sinus rhythm. Transthoracic and transesophageal echocardiography were done to assess LAA contractile function. Patients with LAA-peak emptying velocity <25 cm/sec were defined as having LAAI. RESULTS: The mean age of study subjects was 31.66±8.69 years and 56% were females. 73% patients had LAAI (Group A), while remaining 27% had normal LAA function (Group B). Mitral-valve area (MVA) and lateral annulus systolic velocity (Sa-wave) were significantly lower while mean pressure gradient across mitral valve (MGMV) and serum fibrinogen were significantly higher (all p-values <0.001) in group A patients. On multivariate regression analysis, MGMV (p<0.001), Sa-wave (p=0.02) and serum fibrinogen (p=0.005) were independent predictors of LAAI. Optimal cut-off values of MGMV, Sa-wave and serum fibrinogen for predicting LAAI were 11.5mmHg, 6.8cm/sec and 300mg/dL respectively.67(90.55%) patients in group A compared to 13(48.1%) in group B had LA/LAA smoke. LAAI was the only independent predictor of left atrium (LA)/LAA smoke and associated thrombus. CONCLUSION: There is high prevalence of LAAI in patients of severe MS in SR. MGMV, Sa-wave and serum fibrinogen levels are independent predictors of LAAI. LAAI is an independent predictor of LA/LAA smoke and associated thrombus.

TITLE PAGE

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INTRODUCTION

Systemic thromboembolism is a major cause of morbidity and mortality in patients of mitral stenosis (MS).[1,2] Although thromboembolic events are common in patients of MS with atrial fibrillation (AF), it has also been reported in 5-15% of patients in sinus rhythm (SR).[2-4] · Left atrial appendage(LAA) is the commonest site for thrombus formation and impairment of its contractility leading to stasis is an independent predictor of thromboembolic events in patients of MS.[5,6.]

Serken S et al [4] in an interesting study have shown that in patients of severe MS (Mitral valve area [MVA] [?] 1.5 cm^2) there is an impairment of LAA contractility to a similar extent irrespective of whether a patient is in SR or AF. However, no data is available about the prevalence of LAA hypocontractility/inactivity (defined as LAA peak emptying velocity [LAAEV] <25cm/sec) [7,8] in patients of severe MS in SR that promotes spontaneous echo contrast (SEC) formation(a precursor of thrombus) and is an independent predictor of thromboembolic events. [9,10]

So, the primary aim of this study was to assess the incidence of LAA inactivity (LAAI) in patients of severe MS in sinus rhythm.

The assessment of LAAEV to detect LAAI requires transesophageal echocardiography (TEE) which is invasive, requires expertise and is not readily available. The secondary aim was to assess clinical, hematological and transthoracic echocardiographic variables that can predict presence of LAA inactivity.

Sample size: As the proportion of active and inactive LAA in patients of severe MS in SR is not known in our population, we considered inactive LAA to be present in 50% patients. Considering 50% with 10% regression on either side with 95% confidence interval (CI), we needed 96 patients to attain an adequately powered study.

MATERIAL and METHODS:

The study population consisted of 100 adult patients aged [?] 18 years with isolated severe MS in sinus rhythm recruited from Cardiology Outpatient Department of our Tertiary care hospital between January 2019 and July 2020.

Patients with any of the following were excluded from the study:

1. Concomitant mitral regurgitation (more than mild)
2. Concomitant aortic stenosis and/or regurgitation (more than mild)
3. History of mitral commisurotomy or valvuloplasty
4. Associated congenital heart disease
5. Left ventricular systolic dysfunction (ejection fraction < 50%)
6. Associated diabetes mellitus, hypertension, chronic kidney disease or coronary artery disease.
7. Associated pregnancy
8. Currently on oral anticoagulants or antiplatelet drugs
9. Poor ECHO window The study was approved by the institutional ethical committee and written informed consent was taken from all the subjects. An initial screening transthoracic echocardiography (TTE) was done and patients meeting our inclusion/ exclusion criteria were given an appointment for undergoing both TTE and TEE.

ECHOCARDIOGRAPHY

A one lead electrocardiogram was recorded continuously during the TTE and TEE (informed written consent was taken from all patients before TEE). Two-dimensional and Doppler echocardiographic studies were performed in the left lateral decubitus position in conventional views (parasternal long, short-axis, and apical two and four-chamber view) according to American Society of Echocardiography guidelines.[11] All patients were evaluated using two-dimensional M-mode, pulsed- and continuous-wave Doppler echocardiography. The mitral valve area (MVA) was calculated using planimetry and pressure half-time methods. The maximum and mean pressures gradients across the valve were measured by continuous-wave Doppler from the apical four-chamber view. The left ventricular end-diastolic and end-systolic diameters, interventricular septum and posterior wall thickness, left ventricular ejection fraction and left atrial diameter (LAD) were recorded from the parasternal long-axis view. Modified parasternal short-axis view [as described by Herzog et al[12]] was used to visualize the left atrial appendage.

Tissue Doppler imaging (TDI) :

This was performed in the apical four chamber view, with probe placed in the lateral annulus. A Doppler velocity range of (-20 to 20) cm/sec was selected. The three major velocities were recorded: one positive systolic velocity (Sa-wave) and the two negative diastolic velocities (E- and A-waves). The peak systolic and diastolic velocities were measured at a sweep speed of 50 mm/sec.

Trans-esophageal Echocardiography (TEE)

Multiplane transesophageal echocardiography (TEE) was performed in all patients. The LA and LAA imaging was begun in the horizontal plane at 0°, then the transducer was rotated progressively to 60° and 90°; in the same plane, and images were also evaluated after slight and more pronounced counterclockwise rotation of the probe. Rotation of the transducer to 110° and 130° was coupled with more pronounced counterclockwise rotation of the probe. All images were recorded by optimizing the gain settings to minimize gray-noise artefacts. We examined the LAA in the short and long axis. It has been shown that transesophageal echocardiography is highly sensitive for the detection of left atrial clot, especially in the left atrial appendage.[13,14]

LA or LAA thrombus was diagnosed by the presence of clearly defined echogenic intracavitary mass different from the underlying endocardium. SEC was diagnosed by the presence of dynamic smoke-like echoes in the LA cavity and LAA with a characteristic swirling motion. The severity of SEC was graded from 0 to 4+ as proposed by Fatkin et al.[15.]

Grade 0: None (absence of echogenicity)

Grade 1+: Mild (minimal echogenicity located in the LA appendage or sparely distributed in the main cavity of the left atrium; may be detectable only transiently during the cardiac cycle; imperceptible at operating gain settings for two dimensional echocardiographic analysis)

Grade 2+: Mild to moderate (more dense swirling pattern than grade 1+ but with similar distribution; detectable without increased gain settings)

Grade 3+: Moderate (dense swirling pattern in the LAA, generally associated with somewhat lesser intensity in the main cavity; may fluctuate in intensity but detectable constantly throughout the cardiac cycle)

Grade 4+: Severe (intense echo density and very slow swirling patterns in the LAA, usually with similar density in the main cavity)

The LAA flow profiles were obtained by placing the sample volume of the pulsed Doppler 1 cm below the LAA orifice where there were no wall artefacts and a net flow could be recorded using pulse wave Doppler. The positive flow observed after P-wave of surface ECG, was taken as LAAEV (considered to represent the LAA contractile function). Inactive LAA was defined as late peak LAAEV <25 cm/sec[7,8] (Figure 1A, B). A mean of 3 consecutive cycles was used to calculate all echocardiographic parameters.

All echocardiograms were independently evaluated by two observers and any difference of opinion was settled by mutual consensus.

STATISTICAL ANALYSIS

Statistical analysis was done with SPSS software 25.0 (IBM Corp, Armonk, NY, USA). Continuous variables have been presented as mean +- standard deviation. Categorical variables have been presented as number and percentages. Difference between continuous variables have been tested using the unpaired student 't' test, and between categorical variables by using the Chi-square test and Fisher exact test. Statistical significance was set at a probability level of less than 0.05. Univariable followed by multivariable logistic regression analysis was done to assess the independent predictors of inactive LAA in patients of severe MS in sinus rhythm. Multivariable binary logistic regression analysis was performed on variables which were significant on univariable analysis (p<0.2) to identify the independent predictors of inactive LAA.

Univariate followed by multivariate logistic regression analysis was also done to assess the independent predictors of LA/LAA smoke and thrombus.

Pearson correlation analysis was used to assess the association between various factors which were independent predictors of LAAI. Receiver operating characteristic curve (ROC) were constructed to assess the optimal cut off value of the independent factors to predict inactive LAA. The Youden index was applied to obtain the optimal cut-off point of factors. The diagnostic indices- sensitivity, specificity, positive predictive value, negative predictive value were determined for each factor at optimal cut-off point.

Inter-observer variability in the measurement of LAAEV was expressed as mean coefficient of variation [?] [(observer 1-observer 2)/observer 1]/n and expressed as percentage. Interobserver variability in grading SEC was determined as number of cases in which a discrepancy of grade occurred, expressed as percentage of the total group.

RESULTS:

The mean age of patients in our study was 31.66 +- 8.69 years and 56% were females. Forty-six percent patients were in NYHA class II, 52% in NYHA class III and 2% in class IV. (Table I)

Based on LAAEV of <25 cm/sec or more, the patients were divided into 2 groups: Group A with LAA inactivity (LAAEV <25 cm/sec) and group B without LAA inactivity (LAAEV [?] 25 cm/sec). There were 73 patients in our study who had evidence of LAAI (Group A) while the remaining 27 patients had normal LAA contractile function (Group B, Table II). There was no significant difference in height, weight, age or gender between the two groups. Hemoglobin and erythrocyte sedimentation rate (ESR) were also comparable between the 2 groups. However, serum fibrinogen was significantly higher in group A compared to group B (340 +- 86.56 vs. 266.12 +- 62.84 mg/dL, p<0.001). [Table II]

There was significant difference in MVA (p<0.001), mean gradient across MV (p<0.001) and mitral valve lateral annulus systolic velocity (p<0.001) between the two groups. A significantly higher number of patients in group A had evidence of smoke in LA/LAA than group B (67 [90.5%] vs. 13 [48.1%], p <0.001). Two patients in group A also had associated LAA thrombus compared to none in group B. [Table II]

Majority of patients in both groups had grade 1 or 2 SEC (47 out of 67 patients i.e. 70.1% in group A and 10 out of 13 patients i.e. 76.9% in group B) [Table II]. Twenty patients (29.9%) in group A had grade 3 or 4 SEC compared to 3 (23.1%) patients in group B having grade 3 SEC only and none having grade 4 SEC.

Inter-observer difference in grading of SEC was observed in 8 patients primarily while determining between grade 1 and grade 2 and was 10% in our study. The mean co-efficient of variation for measurement of left atrial peak emptying velocity between observers was 1.8% (range 0 to 18.6%)

Only four variables, having the p<0.2 in univariable analysis, were included in the multivariable analysis: MVA, mean trans-mitral gradient (MVMG), Sa wave amplitude and serum fibrinogen level. On multivariable regression analysis, mean gradient across mitral valve (p=0.001), Sa (p=0.02) and serum fibrinogen (p=

0.005) were found to be independent predictors of LAAI. However, the MVA assessed by planimetry failed to achieve statistical significance to predict LAAI in our study (P=0.06). (Table III)

We found significant positive correlation between LAAEV and Sa-wave by using Pearson correlation analysis (P <0.001, r=0.475) (Figure 2A). The optimal cut-off value of Sa-wave obtained was 6.82 cm/sec, from the ROC curve analysis, for predicting presence of inactive LAA with sensitivity of 66.6% and specificity of 61.8%. The area under ROC curve of 0.67 revealed moderate discrimination. The positive predictive value of Sa- wave to predict LAAI was 44.7% and negative predictive value was 79.2% (Figure 2B).

A significant negative correlation was found between LAAEV and MVMG by using Pearson correlation analysis (P <0.018, r= -0.235) (Figure 3A). The optimal cut-off value of MVMG, obtained from the ROC curve analysis, for prediction of LAAI was 11.5 mm Hg with sensitivity of 82.2% and specificity of 70%. The area under ROC curve of 0.836 revealed good discrimination. The positive predictive value of MVMG to predict LAAI was 73.5% and negative predictive value was 79.8% (Figure 3B).

We also found a significant negative correlation between LAAEV and plasma fibrinogen level by using Pearson correlation analysis (P <0.005, r= -0.391) (Figure 4A). The optimal cut-off value of serum fibrinogen obtained from ROC curve for predicting LAAI was 300 mg/dl with sensitivity of 71.0% and specificity of 74.1%. The area under ROC curve of 0.780 revealed good discrimination. The Positive predictive value of serum fibrinogen to predict LAA inactivity was 73.27% and negative predictive value was 71.87% (Figure 4B).

We also assessed the combined predictive value of aforementioned variables (serum fibrinogen, MVMG and Sa-wave). The AUC for predicting LAAI by combining these three variables improved to 0.89 (95% CI- 0.81 to 0.96) with improvement in sensitivity to 87.7% and positive predictive value to 79.8% (Figure 5, Table IV).

We also compared 80 patients in our study with LA/LAA smoke with associated thrombus (Group C) with 20 patients(Group D) without LA/LAA smoke or thrombus. On univariate analysis, MVA by planimetry (p=0.007), MVMG (p = 0.002), serum fibrinogen (p=0.001) and percentage of patients with inactive LAA (p<0.001) had p value < 0.2 (Table V). Multivariable binary logistic regression analysis was done on these four variables to identify the independent predictors of LA/LAA smoke. Only LAAI was found to be an independent predictor of LA/LAA smoke with associated thrombus (p=0.04) (Table VI)

DISCUSSSION

This is the first prospective study that systematically assessed the frequency of LAAI (defined by peak LAA emptying velocity <25cm/sec) [7,8] in patients of severe isolated RMS (MVA[?]1.5cm2) in sinus rhythm. In our study 73% patient had inactive LAA of which 53% had very severe MS (MVA [?] 1 cm^2) and 20% had severe MS (MVA >1 but [?]1.5cm^2). On multivariable regression analysis, mean gradient across mitral valve, serum fibrinogen and lateral mitral annulus systolic velocity were found to be independent predictors of LAAI. MVA assessed by planimetry failed to achieve statistical significance as an independent predictor of LAAI in our study.

Hoit et al [16] and Bilge et al [17]have shown that elevation of LA pressure causes reduction in LAA emptying velocity. The degree of obstruction to outflow across mitral valve is a predictor of LA pressure. In spite of similar mitral valve areas, patients have variable LA pressure due to variable resistance to flow across the mitral valve apparatus determined by the degree of pliability of the valves and sub-valvular obstruction. These aspects of obstruction across mitral valve apparatus are better reflected by the mean transmitral gradient across MV than the MVA determined by 2D. Hence, in our study, mean transmitral gradient was found to be an independent predictor of LAAI over MVA assessed by planimetry.

In our study, another independent predictor of LAAI was serum fibrinogen level. In patients of MS, local stagnation of blood in left atrium and its appendage leads to activation of coagulation system and reversible intercellular bridging between RBC principally by fibrinogen.[18] This local alteration of the coagulation system also leads to increased levels of fibrinogen in peripheral blood[19] and accordingly in our study the serum fibrinogen level was significantly higher in patients with LAAI. Fibrinogen by increasing blood viscosity contributes to increase in LAA afterload and impairment in its contractility. [20] In our study, we found that serum fibrinogen of [?]300 mg/dl had a sensitivity of 71.0% and PPV of 73.27% in predicting LAAI.

Mitral annulus has an important role for LA and left ventricular (LV) function by moving throughout cardiac cycle along the LV long axis.[21-23] The excursion of the mitral annulus is responsible for approximately 20% of total LV filling and emptying in healthy subjects. [16] It also contributes to LA filling by creating a suction effect during systole and contributes to LA emptying by decreasing LA blood volume during diastole.[16-18] In patients of MS LV, LA and LAA function are impaired and the excursion of the mitral annulus is reduced due to scaring and inflammatory processes. In our study, we found a strong positive correlation between Sa-wave and LAA peak emptying velocity. The cut off value of Sa-wave to predict LAAI in our study was 6.8 cm/sec which was lower then cut off value reported by Cayle et al[7] of 13.5 cm/sec and higher than the cut off value of 5.5 cm/sec reported by Arava et al. [24] This is due to the fact Cayle et al [7] had enrolled patients with MVA [?]1.5 cm^2 whereas Arava et al [24] had enrolled patients of critical MS with MVA <1 cm^2. The mean Wilkins score in our study was 7.3+-0.8 which is less compared to the mean Wilkins score of 7.9+-0.9 by Arava et al. [24] The degree of damage to the MV apparatus in our study was lesser than patients recruited by Arava et al[24] and more than patients studied by Cayle et al.[7] Accordingly, the cut-off value of Sa obtained in our study was lower than that by Cayle et al. and higher than that of Arava et al.

In our study, two echocardiographic parameters assessed by TTE- mean transmitral pressure gradient and lateral mitral annulus systolic velocity were found to be independent predictors of LAAI. As TEE is an invasive procedure requiring skill and has limited availability, determination of mean transmitral gradient and lateral annulus systolic velocity can help to predict LAAI by a non-invasive modality like TTE.

To the best of our knowledge, this is the first study that has analysed and reported about two echocardiographic variables along with one haematological factor (Serum fibrinogen) that can predict the presence of LAAI with combined positive predictive value of around 80%.

In our study, LAAI was the only variable found to be an independent predictor of LA/LAA smoke and associated thrombus. Ninety percent patients with LAAI had evidence of LA/LAA smoke which is a risk factor for thromboembolism. It has already been shown by Serkan et al[4] that in patients of severe MS, there is similar degree of impairment of LAA contractility, irrespective of whether the patients are in AF or sinus rhythm.

So we feel that just as the presence of AF in patients of MS is considered an indication for initiating oral anticoagulant therapy [OAC] [25], presence of LAAI in patients of severe MS in sinus rhythm should also be considered as an indication for initiating OAC. Therapy with OAC should be continued till LAA afterload imposed by the high transmitral gradient can be significantly reduced by mitral valvuloplasty which have been shown to improve LAA contractility.[24, 26]

LIMITATIONS

It is a single centre study.

Undiagnosed intermittent AF could not be ruled out in our patient population.

CONCLUSION

There is a high prevalence of LAAI in patients of severe MS in sinus rhythm. Mean transmitral pressure gradient, lateral annulus systolic velocity and serum fibrinogen are independent predictors of LAAI. LAAI is also an independent predictor of LA/LAA smoke and associated thrombus.

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TABLE I. Baseline demographic and clinical functional class of patients.

Variables	Patients (n=100)
Age (years)	31.66 ±8.69
Gender (Female/Male)	56/44
Height (Cm)	161.03 ± 5.83
Weight (Kg)	52.57 ± 5.23
NYHA functional class	NYHA functional class
Class I (n= 0)	0%
Class II (n=46)	46%
Class III (n=52)	52%
Class IV (n=2)	02%

Values expressed as mean ± standard deviation.

NYHA: New York Heart Association

Table II. Comparison of baseline demographic, hematological and Echocardiographic parameters of **Group A** and **Group B**patients.

Parameters	**GROUP-A** (n=73)	**GROUP-B** (n=27)	P-value
Age (years)	31.64 ± 8.85	31.73 ± 8.36	0.962
Sex (female) n(%)	39 (53.4)	17 (62.9)	0.508*
Height (cm)	161.36 ± 5.82	160.08 ± 5.89	0.335
Weight (kg)	52.64 ± 4.88	52.38 ± 6.50	0.835
Hb (gm/dl)	12.82 ± 1.28	12.84 ± 1.51	0.949
ESR (mm/hour)	29.55 ± 21.40	26.12 ± 21.99	0.486
Serum FIB (mg/dl)	340.5 ± 86.56	266.12 ± 62.84	<0.001
MVA (planimetry) ($cm^{2)}$	0.87 ± 0.25	1.08 ± 0.22	<0.001
MVPG (mmHg)	22.39 ± 7.75	21.27 ± 5.10	0.494
MVMG (mmHg)	15.74 ± 5.18	10.83 ± 3.00	<0.001
LAD (cm)	4.43 ± 0.56	4.35 ± 0.53	0.557
Wilkins score	8.01 ± 0.94	7.76 ± 0.95	0.260
Sa-wave (cm/sec)	6.75 ± 1.06	7.67 ± 1.11	<0.001
PASP (mmHg)	47.40 ± 5.71	46.66 ± 5.11	0.43
HR (TEE)	89.61 ± 14.77	93.15 ± 17.46	0.318
HR (TTE)	80.10 ± 9.4	76.69 ± 11.52	0.318
Thrombus (Present)/ n (%)	2 (2.7)	0 (0.0)	1.00*

Parameters	**GROUP-A** (n=73)	**GROUP-B** (n=27)	P-value
Smoke TEE (present)/n (%)	67(90.5)	13(48.1)	<0.001*
TEE Grade of smoke	n (%)	n (%)	
1+	17(23.3)	6(22.2)	1.000
2+	30(41.2)	4(14.8)	0.017
3+	13(17.8)	3(11.1)	0.55
4+	7(9.6%)	0(0.0)	0.18

Values expressed as mean ± standard deviation.

Hb= Hemoglobin; ESR= erythrocyte sedimentation rate; FIB= Fibrinogen; MVA= mitral valve area; MVPG = mitral valve peak gradient; MVMG = mitral valve mean gradient; LAD = left atrial diameter; SEC = spontaneous echo contrast; Sa = mitral annulus systolic velocity; PASP= pulmonary artery systolic pressure; HR= heart rate; TEE= trans esophageal echocardiography.

Table III. Odds ratio of variables which are independent predictors of LAA inactitvity.

Predictor	B(S.E. of B)	Odds ratio (95% CI)	P-value
MVA (by planimetry)	1.205(0.655)	3.34(0.924-12.05)	0.066
Serum FIB. (per unit)	0.013(0.004)	1.013(1.004-1.021)	0.005
MVMG (per unit)	0.439(0.137)	1.552(1.19-2.03)	0.001
Sa-wave (per unit)	-0.697(0.300)	0.498(0.277-0.896)	0.020

MVA= mitral valve area; FIB= Fibrinogen; MVMG= mitral valve mean gradient; Sa= mitral annular systolic velocity.

Table IV. Predictive values of various variables of LAA inactivity

Variables	AUC(95% CI)	Sensitivity	Specificity	PPV	NPV
Sa-wave	0.67 (0.56-0.78)	66.6%	61.8%	44.7%	79.2%
MVMG	0.83 (0.75-0.93)	82.2%	70.4%	73.5%	79.8%
Serum FIB	0.780 (0.68-0.88)	71.0%	74.1%	73.27%	71.87%
Sa + MVMG + Serum. FIB. (Cumulative ROC)	0.891 (0.82-0.97)	87.7%	77.87%	79.8%	86.3%

CI: Confidence interval; MVMG= mitral valve mean gradient; Sa= mitral annulus systolic velocity; FIB: Fibrinogen; ROC: Receiver Operating Characteristic; PPV: Positive predictive value; NPV: negative predictive value; AUC: Area under curve

Parameters	**Group C** (N=80)	**Group D** (N=20)	P-value
Age (years)	31.85(9.11)	31.85(6.89)	0.664
Sex (Female) n (%)	43 (53.7)	13 (65)	0.365
Height (cm)	161.05(5.83)	160.65(6.00)	0.946
Weight (kg)	52.50(5.01)	52.85(6.19)	0.791
Hb (gm/dl)	12.86(1.30)	12.67(1.50)	0.578
ESR (mm/hour)	29.15(21.15)	26.70(23.31)	0.651
Serum FIB (mg/dl)	334.88(85.94)	266.3(70.12)	0.001

Parameters	**Group C** (N=80)	**Group D** (N=20)	P-value
MVA (cm^2) by planimetry	0.89(0.25)	1.07(0.26)	**0.007**
MVPG (mmHg)	22.71(7.34)	19.65(5.85)	0.087
MVMG (mmHg)	15.14(5.13)	11.25(4.30)	**0.002**
LAD (cm)	4.43(0.55)	4.34(0.59)	0.523
Wilkinson score	8.02(0.89)	7.65(1.14)	0.114
Sa-wave (cm/sec)	6.93(1.14)	7.23(1.18)	0.295
PASP (mmHg)	46.18(5.84)	44.35(4.12)	0.45
LAAI [n (%)]	67 (83.75%)	6 (30%)	<**0.001**
HR (TEE)	89.96 (14.72)	92.80 (18.56)	0.467
HR (TTE)	74.40 (13.25)	75.95 (13.18)	0.638
Thrombus / n (%)	2(2.5)	0(0.0)	1.00

Table V: Baseline and Echocardiographic Comparison of patients with or without LA/LAA Smoke and associated thrombus.

Values expressed as mean ± standard deviation.

Hb= hemoglobin; ESR= erythrocyte sedimentation rate; FIB= Fibrinogen; MVA= mitral valve area;

MVPG = mitral valve peak gradient; MVMG = mitral valve mean gradient; LAD = left atrial diameter; Sa = mitral annulus systolic velocity; LAAI = left atrial appendage inactivity; PASP: Pulmonary artery systolic pressure; HR: Heart rate

Table VI: Multivariable regression analysis to show independent predictor of LA/LAA smoke.

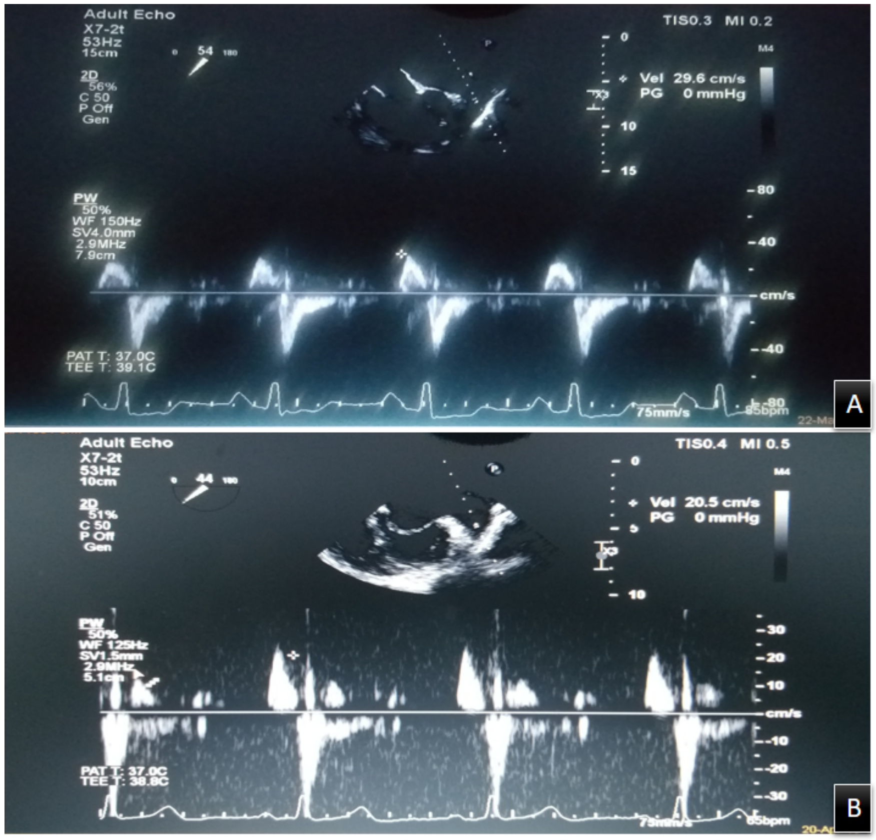
Predictor name	B(SE of B)	Odds ratio (95% CI)	P-value
MVA (planimetry) ([?]1)	0.871(0.636)	2.39(0.687-8.313)	0.171
Serum FIB (per unit)	0.007(0.004)	1.007(0.999-1.015)	0.094
MVMG	0.092(0.089)	1.097(0.921-1.305)	0.299
LAAI	1.39(0.71)	4.02(1.01-16.04)	**0.042**

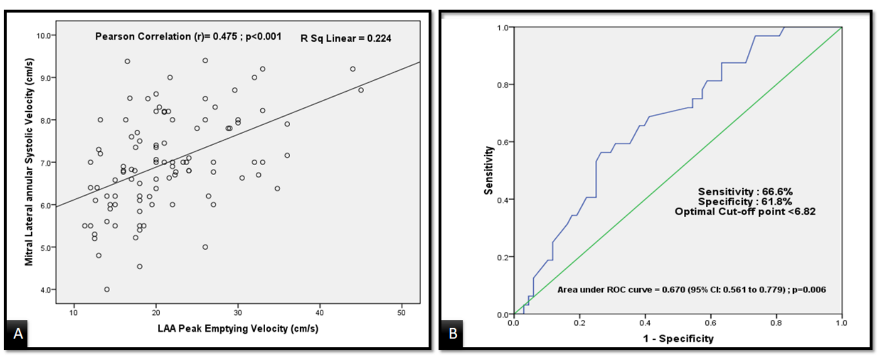
MVA= mitral valve area; FIB= Fibrinogen; MVMG= mitral valve mean gradient; LAAI= left atrial appendages inactivity.

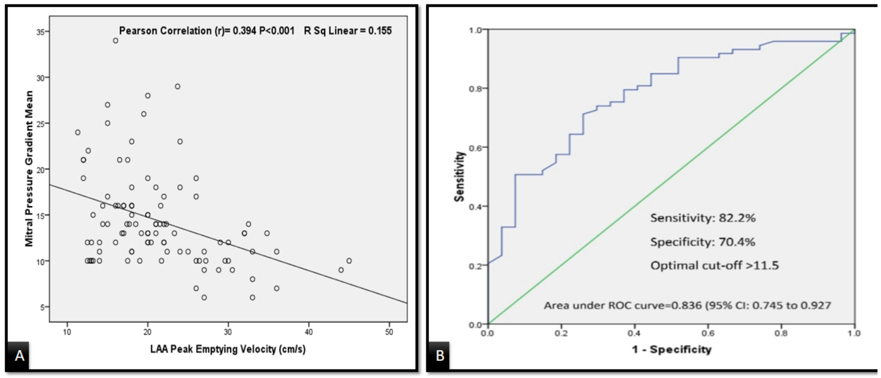
Figures	Legends
1	Pulsed wave Doppler tracing of LAA flow in sinus rhythm on TEE showing normal LAAEV (29.6 cm/sec) Pulsed wave Doppler tracing of LAA flow in sinus rhythm on TEE showing reduced LAAEV (20.5 cm/sec) Abbreviations: LAA: Left atrial appendage, TEE: Transesophageal echocardiography, LAAEV: Left atrial appendage emptying velocity

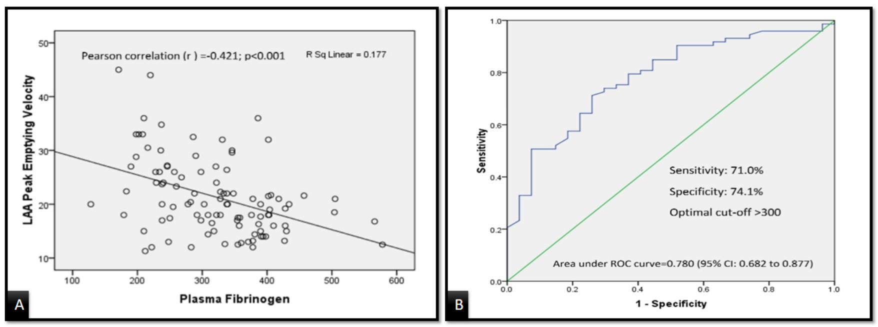
Figures	Legends
2	Correlation between LAAEV and Sa-wave velocity ROC curve analysis of Sa-wave velocity for prediction of inactive LAA Abbreviations: LAAEV: Left atrial appendage emptying velocity; Sa : mitral annulus systolic velocity, ROC: Receiver Operating Characteristic
3	Correlation between LAAEV and MGMV ROC curve analysis of MVMG for prediction of inactive LAA Abbreviations: LAAEV: Left atrial appendage emptying velocity; MVMG= mitral valve mean gradient , ROC: Receiver Operating Characteristic
4	Correlation between LAAEV and plasma fibrinogen ROC curve analysis of plasma fibrinogen level for prediction of inactive LAA Abbreviations: LAAEV: Left atrial appendage emptying velocity; LAA: Left atrial appendage
5	Cumulative ROC curve for prediction of LAAI (LAA inactivity) ROC: Receiver Operating Characteristic

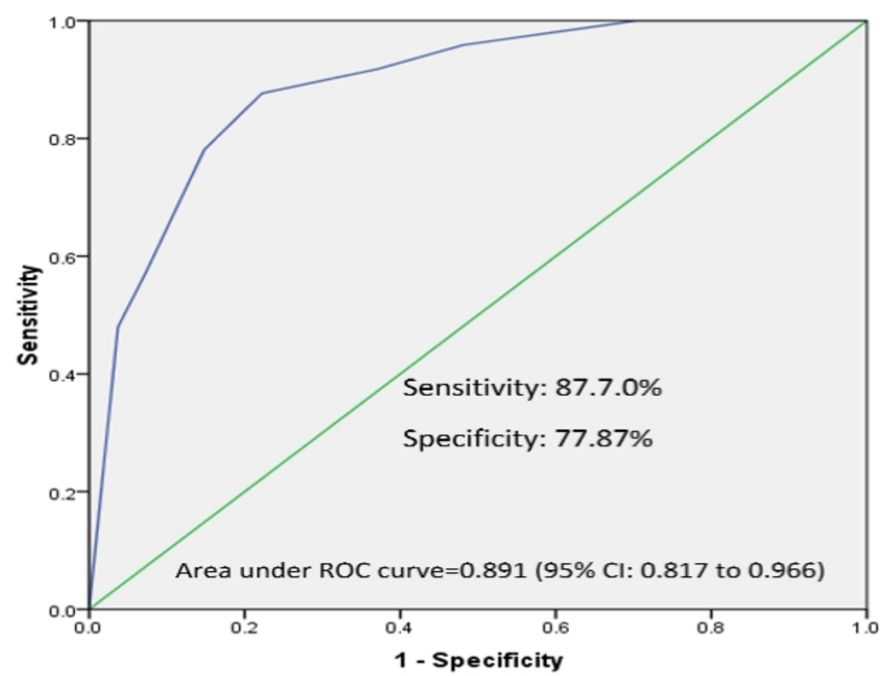
FIGURE LEGENDS


Adult Echo
X7-2t
53Hz
15cm
TIS0.3 MI 0.2
Vel 29.6 cm/s
PG 0 mmHg
PW
50%
WF 150Hz
SV4.0mm
2.9MHz
7.9cm
PAT T: 37.0C
TEE T: 39.1C
75mm/s
A
Adult Echo
X7-2t
53Hz
10cm
TIS0.4 MI 0.5
Vel 20.5 cm/s
PG 0 mmHg
PW
50%
WF 125Hz
SV1.5mm
2.9MHz
5.1cm
PAT T: 37.0C
TEE T: 38.8C
75mm/s
B


Pearson Correlation (r)= 0.475 ; p<0.001
R Sq Linear = 0.224
Mitral Lateral annular Systolic Velocity (cm/s)
LAA Peak Emptying Velocity (cm/s)
A
Sensitivity
1 - Specificity
Sensitivity : 66.6%
Specificity : 61.8%
Optimal Cut-off point <6.82
Area under ROC curve = 0.670 (95% CI: 0.561 to 0.779) ; p=0.006
B


Pearson Correlation (r)= 0.394 P<0.001 R Sq Linear = 0.155
Mitral Pressure Gradient Mean
LAA Peak Emptying Velocity (cm/s)
A
Sensitivity
1 - Specificity
Sensitivity: 82.2%
Specificity: 70.4%
Optimal cut-off >11.5
Area under ROC curve=0.836 (95% CI: 0.745 to 0.927
B


Pearson correlation (r) =-0.421; p<0.001
R Sq Linear = 0.177
LAA Peak Emptying Velocity
Plasma Fibrinogen
A
Sensitivity
1 - Specificity
Sensitivity: 71.0%
Specificity: 74.1%
Optimal cut-off >300
Area under ROC curve=0.780 (95% CI: 0.682 to 0.877)
B


Sensitivity
1 - Specificity
Sensitivity: 87.7.0%
Specificity: 77.87%
Area under ROC curve=0.891 (95% CI: 0.817 to 0.966)