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The Value of D-Dimer Blood Concentrations in Prediction of Presence of Left Atrial Thrombus in Patients with non-valvular Atrial Fibrillation

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Abstract

Background: Atrial fibrillation (AF) is the most typical sustained cardiac disturbance all over the world, it increases the risk of left atrial (LA) thrombus, Plasma fibrin D-dimers seems to be a helpful parameter for assessing the degrees of hypercoagulability. Higher risk of recurrent ischemic stroke was found to be associated with baseline elevated D-dimers levels. **Aim:** To assess the value of D-Dimer examination in prediction of presence of LA thrombus in patients with AF instead of transesophageal echocardiography (TEE) examination. **Patients and Methods:** Analytical cross-sectional study was conducted. It included 250 patients divided according to presence of LA thrombus into two groups; group without LA thrombus (n=224), and group with LA thrombus (n=26), referred to cardiology department, Mansoura Specialized Medicine Hospital. History was taken, blood was collected for D-dimer testing on the same day of the TEE. **Results:** CHADS2-VASc, Heart failure, Diastolic dysfunction, D-dimers (ng/mL), D Dimer more than 500 ng/mL, and D Dimer more than 10×patient's age have positive and statistically significant impact on LA thrombus formation. Similarly, Paroxysmal AF and left ventricle ejection fraction (%) had negative and statistically significant impact on LA thrombus formation. The optimal cutoff point of D-dimers was 1247.9 (ng/mL), its accuracy was 86.4%, (AUC = 0.711) with sensitivity (50%) and specificity (90.6%). **Conclusion:** D-dimer can be beneficial in clinical practice to exclude LA thrombus avoiding TEE, particularly in patients with low thromboembolic risk such as normal left atrial dimensions, no previous attacks of AF, no valvular heart disease, female patient, CHAD2VASC score less than 2 and no history of thromboembolic attacks.

Introduction

Atrial fibrillation (AF) is that the most typical sustained cardiac disturbance all over the world ⁽¹⁾. It is an electrocardiographic documentation of irregular RR intervals and not noticeable, distinct P waves lasting for at least 30 s ⁽²⁾. It is the most common cause responsible for supraventricular arrhythmia and one of the main causes of cardioembolic stroke (3). As, it increases the risk of left atrial thrombus (LAT), and is the main source of emboli (>90%) in patients with nonvalvular AF ⁽⁴⁾.

Thrombus is formed due to the disorganized atrial electrical activity, this results in an ineffective contraction and blood stasis, especially in the left atrial appendage ⁽⁵⁾, which is the main source of thrombus in patients with valvular and nonvalvular AF. The other two components of Virchow's triad for thrombogenesis (endocardial injury and hypercoagulability) also play an important role in the thrombus formation, which finally lead to a prothrombotic state in AF ⁽⁶⁾.

Cardioembolic stroke is one of the most significant complications of AF because it can result in increasing morbidity, mortality and disability rates ⁽⁷⁾.

In AF patients, electrical cardioversion has proven to be the most rapid and effective method to restore sinus rhythm back to normal ⁽⁸⁾. Because of the potentiality of thrombus presence in the left atrium (LA) in those patients, cardioversion has high thromboembolic risk, which can extended up to ten days post cardioversion. So, prior to cardioversion, efficient anticoagulation therapy for a minimum of three weeks or transesophageal echocardiography (TEE) are necessary to

minimize the thromboembolic risk in AF lasting for >48 hours ⁽⁸⁾.

Pre cardioversion TEE is a sensitive approach for detecting intracardiac thrombus ⁽⁵⁾, which usually originates in the left atrial appendage, visualization of LA thrombus is estimated to range between 8.5% and 12% ⁽⁹⁾.

Although, TEE is a semi-invasive technique, it has several disadvantages and risks to the patient, as it depends on the operator, potentially incurs esophageal lesions, and can result in transmission of infectious disease by droplets and aerosols can occur ⁽¹⁰⁾.

Though, there's no identified laboratory test that help the diagnosing of left atrial thrombus (LAT), Plasma fibrin D-dimers seems to be a helpful parameter for assessing the degrees of hypercoagulability. They can be considered as biological markers of coagulation activation and fibrinolysis, and their presence might indicate thromboembolic phenomena, such as pulmonary embolism (PE), DVT, acute coronary syndrome or aortic dissection ⁽¹¹⁾.

Because the D-dimer is derived from the cleavage of cross-linked fibrin reflecting both thrombin production and activation of fibrinolysis, its elevated levels may occur in all diseases that included an activation of the coagulation system such as the inflammatory diseases, cancers or ischemic cardiovascular diseases ⁽¹²⁾.

Higher risk of recurrent ischemic stroke was found to be associated with baseline elevated d-dimers levels ($\geq 2 \mu\text{g/mL}$) in patients with AF ⁽¹³⁾. Some studies have shown that raised d-dimer levels are considered to be an independent predictor of the presence of left atrial thrombus in patients with AF ⁽¹⁴⁾.

Levels of D-dimer are increasing with age, thereby decreasing the specificity (Sp) of cut-off values, especially if the patients are over 60 years of age⁽¹⁵⁾. Two D-dimer cut-offs are usually defined, the fixed standard D-dimer value of 500 ng/mL, DD500; and age-adjusted D-dimer value defined as 10 times the patient's age, DDAge⁽⁴⁾.

The association between D-dimer levels, age-adjusted D-dimer and the absence of LA thrombus has not yet been investigated. So, our study aims to evaluate the diagnostic ability of D-dimer cut-off values to exclude the presence of LA thrombus in patients with AF and to reduce the number of TEE examinations showing absence of LA thrombus by presenting the D-dimers as a useful predictive factor.

PATIENTS AND METHODS

• Study setting and Study population

This study was carried out in the cardiology department at Mansoura Specialized Medicine Hospital, included 250 patients with non-valvular AF were enrolled in the study from January 2022 till March 2022.

Inclusion criteria

Patients with non-valvular AF or flutter.

Exclusion criteria

- 1- Age below 18 years or above 90 years,
- 2- Moderate and severe valvular heart disease,
- 3- Valvular mechanical prostheses,
- 4- Aortic aneurysm or dissection,
- 5- Presence of ventricular thrombus,
- 6- Pregnancy,
- 7- Active neoplasia, inflammatory disease,
- 8- Recent surgery, stroke, deep venous thrombosis or PE.

• Study design

An analytical cross-sectional study design was carried out in cardiology department at Mansoura medical specialized hospital, 250 consecutive patients with non-valvular AF were enrolled in the study, they were divided in the analysis into two groups according to presence of LA thrombus, the first group without LA thrombus (n=224), and the second group with LA thrombus (n=26).

• Sample Size Justification

Sample size was calculated using Power Analysis and Sample Size software program (PASS) version 15.0.5 for windows (2017) using data published by D. Almorad et al (2021) with the ability of D-dimer blood concentrations to exclude left atrial thrombus in patients with atrial fibrillation as the primary outcome.

The null hypothesis was considered as the inability of D-dimer blood concentrations to exclude left atrial thrombus in patients with atrial fibrillation.

Almorad et al reported the area under the ROC curve to be 0.96 with incidence of left atrial thrombus 9.2%. A sample size of 250 patients is needed to achieve 80% power ($1-\beta$ or the probability of rejecting the null hypothesis when it is false) in the proposed study using an F test with a significance level (α or the probability of rejecting the null hypothesis when it is true) of 5%⁽¹⁴⁾. The ratio between the two groups was: 1 diseased to 10 controls.

• Data collection tool

- ◆ All the studied participants were subjected to:
 - History taking: Patient data, including baseline demographic characteristics (age and sex), medical history (hypertension, diabetes mellitus, coronary

heart disease, myocardial infarction, paroxysmal or persistent AF, prior stroke or transient ischemic attack (TIA), anticoagulant use prior to reference TEE and its type, time between AF attack and cardioversion.

- Blood was collected for D-dimer testing on the same day of the TEE.

- A follow-up visit was scheduled 1 month after cardioversion and included a clinical examination and an ECG.

D-dimer testing

First, the blood samples were collected in sodium citrate tubes within 24 hours before TEE and processed to the lab.

Then, the assay is based on a rapid ELISA, whereby latex microspheres are coated with two anti-D- dimer monoclonal antibodies. The presence of D-dimer in the samples causes an agglutination of the microparticles, which lead to increasing the turbidity in the reaction mixture.

D-dimer levels were assessed using the STAÒ analyzer range (Diagnostica Stago; Asnières, France), and expressed in ng/mL unit. According to the manufacturers' instructions, the standard ELISA cut-off value was 500 ng/mL.

Age-adjusted D-dimer values are used as part of an algorithm to exclude PE ⁽³³⁾, two D-dimer cut-offs were demarcated, the fixed standard D-dimer value of more than 500 ng/mL, and age-adjusted D-dimer value was defined to be 10 times the patient's age.

Transesophageal echography

All TEE were performed only according to the ESC guidelines to exclude LA before cardioversion, as; anticoagulation duration shorter than 3 weeks at the time of cardioversion, a time in therapeutic range of <70% in patients receiving

vitamin K antagonists and no anticoagulation with undetermined onset of arrhythmia ⁽⁸⁾.

TEE was performed either under local anesthesia or mild sedation and with continuous monitoring of blood pressure and oximetry. A 5–7 MHz multiplane probe was used; the images were assessed by two experienced echocardiographers independently.

All TEE operators and assessors were blinded to the D-dimer values of the patients. Images were taken in multiple standard tomographic planes. LA thrombus was determined as a local, uniform, ultrasound-dense, multiplane intracavitary structure discrete from the LA wall or its appendage pectinate muscle.

Statistical analysis

IBM's SPSS statistics (Statistical Package for the Social Sciences) for windows (version 26) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution.

Normally distributed continuous variables were expressed as mean \pm SD while categorical variables and the abnormally distributed continuous ones was expressed as median and inter-quartile range or number and percentage (as appropriate).

Student t test and Mann-Whitney was used for normally and abnormally distributed continuous data respectively. Chi square test was used for categorical data using the crosstabs function. All tests were conducted with 95% confidence interval.

If needed, bivariate correlations were assessed using Pearson's or Spearman's correlation coefficient depending on the nature of

data. P (probability) value < 0.05 was considered statistically significant.

RESULTS

Two hundred and fifty patients were included in this study, they were divided according to presence of LA thrombus into two groups, the first group without LA thrombus ($n=224$), and the second group with LA thrombus ($n=26$).

I. Characteristics and history of the studied participants

Table (1) shows patient characteristics and history of the studied patients divided according to presence of LA thrombus, there was statistically significant difference between the two groups only regarding paroxysmal AF ($p = 0.001$).

II. Echo and clinical examination findings of the studied participants.

Table (2) shows the Echo and clinical examination findings of the studied participants. There was statistically significant difference between the two studied groups regarding LVEF (%) ($p = < 0.001$), CHADS2-VASc ($p = 0.047$), Heart failure ($p = < 0.001$), and Diastolic dysfunction ($p = < 0.001$)

III. D-dimer and its calculated derivatives of the studied patients.

Table 3 shows that there was statistically significant difference between the two studied groups regarding D-dimers (ng/mL) ($p = 0.020$), D Dimer more than 500 ng/mL ($p = 0.001$), D Dimer more than $10 \times$ patient's age ($p = < 0.001$), and Diastolic dysfunction ($p = 0.001$).

IV. Risk factors of LA thrombus formation.

Table 4 shows univariate regression analysis of risk factors of LA thrombus formation, CHADS2-VASc, Heart failure, Diastolic dysfunction, D-dimers (ng/mL), D Dimer more than 500 ng/mL, and D Dimer more than $10 \times$ patient's age have positive and statistically significant impact on LA thrombus formation. Similarly, Paroxysmal AF and LVEF (%) had negative and statistically significant impact on LA thrombus formation. We used the beta coefficient for each 1 unit increase in D-dimer.

V. Diagnostic profile of D-dimer and its calculated derivatives for diagnosis of LA thrombus presence.

Table 5 and figure 1, show the diagnostic profile of D-dimer in diagnosis of LA thrombus presence the optimal cutoff point of D-dimers was 1247.9 (ng/mL), its accuracy was 86.4%, (AUC = 0.711) with sensitivity (50%) and specificity (90.6%).

When the D Dimer was more than 500 ng/mL, the accuracy was founded to be 56.4% with sensitivity (23.8%) and specificity (100%). In case of D Dimer more than $10 \times$ patient's age, the accuracy was 70 % with sensitivity (31.2%) and specificity (100%). The discrepancy between the PPV of the generated cut off point and the other pre-specified cut points (i.e >500 or age adjusted) can be explained that in the current study, about 21 patients of No LA thrombus group had higher levels of D dimer than the proposed cut off points ranging between 1348 and 2120. These cases accounted for a fair number of false positive cases hence the low PPV. The receiver operating characteristic (ROC) curve is the plot the trade-off between the sensitivity and (1-specificity) across a

series of cut-off points when the diagnostic test is continuous or on an ordinal scale (minimum five categories). So there is no value for generating curves for pre-specified cut-off (I.e, 500), in this case likelihood ratio is used to describe the

accuracy. In fact, cross-tabulation of data was used for calculation of the diagnostic profile parameters while ROC curve was used merely for calculation of AUC and visual demonstration.

Table (1) Patient characteristics and history of the studied patients divided according to presence of LA thrombus:

		No LA thrombus (n= 224)	LA thrombus (n= 26)	P
Age (years)		59.83 ± 7.538	60.19 ± 8.348	0.812
Gender	Male	62.1% (139)	42.3% (11)	0.52
	Female	37.9% (85)	57.7% (15)	
Paroxysmal AF		53.1% (119)	19.2% (5)	0.001
Diabetes		24.1% (54)	7.7% (2)	0.057
Vascular disease		12.9% (29)	19.2% (5)	0.376
History of stroke		4.5% (10)	11.5% (3)	0.124
History of thromboembolic events		1.3% (3)	3.8% (1)	0.335
Antiarrhythmic drugs		18.3% (41)	26.9% (7)	0.291
Beta-blockers		50.4% (113)	42.3% (11)	0.432
Novel oral anticoagulant		39.7% (89)	42.3% (11)	0.800
Vitamin K antagonists		12.1% (27)	11.5% (3)	0.939
Data is expressed as mean and standard deviation or as percentage and frequency. P is significant when < 0.05.				

Table (2) Echo and clinical examination findings of the studied patients divided according to presence of LA thrombus:

	No LA thrombus (n= 224)	LA thrombus (n= 26)	P
LVEF (%)	61.62 ± 5.370	52.12 ± 8.199	< 0.001
LA diameter (mm)	44.78 ± 8.049	46.08 ± 6.945	0.278
CHADS2-VASc	1.96 ± 1.122	2.50 ± 1.304	0.047
Heart failure	20.1% (45)	57.7% (15)	< 0.001
Diastolic dysfunction	19.2% (43)	53.8% (14)	< 0.001
Ischemic cardiomyopathy	21.4% (48)	23.1% (6)	0.847
Arterial hypertension	67.4% (151)	57.7% (15)	0.321
Mitral regurgitation	6.7% (15)	7.7% (2)	0.849
Aortic stenosis	3.1% (7)	3.8% (1)	0.843
Data is expressed as mean and standard deviation or as percentage and frequency. P is significant when < 0.05.			

Table (3) D-dimer and its calculated derivatives of the studied patients divided according to presence of LA thrombus:

	No LA thrombus (n= 224)	LA thrombus (n= 26)	P
D-dimers (ng/mL)	614.7 ± 452.3	1236.2 ± 1042.6	0.020
D Dimer more than 500 ng/mL	53.6% (120)	88.5% (23)	0.001
D Dimer more than 10×patient's age	40.2% (90)	73.1% (19)	0.001
Data is expressed as mean and standard deviation or as percentage and frequency. P is significant when < 0.05.			

Table (4) Univariate regression analysis of risk factors of LA thrombus formation:

	B	P
Paroxysmal AF	-1.560	0.002
LVEF (%)	-0.296	< 0.001
CHADS2-VASc	0.371	0.026
Heart failure	1.691	< 0.001
Diastolic dysfunction	1.591	< 0.001
D-dimers (ng/mL)	0.002	< 0.001
D Dimer more than 500 ng/mL	1.894	0.003
D Dimer more than 10×patient’s age	1.397	0.003
P is significant when < 0.05.		

Table (5) Diagnostic profile of D-dimer and its calculated derivatives for diagnosis of LA thrombus presence:

	D-dimers (ng/mL)	D Dimer more than 500 ng/mL	D Dimer more than 10×patient’s age
AUC (95% CI)	0.711 (0.584, 0.839)	0.674 (0.580, 0.769)	0.664 (0.558, 0.771)
P	< 0.001	0.004	0.006
Cut off point	1247.9	-	-
Youden's index	0.41	-	-
Sensitivity	50.0%	88.5%	73.1%
Specificity	90.6%	16.1%	59.8%
PPV	38.2%	46.4%	17.4%
NPV	94.0%	97.2%	95.0%
Accuracy	86.4%	50.8%	61.2%
Positive likelihood	5.33	1.65	1.82
Negative likelihood	0.55	0.25	0.45
P is significant when < 0.05.			

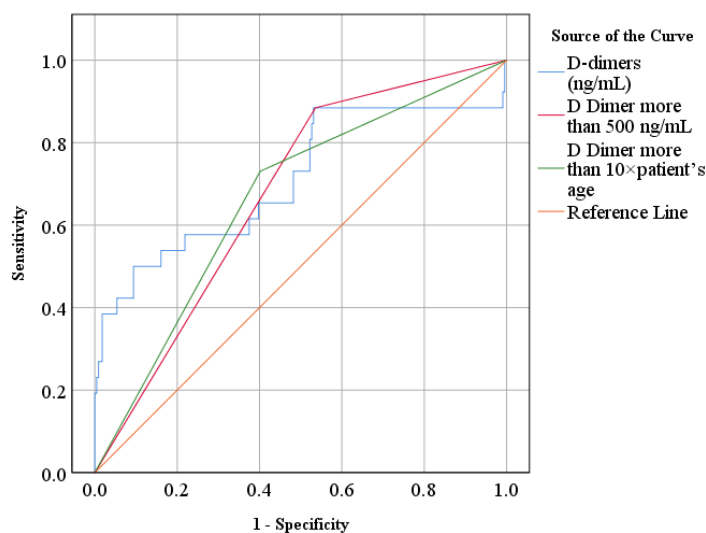


Figure (1) ROC curve of D-dimer and its calculated derivatives for diagnosis of LA thrombus presence.

DISCUSSION

Patients with AF have more risk of thromboembolism and higher D-dimer levels than the patients with sinus rhythm. The

pathophysiology of thrombosis is clarified by the alterations in the Virchow’s triad which consists of blood flow, vascular endothelial injury and hypercoagulability state⁽¹⁶⁾.

Due to LA appendage stasis, the blood flow is interrupted in AF patients. This results in localization of AF-associated intracardiac thrombi in this region in about ninety percent of patients⁽¹⁷⁾. The state of LA fibrosis which results from prolonged fibrillatory activity can lead to LA dilatation and dysfunction, which is accompanying with increased the risk of thromboembolic occurrence⁽¹⁸⁾. Also, AF is implicated with a hypercoagulability state⁽¹⁹⁾.

TEE should be performed before cardioversion in order to help in assessing the existence of LA thrombus⁽⁸⁾. TEE examinations can give positive results from 8.5% to 12% in detection of the presence of LA thrombus prior to cardioversion for AF⁽¹⁴⁾.

In our study the diagnostic ability of D-dimer cut-off values was evaluated to exclude the presence of LA thrombus in patients with AF, we included 250 patients with non-valvular AF. The study population was divided into two groups in the analysis, group without LA thrombus (n=224), and the other group with LA thrombus (n=26) in cardiology department at Mansoura medical specialized hospital.

We aimed to reduce the number of TEE showing absence of LA thrombus by providing the D-dimers as a valuable predictive factor. Similar to current literature, our results show elevated D-dimer levels in patients with AF, suggesting it as a strong discriminant between patient with and without LA thrombus⁽²⁰⁾.

We have considered that a D-dimer-based strategy is an effective and safe to decide the need for TEE to rule out LAT in selected patients with AF, especially those with a low risk of thromboembolism, as the negative predictive value

may be even theoretically higher. This approach actually will reduce the number of TEE examination before cardioversion and cardiac ablation by using a noninvasive biomarker⁽¹⁾.

Previous various studies suggested fixed D-dimer cut-offs either alone or with other parameters to exclude the presence of LA thrombus, with values are variable between 270 and >1000 ng/mL^(21, 22). However, choosing one certain value from these studies is challenging due to the lack of specificity of D-Dimers and their weak specificity and/or PPVs.

In this study, D-dimers are strongly associated with the presence of LA thrombus, showing significantly different values between groups. ROC curve analysis confirmed high D-dimer values to be strongly predictive of the presence of LA thrombus. These findings are also in accordance with previous reports⁽²¹⁾.

Our results showed that a D-dimer cut-off value 1247.9 is highly efficient in excluding LA thrombus, as the ROC analysis revealed the accuracy of D-dimer values to predict the presence of LA thrombus (AUC = 0.711), corresponds to a Se of 50 % and a Sp of 90.6% for the prediction of LA thrombus.

Increased D-dimer levels were associated with the presence of LA thrombus, which recommended that it is a strong discriminant between patient with and without LA thrombus^(20,21), in addition to the CHA2DS2-VASc score, Heart failure, Diastolic dysfunction, LVEF and non-paroxysmal AF.

This value is near to Habara et al where best cut-off was established at 1150 ng/mL with Se/Sp (76%/73%) and NPV of 100%⁽²¹⁾, also close to Almorad et al study, which results show

elevated D-dimer levels in patients with LA thrombus than without LA thrombus, as the ROC analysis revealed the accuracy of high D-dimer values to predict the presence of LA thrombus (AUC= 0.96). A value of 1344 ng/mL corresponds to a Se of 100% and a Sp of 86% for the prediction of LA thrombus⁽¹⁴⁾.

And, similar to previous studies which assessed D-dimer at 500 ng/mL^(21, 22,23,24) in which the estimates of sensitivity ranged from 12% to 92% and of specificity ranged from 65% to 99%. The AUC was 0.81. Based on a prevalence of LAT of 10% in patients with AF⁽²⁵⁾, the positive predictive value and negative predictive value were 31.6% and 94.1%, respectively.

In Meta-analysis of previous studies, regarding the D-dimer at the optimal cutoff^(21,22, 23,24) The pooled sensitivity and specificity of D dimer at 500 ng/mL to detect LAT in patients with valvular and nonvalvular AF were founded to be 50% and 88%, respectively. The optimum cutoff of D-dimer was 390 ng/mL with a pooled sensitivity and specificity of 68% and 73%, respectively. The negative predictive value of D-dimer was high via different cutoffs (390 and 500 ng/mL) and age-adjusted D dimer. Numerous cutoff points of D-dimer have been previously evaluated to predict LAT, resulting in diverse diagnostic accuracies.

The collective optimal cutoff of D-dimer was founded to be 390 ng/mL with a high negative predictive value of 95.4% to dismiss the presence of thrombus. Likewise, D-dimer at 500 ng/mL, which is the threshold mostly recommended to exclude acute pulmonary embolism in patients with low or intermediate pretest probability, showed a high negative predictive value (94.1%).

It is not clear if that the negative predictive value of 95% is high enough for D-dimer to be used in clinical practice to exclude LAT in patients with AF, as this decision must be modified according to the clinical context of each patient.

The use of age-adjusted D-dimer has been suggested as an alternative test to the fixed cutoff of D-dimer because the plasma levels of D-dimer are increasing with age. The validity of this test has been demonstrated in previous studies to exclude acute pulmonary embolism in patients with a low or intermediate low pretest probability⁽²⁶⁾.

Our study results have founded that, D-Dimer more than 500 ng/mL (AUC = 0.674), the sensitivity was 23.8 % and the specificity was 100%. Age-adjusted D-dimer was assessed, (AUC =0.664), the sensitivity was 31.2% and the specificity was 100%.

In two previous studies that assessed age-adjusted D-dimer^(14,27), the sensitivity was 24% and 52% and the specificity was 99% and 99%. The pooled sensitivity and specificity were 36% (95% CI 14%–66%) and 99% (95% CI 96%–99%), respectively. The AUC was 0.99. depending on the prevalence of LAT of 10% in patients with AF⁽²⁵⁾, the positive predictive value and negative predictive value were 80% and 93.3%, respectively.

There are many clinical characteristics (such as CHA2DS2-VASc score, type of AF, previous stroke, anticoagulation, and mitral stenosis) that can impact the existence of LAT in patients with AF⁽⁵⁾.

In the present study, with the mean CHA2DS2-VASc score among patients with LA thrombus (2.50 ± 1.304) was statistically

significantly higher than among patients without LA thrombus (1.96 ± 1.122) ($p=0.047$).

Similar to Almorad et al study, in which 109 patients (76.7%) had an elevated CHA2DS2-VASc score (≥ 2), of which 12 were diagnosed with LA thrombus by TEE, the difference in CHA2DS2-VASc score between patients with and without LA thrombus was founded to be significant ($p<0.05$)⁽¹⁴⁾.

Also, in accordance with previous findings that showing a relationship between the a priori estimation of thromboembolic risk through CHA2DS2-VASc score and the actual presence of LA thrombus⁽²⁸⁾.

Our study results revealed that LVEF (%) had negative and statistically significant impact on LA thrombus formation. This is similar to Almorad et al study, in which low LVEF was significantly more frequent in patients with LA thrombus⁽¹⁴⁾, also consistent with the presence of heart failure in the calculation of the CHA2DS2-VASc score⁽²⁹⁾.

In our study, paroxysmal AF had negative and statistically significant impact on LA thrombus formation, similar to Almorad et al study results which showed that non-paroxysmal patients with AF had higher risk of LA thrombus⁽¹⁴⁾.

In our study, regarding receiving anticoagulation therapy, there was no statistically significant difference between the two groups, this was in concordance with Almorad et al study⁽¹⁴⁾ in which of the 83 patients receiving anticoagulation therapy, five had a LA thrombus ; however, the difference with patients without LA thrombus was found to be not significant.

In previous meta analyses, the negative predictive value stills high across subgroups

(current use of anticoagulation, history of stroke, and paroxysmal AF) and could potentially be useful within each subgroup⁽¹⁾.

A previously published meta-analysis has reported that cardiac computed tomography has a high diagnostic accuracy for excluding the presence of LAT in patients with AF with a negative predictive value of 99%⁽³⁰⁾. However, the decision of which noninvasive test (D-dimer or cardiac computed tomography) is better needs studies that compare both tests directly, since the comparison of the pooled negative predictive values (95% vs 99%), as a result of combining different sets of studies, is not suitable.

Cardiac computed tomography has noteworthy disadvantages when compared with D-dimer, such as the cost is higher, it requires contrast material, and the exposure to ionizing radiation can be significantly high⁽³¹⁾.

Our study has some limitations, such as; the rapid ELISA test was used to measure D-dimer levels. However, with high Sensitivity and negative predictive value levels, the rapid ELISA test can be one of the most greater performing diagnostic tools available for D-dimer testing. Nevertheless; data, conclusions and the cut-off values cannot be extrapolated to techniques other than ELISA.

Also, many clinical limitations have been included, these clinical situations can affect D-dimers upwards, which does not impact the NPVs of the selected thresholds and thus their safety.

Another limitation of our study is the limited number of patients who included. A larger number of patients can allow a better definition of the best cut-off value of D-dimers to measure the risk of LA thrombus occurrence. However, the

lack of specificity will always hinder the interpretation of their value.

Our study recommendations are that prospective studies with larger samples assessing the optimal clinical scenario in which D-dimer works best to exclude LAT are still needed, and whether D-dimer should be used alone or in combination with other clinical parameters (such as CHA2DS2-VASc score, type of AF, previous stroke, anticoagulation, and mitral stenosis) remains unknown and needs to be further explored.

CONCLUSION

Our study helps to determine the efficacy of D-dimer cut-off to exclude the presence of a LA thrombus in patients with AF. The plasma levels of D-dimer were higher in patients with AF and LAT than in patients without thrombus.

The optimal cutoff D-dimer was 1247.9 ng/mL with a sensitivity of 50% and a specificity of 90.6 %.

Both of D-dimer more than 500 ng/mL and D Dimer more than 10×patient's age showed high specificity (100%) to exclude LAT. So, D-dimer can be beneficial in clinical practice to exclude LAT avoiding TEE, particularly in patients with low thromboembolic risk.

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