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Original Article

Implication of d-dimer in rheumatic severe mitral stenosis – A tertiary centre study

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ABSTRACT

Background: In rheumatic mitral stenosis (MS), left atrial (LA) thrombus and LA spontaneous echo contrast (LA SEC) reflect hypercoagulability. The study focuses on whether D-dimer levels predict the existence of LA thrombus and SEC in patients with severe MS.

Methods: 95 consecutive patients with severe MS referred for transesophageal echocardiogram (TEE) between July 2011 and March 2012 to evaluate LA thrombus prior to balloon mitral valvotomy (BMV) were included in the study. D-Dimer levels in these patients were observed.

Results: Out of the 95 patients, 15 (15.8%) had LA thrombus and 52 patients had LA SEC (54.7%). Any correlation between D-Dimer levels and existence (or non-existence) of LA thrombus was not noticed from the receiver operating characteristics (ROC) curve with an area of .535. For patients with LA SEC, the D-Dimer levels were found to be considerably higher (776 ± 866 μg/L vs. 294 ± 331 μg/L, p = .001). An ideal cut-off level of 393 μg/L for diagnosing LA SEC was illustrated by the ROC curve with a sensitivity of 63.4%, specificity of 83.72%, positive predictive value of 82.5% and a negative predictive value of 65.45%.

Conclusions: D-dimer levels were not representative of the presence or absence of LA thrombus in patients with severe MS. Nonetheless, this study demonstrated the substantial link between D-Dimer level and LA SEC. If a D-Dimer level of 400 μg/L or higher is taken as positive, it has high specificity and positive predictive value for diagnosing LA SEC.

1. Introduction

Patients with mitral stenosis (MS), and specifically ones associated with atrial fibrillation (AF), are at heightened risk of developing left atrial (LA) thrombus and the related complications of stroke and peripheral embolism.[1] Non-covalent binding between red cells and plasma proteins under low flow and low shear conditions[2] causes aggregate formation. Ultrasonic backscatter from these red blood cells aggregates results in increased blood echogenicity giving rise to spontaneous echocardiographic contrast (SEC) or “smoke” in the LA.

Transesophageal echocardiography (TEE) is the most prevalent test to identify nearly every cardiac source of thromboembolism, and is considered the most reliable in ruling out LA thrombus.[3] TEE is semi-invasive, operator-dependent, and requires light sedation with a small but genuine risk of complications. It would be advisable to identify patients who could be prospectively sorted to distinguish those who would benefit from TEE to detect LA thrombus and LA SEC from those in whom the likelihood of LA thrombus and LA SEC is very low.

Being an indirect marker of fibrin formation, D-dimer is an established blood test that reflects actuation of the coagulation system. D-dimer is well examined in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE), with an excellent negative predictive value.[4,5] Elevated D-dimer levels have been reported in patients with AF with LA thrombus and LA spontaneous contrast.[6,7] The study aimed to evaluate the predictive value of D-dimer in determining LA thrombus and LA SEC in rheumatic severe MS, and to find if these markers, when combined with clinical and echocardiographic variables, could help pinpoint patients with LA thrombus and LA SEC in which cases TEE can be deferred.

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2. Methods

2.1. Aims of the study

The aims of the study were (1) to determine if D-Dimer levels predict LA thrombus and LA SEC in patients with severe MS and (2) to derive a cut off value for D-Dimer levels to rule in or rule out LA thrombus and LA SEC.

2.2. Population

Consecutive patients with rheumatic severe MS referred for TEE prior to Balloon Mitral Valvotomy (BMV) between July 2011 and March 2012 for evaluation of LA thrombus at a single tertiary care center were included in the study. Exclusion criteria were: ages less than 12 years, moderate to severe mitral regurgitation, moderate to severe aortic stenosis or aortic regurgitation, pregnancy and documented intravascular thrombus. The project was approved by the institutional ethics committee. Informed consent was obtained from all patients included in the study.

2.3. Transesophageal echocardiography (TEE)

All TEEs were carried out post obtaining signed patient consent. A Philips IE 33 (Philips, Andover, MA, USA) ultrasound machine with an equipped multiplane TEE probe was used for all TEEs. TEE was considered the gold standard for determining LA thrombus and LA SEC. Procedure was performed under local anesthesia. SEC was defined as a fine reticular pattern of dynamic, swirling intracavitary echoes imaged with gain settings adjusted to distinguish background 'white' noise. LA thrombus was defined as an echodense mass, either in the body of LA or appendage, adjacent to the endocardial surface clearly differentiated from normal structures [such as pectinate muscles in the case of LA appendage].

2.4. Sample collection and D-Dimer assay

2 ml of blood was collected in a citrated vaccutainer tube (BD Science, USA) from these patients prior to TEE. The blood samples were centrifuged and the supernatant plasma was aliquoted in Eppendorff vials, stored at −20 °C, till the date of testing. The samples were analysed at the end of the study. D-Dimer levels in plasma samples were quantified using IMUCLONE D-Dimer ELISA kit from American diagnostic Inc.

Baseline characters as well as D-dimer levels were compared between patients having LA thrombus vs. not having LA thrombus and patients having LA SEC vs. not having LA SEC.

2.5. Statistical analysis

The SPSS statistical software package (version 16.0, SPSS Inc. Chicago, IL, USA) was used for all statistical calculations. The data were expressed as mean ± SD, and categorical variables as percentages. Unpaired *t*-test was used to compare continuous variables while chi-square test compared discrete variables. The optimal cut-off points were determined by receiver operating characteristic (ROC) curves, and the sensitivity and specificity of D-dimer levels for group distinction were computed according to: sensitivity = true positives/(true positives + false negatives) x 100%, specificity = true negatives/(true negatives + false positives) x 100%, positive predictive value = true positives/(true positives + false positives) x 100%, and negative predictive value = true negatives/(true negatives + false negatives) x 100%. For all statistical analysis, a p value of less than .05 was considered statistically significant.

To get .75 as the area under the ROC curve at 5% alpha error and 80% power when the ratio of negative to positive group is 6[14] and .5 is considered as null hypothesis, the number of positive cases required was 12 and the number of negative cases required was 72. By considering 10% rejection/exclusion rate, the total sample size was rounded to 95. The sample size was calculated using MedCalc for Windows, version 11.6 [MedCalc Software, Ostend, Belgium].

3. Results

95 consecutive patients with severe MS referred for TEE for evaluation of LA thrombus between July 2011 and March 2012 were included in the study out of which 73 were females (76.8%). The mean age was 39.11 ± 10.9 years. 15 patients (15.8%) had LA thrombus while 80 patients (84.2%) did not have a LA thrombus. LA SEC was present in 52 patients (54.7%). 29 patients (30.5%) were in AF and all these patients were on oral anticoagulants.

A comparison of the baseline characteristics of patients with and without LA thrombus is shown in Table 1. AF was more frequent in patients with LA thrombus than in patients without LA thrombus (80% vs. 21.2%, $p < .005$). LA SEC was predominantly higher in patients with LA thrombus (86.7% vs. 48.8%, $p = .007$). The mitral valve area was lower in patients with LA thrombus but was not statistically significant (Table 2).

The baseline characteristics of the patients with and without LA SEC were compared (Table 2). AF was more common in patients with LA SEC as opposed to patients without LA SEC (40.4% vs. 18.6%, $p = .022$). Patients with LA SEC had higher prevalence of LA thrombus as compared to patients without LA SEC (25% vs. 4.7%, $p = .007$).

There was no significant difference in D-dimer levels in patients with and without LA thrombus with a mean D-Dimer level of 520 ± 442 μg/L, range 100–1400 μg/L and 565 ± 760 μg/L, range 20–5319 μg/L ($p = .826$) respectively. D-Dimer levels were also compared in patients with and without LA SEC and it was significantly higher in patients with LA SEC (776 ± 866 μg/L vs. 294 ± 331 μg/L, $p = .001$). Among patients with LA SEC, patients in AF had lower D-Dimer levels as compared to patients in sinus rhythm (475 ± 449 μg/L vs. 980 ± 1017 μg/L, $p = .038$). Among patients without LA SEC, there was no significant difference in D-Dimer levels between AF and sinus rhythm patients (307 ± 270 μg/L vs. 270 ± 200 μg/L, $p = .335$) (Table 3).

An arbitrary D-Dimer level of 500 μg/L and above was taken as positive and D-Dimer levels below 500 μg/L was taken as negative and a 2 × 2 table was plotted for calculating sensitivity, specificity, positive predictive value and negative predictive value of D-dimer in diagnosing LA thrombus and LA SEC (Tables 3 & 4). Assuming an arbitrary D-Dimer level of 500 μg/L and above as positive, D-Dimer estimation has a sensitivity of 33.33%, specificity of 62.5%, positive predictive value of 14% and a negative predictive value of 83.33% for diagnosing LA thrombus Table 3. Assuming an arbitrary D-Dimer level of 500 μg/L and above as positive, D-Dimer estimation has a sensitivity of 53.8%, specificity of 83.7%, positive predictive value of 80% and a negative predictive value of 60% for diagnosing LA SEC (Table 4).

Receiver operating characteristics (ROC) curve was used to derive the optimal cut off value for diagnosing LA thrombus using D-Dimer levels. The area under the curve was .535 (Null hypothesis: true area = .5) which showed that there was no significant correlation between D-Dimer levels and presence or absence of LA thrombus. ROC curve was also used to derive the optimal cut-off value for diagnosing LA SEC using D-Dimer levels. The area under the curve was .761. The optimal cut off level of 393 μg/L was obtained from the ROC curve for diagnosing LA SEC from D-Dimer levels (Fig. 1). Based on this, D-Dimer level of 393 μg/L and above

Table 1
Baseline characteristics of patients with and without LA thrombus.

Variable	LA thrombus present (N = 15)	LA thrombus absent (N = 80)	p value
Age (years)	41.73	38.62	.314
Female Sex (%)	86.7%	75.0%	.326
Height (cm)	154.80 (5.833)	155.22 (8.977)	.861
Weight (kg)	54.40 (9.57)	51.96 (11.57)	.445
Functional Class	2.6 (.507)	2.356 (.47)	.073
Duration of symptoms (years)	8.267 (7.26)	8.624 (8.39)	.878
Pulse rate	88.47 (16.09)	76.62 (11.94)	.001
Mean BP (mm of Hg)	89.87 (7.87)	87.32 (6.852)	.201
AF (%)	80	21.2	<.005
LA diameter (cm)	49.6 (10.04)	45.8 (6.51)	.062
Ejection Fraction (%)	59.47 (5.50)	64.25 (8.04)	.03
2D MVA (cm^2)	.812 (.132)	.909 (.183)	.055
Peak Mitral valve gradient (mm of Hg)	22.87 (4.518)	24.54 (8.318)	.452
Mean Mitral valve gradient (mm of Hg)	14.07 (3.369)	14.74 (5.923)	.672
MR grade	1.367 (.611)	1.49 (.663)	.493
Aortic valve involvement (%)	33.3	42.5	.711
Tricuspid Valve involved (%)	26.7	42.5	.251
LA SEC present	86.7	48.8	.007

Data are expressed as mean ± SD, or percentage (%) of patients.
CMV – closed mitral valvotomy, BMV- balloon mitral valvotomy, AF- Atrial fibrillation, MVA-mitral valve area.

Table 2
Baseline characteristics of patients with and without LA SEC.

Variable	LA SEC present (N = 52)	LA SEC absent (N = 43)	P value
Age (years)	42.08 (10.87)	35.53 (9.97)	.003
Female Sex (%)	76.9	76.7	.984
Height (cm)	155.37 (8.41)	154.91 (8.76)	.796
Weight (kg)	52.46 (12.23)	52.21 (10.13)	.914
Functional Class	2.4 (.49)	2.38 (.47)	.841
Duration of symptoms (years)	8.60 (8.93)	8.52 (7.30)	.960
Pulse rate	81.25 (9.72)	75.16 (16.16)	.026
Mean BP (mm of Hg)	87.73 (6.66)	87.72 (7.55)	.995
AF (%)	40.4	18.6	.022
LA diameter (cm)	46.98 (7.27)	45.70 (7.25)	.394
Ejection Fraction (%)	63.23 (7.79)	63.81 (8.05)	.721
2D MVA (cm^2)	.895 (.193)	.892 (.164)	.927
Peak Mitral valve gradient (mm of Hg)	23.83 (7.982)	24.81 (7.738)	.545
Mean Mitral valve gradient (mm of Hg)	14.58 (5.425)	14.70 (5.485)	.917
MR grade	1.53 (.609)	1.39 (.703)	.291
Aortic valve involvement (%)	42.3	39.5	.53
Tricuspid Valve involved (%)	32.7	48.8	.11
LA thrombus present (%)	25	4.7	.007

Data are expressed as mean ± SD, or percentage (%) of patients.

was taken as positive and D-Dimer levels below 393 μg/L was taken as negative and a 2 × 2 table was plotted for calculating sensitivity, specificity, positive predictive value and negative predictive value of D-dimer in diagnosing LA SEC (Table 5). The optimal cut-off D-Dimer level of 393 μg/L for diagnosing LA SEC obtained a sensitivity of 63.4% (95% CI 53.5–73.3%), specificity of 83.72% (95% CI 76.15–91.29%), positive predictive value of 82.5% (95% CI 74.71–90.29%) and a negative predictive value of 65.45% (95% CI 55.7–75.2%) for diagnosing LA SEC.

4. Discussion

Cleavage of plasmin in clot yields a variety of fragments which are collectively called D-Dimers.[8] Various qualitative and quantifiable assays are available for D-dimer but the enzyme-linked immunosorbent assay (ELISA) methods are generally more sensitive than the latex agglutination techniques.[9]

LA SEC is caused by red blood cell (RBC) aggregation in the left atrium in low shear rate conditions. Reversible intercellular bridging,

Table 3
2 × 2 table created for patients with and without LA thrombus taking a D dimer value of 500 μg/L as positive.

	LA thrombus present (n = 15)	LA thrombus absent (n = 80)
D Dimer + ve (500 μg/L and above)	5	30
D Dimer −ve (Below 500 μg/L)	10	50

Table 4
2 × 2 table created for patients with and without LA SEC taking a D dimer value of 500 μg/L as positive.

	LA SEC present (n = 52)	LA SEC absent (n = 43)
D Dimer + ve (500 μg/L and above)	28	7
D Dimer −ve (Below 500 μg/L)	24	36

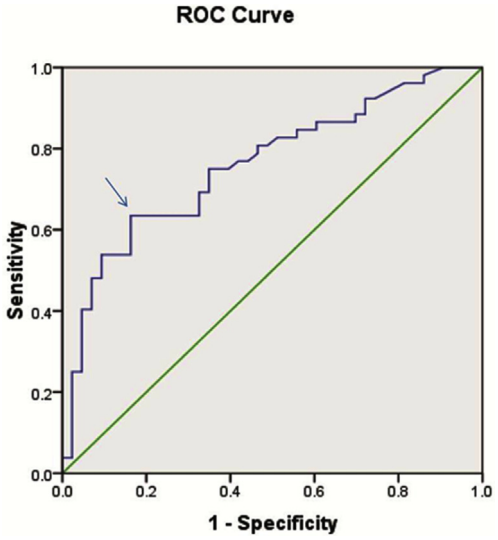

Fig. 1. The optimal cut off level of 393 μg/L was obtained from the ROC curve for diagnosing LA SEC from D-Dimer levels.

Table 5
v2 x 2 table created for patients with and without LA SEC taking a D dimer value of 393 μg/L as positive.

	LA SEC present (n = 52)	LA SEC absent (n = 43)
D Dimer + ve	33	7
D Dimer -ve	19	36

principally by fibrinogen, reduces electrostatic repulsion between RBCs by increasing the intracellular distance.[10,11] RBC aggregation appears to be a precursor to thrombosis as LA thrombi are rich in fibrin and RBCs, bearing more resemblance to venous than arterial thrombi. A transition stage in the development of a fibrin-rich red thrombus may be indicated by dense SEC while the frame-work for subsequent thrombus formation is set by the network of red cells and fibrinogen.[12] The bigger size of red cell aggregates than single cells increases the amplitude of back scattered ultrasonic signals and produces SEC.[13]

In our study, about 15 (15.8%) patients had LA thrombus detected by TEE. Previous studies have reported an incidence of 18%–23% of LA thrombus in patients with mitral stenosis.[14] TEE can be considered the gold standard for diagnosing LA thrombus. Manning et al analysed 231 consecutive patients having TEE before elective repair or replacement of the mitral valve or excision of a left atrial tumour. In their study, TEE had a sensitivity of 100% [95% CI, 74%–100%], specificity of 99% [CI, 97%–99.9%], positive predictive value of 86% and negative predictive value of 100% for a population that had a 5.2% prevalence of thrombi.[3]

The role of D-Dimer together with TEE was evaluated in this study to predict LA thrombus and LA SEC. Our results demonstrated that D-Dimer levels were not predictive of the presence or absence of LA thrombus with a mean D-Dimer level of 520 ± 442 μg/L and 565 ± 760 μg/L (p = .826) respectively. This can be explained by the following 2 reasons (1) the age of the clot and (2) oral anticoagulation. The LA thrombi detected by TEE in our patients might have formed few weeks or months prior to TEE and as the clot ages, the level of D-Dimer which indicates active thrombosis and fibrinolysis also decrease. D′ Angelo assessed the D-Dimer levels in patients with deep vein thrombosis (DVT) and found that values were considerably lower in patients who presented 7 days after the onset of symptoms as compared to patients who presented within 3 days.[4] Even though some of these patients were on anticoagulation, Sie et al had shown that the D-Dimer levels had come down to baseline levels 3 months after a DVT in patients who had stopped anticoagulation.[15] Most of the patients with LA thrombus had AF and were on oral anticoagulation which can lower the D - Dimer levels in peripheral venous blood. This fact is evident in our data also as patients with LA SEC in AF and on oral anticoagulation had significantly lower D-Dimer levels as compared to patients with LA SEC in sinus rhythm.

Khalid Abd El Salam et al had published their data on the prognostic value of mitral annular TDI systolic velocity and D-dimer for the detection of left atrial appendage (LAA) thrombus in patients with MS in sinus rhythm (SR). Fifteen patients (16.48%) had LAA thrombi. Patients with LA thrombus showed predominantly higher D-dimer levels (965.67 ± 570.27 μg/L vs. 261.20 ± 193.80 μg/L, P < .0001). ROC analysis yielded an optimal D-dimer cut-off level of 423.25 μg/L for prediction of LAA thrombi with a sensitivity of 85.7%, a specificity of 92.1%, a positive predictive value of 66.7% and a negative predictive value of 95.9%.[16]This data is contradictory to our data. However, our study is different in that (1) a different D-Dimer assay was used (ELISA), (2) the exclusion criteria were more stringent, and (3) patients with AF were also included.

D-Dimer levels were compared in patients with and without LA SEC and it was much higher in patients with LA SEC (776 ± 866 μg/L vs. 294 ± 331 μg/L, p = .001). Fibrinogen, associated with LA SEC, is intimately involved in blood coagulation and platelet aggregation.[17] Our study reveals the fact that LA SEC is actively associated with ongoing thrombosis and fibrinolysis in the LA, with the network of erythrocytes and fibrinogen forming a basis for thrombus formation in LA and subsequent systemic embolism. LA SEC reflected not only blood stasis but also altered blood characteristics, thus reflecting two arms of Virchow's triad of factors relating to thrombus formation.[2] The stroke or other embolic event rate was 12% per year in-patients with baseline LA SEC and 3% per year in patients without LA SEC (P = .002).[18]

AF was more common in patients with LA thrombus than in patients without LA thrombus (80% vs. 21.2%, p < .005) which accounts for the higher pulse rate and lower ejection fraction in this group. AF is connected to increased risk of LA thrombus and systemic embolism in mitral stenosis with an 8% incidence of systemic embolism in MS patients with sinus rhythm as compared to 31.5% in MS patients in AF.[19]The higher rate of AF in patients with LA thrombus has been reported in previous studies.[20]

Atrial fibrillation was more common in patients with LA SEC as compared to patients without LA SEC (40.4% vs. 18.6%, p = .022). Previous studies had reported that LA SEC in MS patients was associated with larger LA size, smaller mitral valve area, higher mitral valve gradient and absence of significant MR.[18,21,22] Our analysis did not reveal any significant association between these parameters and LA SEC as our sample was biased in that it included only symptomatic patients planned for BMV. Daniel et al who studied a similar subset of patients as ours showed that LA SEC was significantly associated with LA diameter but unrelated to mitral valve gradient and mitral valve area.[23]

Majority of studies based on D-Dimer levels for diagnosing DVT and pulmonary embolism have used a cut-off level of 500 μg/L.[5] Using this value, D-Dimer had 100% sensitivity and 100% negative predictive value for diagnosing these thrombotic events.[4] We used the same cut-off level and it revealed that D-Dimer estimation has a sensitivity of 33.33%, specificity of 62.5%, positive predictive value of 14% and a negative predictive value of 83.33% for diagnosing LA thrombus. The optimal cut-off level computed from the ROC curve was used to diagnose LA thrombus using D-Dimer level. The area under the curve was .535 (Null hypothesis: true area = .5) which showed that there was no relevant correlation between D-Dimer levels and existence of LA thrombus.

Our study is one of the first of its kind to assess the significant relation between LA SEC and D-Dimer levels. Assuming an arbitrary D-Dimer levels of 500 μg/Land above as positive, D-Dimer estimation has a sensitivity of 53.8%, specificity of 83.7%, positive predictive value of 80% and a negative predictive value of 60% on diagnosing LA SEC. ROC curve was also used to derive the optimal cut off value for diagnosing LA SEC using D-Dimer levels. The area under the curve was .761. The optimal cut off value of 393 μg/L was obtained from the ROC curve for diagnosing LA SEC from D-Dimer levels (Fig. 1). Based on this, D-Dimer levels of 393 μg/L and above was taken as positive and D-Dimer levels below 393 μg/L was taken as negative and a 2 × 2 table was plotted for calculating sensitivity, specificity, positive predictive value and negative predictive value of D-dimer in diagnosing LA SEC (Table 5). The optimal cut-off D-Dimer level of 393 μg/L for diagnosing LA SEC obtained a sensitivity of 63.4%, specificity of 83.72%, positive predictive value of 82.5% and a negative predictive value of 65.45% for diagnosing LA SEC. The high specificity and positive predictive value highlights the fact that a D-Dimer levels higher than 400 μg/L in a patient with rheumatic MS points to the highly thrombogenic milieu in the LA with related risk of stroke and systemic embolism.

Nozawa et al, concluded that in non-valvar AF (NVAF) patients, while thromboembolic risk in patients without the clinical risk factors was quite low (.7%/year) when D-dimer was <150 ng/ml, the risk was considerably higher (3.8%/year) when D-dimer was 150 ng/ml. They concluded that D-dimer level consolidated with clinical risk factors were compelling predictors of subsequent thromboembolic events in patients with NVAF.[24] Higher D-dimer levels are vitally associated with both thromboembolic events in AF patients treated with warfarin25. Sadanandan et al, studied LA SEC in 24 patients in sinus rhythm.There was a higher prevalence of cerebrovascular accident (CVA) in patients with SEC in comparison to controls with no SEC (83% versus 56%, p = .02).[14] The above two studies highlight the need for aggressive anticoagulation in patients with higher D-Dimer levels and presence of LA SEC.

5. Limitations of the study

This study had few limitations. First, it was a single centre study with the sample size of patients having LA thrombus being small. This may have failed to show any significant association between LA thrombus and the variables analysed. Second, the sample population studied was not a true representation of the patients with rheumatic MS in the community and was biased by the fact that only symptomatic patients with significant mitral stenosis planned for BMV were included in the study. This may explain the lack of association of LA thrombus and LA SEC with various variables which had shown a significant association in the previous studies. Thirdly, concomitant oral anticoagulation must have influenced D dimer levels. Finally, D-dimer level was checked only once and not repeated which might have influenced the outcome.

6. Conclusions

Our study revealed that D-dimer levels had no dominant association with the existence of LA thrombus in patients with rheumatic severe mitral stenosis. Patients with LA thrombus may have low D-Dimer levels based on the fact that the LA thrombus might have formed few weeks or months prior to TEE and these patients may be on optimal oral anticoagulation. Thus D-Dimer levels cannot be used to classify patients planned for BMV prior to TEE. This study revealed significant association of D-Dimer with LA SEC which explains the highly thrombogenic nature of LA SEC and the need for optimal anticoagulation of these patients to prevent LA thrombus and systemic thromboembolism even if they are in sinus rhythm. ROC curve analysis illustrated the most favorable D-Dimer cut-off level of 393 μg/L for diagnosing LA SEC. Based on this, if a D-Dimer level of 400 μg/L or higher is taken as positive, it has high specificity and positive predictive value for diagnosing LA SEC and such patients have to be optimally anticoagulated and closely followed up. Further prospective controlled studies can be undertaken and patients can be followed up for several years to detect the higher extent of systemic embolism in those rheumatic patients with higher D-Dimer levels.

Declaration of Competing Interest

All authors have none to declare.

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