Bangladesh Med Res Counc Bull 2022; 48: 231-235 DOI: 10.3329/bmrcb.v48i3.62672

RESEARCH PAPER

Predictive Value of D-dimer Levels for Detection of Left Atrial Thrombus in Patients with Rheumatic Severe Mitral Stenosis

Md Abidur Reza Chowdhury*, Amal Kumar Choudhury, Zillur Rahman, Abdul Momen

Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Sher-E-Bangla Nagar, Dhaka, Bangladesh

Abstract

Background: Systemic embolism is one of the most common complications of mitral stenosis (MS). Systemic embolism in patients with MS is caused by left atrial (LA) thrombus. Trans Esophageal Echocardiography (TEE) is considered the most reliable in ruling out LA thrombus, however, it is semi-invasive, operator-dependent, and not widely available. On the other hand, D-dimer is an indirect marker of fibrin formation. It reflects the activation of coagulation system.

Objective: To measure D-dimer levels in patients with and without LA thrombus and find out predictive value of D-dimer levels to detect LA thrombus.

Methods: In this cross-sectional observational study 50 patients with rheumatic severe mitral stenosis have been assessed. Patients underwent Trans Thoracic Echocardiography (TTE) and TEE to rule out LA thrombus. If TTE showed LA thrombus, TEE was not done. Patients were divided into two groups based on presence of LA thrombus; group I- patients with LA thrombus, and group II- patients without LA thrombus. D-dimer level was measured in two groups and comparison was done.

Results: D-dimer was significantly elevated in group I compared to group II (2.8±1.9 µg/ml vs. 0.43±0.13µg/ml, p<0.001). Receiver Operator Characteristic (ROC) Curve showed D-dimer level > 0.6 µg/ml can predict LA thrombus with sensitivity of 84% & specificity of 88% .

***Conclusion*:** A higher level of D-dimer can predict LA thrombus in patients with rheumatic severe MS, and can be used as a noninvasive marker to rule out LA thrombus in patients with rheumatic severe MS.

Keywords: Mitral Stenosis, Thrombus, Embolism, D-dimer, Left-Atrium

Introduction

Worldwide, most cases of mitral stenosis (MS) are caused by rheumatic heart disease (RHD).[1] Although RHD has become quite rare in developed countries, it is still prevalent in developing countries. The prevalence of RHD ranges from 20 to 30 per 1000 school children, which leads to a large pool of rheumatic MS.

Systemic embolism is one of the most common complications of MS. Systemic embolism in patients with MS is caused by left atrial (LA) thrombus formation. Although systemic embolization most often occurs in patients with atrial fibrillation (AF), 20% of patients with MS with embolic events are in sinus rhythm. It is postulated that the loss of atrial appendage contractile function, despite electrical evidence of sinus rhythm, leads to blood flow stasis and thrombus formation.[2]

Transesophageal echocardiography (TEE) is the most prevalent test to identify nearly every cardiac source of thromboembolism, and is considered the gold standard in ruling out LA thrombus.[3] Moreover, TEE is also recommended in patients before undergoing Percutaneous Transvenous Mitral Commissurotomy (PTMC) in patients with MS. However, TEE is semi-invasive, operator-dependent, and not widely available in resource-poor country like Bangladesh. Therefore, a non-invasive marker would be of great value as an alternative to TEE to rule out LA thrombus in patients

***Correspondence:** Md Abidur Reza Chowdhury, Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Sher-E-Bangla Nagar, Dhaka, Bangladesh*

Email: abidurrezac@gmail.com

ORCID: 0000-0003-3417-2479

with MS who are to undergo PTMC or are suffering from systemic embolism.

D-dimer is an indirect marker of fibrin formation. It reflects activation of coagulation system. D-dimer is well established 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 atrial fibrillation (AF) with LA thrombus and LA spontaneous echo contrast (SEC).[6,7] Moreover, there has been evidence that D-dimer level can predict thromboembolic events in patients with AF.[8,9] This study aims to evaluate the predictive value of D-dimer in determining LA thrombus in patients with MS and also its potential in sorting out patients who would benefit from TEE to detect LA thrombus from those in whom the likelihood of LA thrombus is very low.

Materials and Methods

This was a cross-sectional observational study conducted from November 2020 to October 2021 in Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka. Study population was patients with rheumatic severe mitral stenosis admitted in Department of Cardiology, NICVD. Sampling method was purposive sampling. Patients with moderate to severe mitral regurgitation (MR), and moderate to severe aortic valve disease were excluded from study. Similarly, patients with renal failure, hepatic failure, pregnancy, concomitant COVID-19 infection, acute/chronic infection, malignancy, documented intravascular thrombus and patients on warfarin were excluded from the study as these factors can confound D-dimer values.

A total sample of 50 patients was taken, and patients were divided into two groups according to the presence of LA thrombus, with group I being patients with LA thrombus and group II being patients without LA thrombus.

In this study dependent variable was LA thrombus and independent variable was D-dimer level. Other than these two, confounding variables were LA size, mean mitral valve gradient, mitral valve area (MVA) (planimetry), New York Heart Association (NYHA) class, atrial fibrillation (AF), and demographic variables were age and sex.

After giving informed written consent, all patients with rheumatic severe MS admitted in the Department of Cardiology, NICVD were considered for the study. Meticulous history was taken and demographic data such as age and sex were recorded in predesigned data collection form. A 12 lead ECG was done in all patients after admission.

All patients underwent TTE using Philips EPIQ 7C Ultrasound system equipped with 3.5 MHz phased array transducer. Echocardiographic variables, such as MVA, LA diameter, mean mitral valve gradient were recorded. In patients with no LA thrombus in TTE, TEE was performed. On the other hand, those with LA thrombus detected on TTE, TEE was not performed. For TEE 5 MHz transducer was used. After pharyngeal local anesthesia with lidocaine spray, the probe was initially carried forward to a depth of 25-35cm for optimum imaging. Left Atrial Appendage (LAA) clot was diagnosed by the presence of clearly defined echogenic intracavitary mass with an echo texture different from that of the underlying endocardium and not due to pectinate muscle.

In all patients, 2 ml of venous blood was collected for measurement of D-dimer levels. The blood was centrifuged and supernatant plasma was taken to measure D-dimer level. It was measured in Nephelometric Immunoassay by Mispa-i2 protein analyzer.

Collected data were analyzed using SPSS (Statistical Package for Social Sciences) Version 16. Quantitative data were expressed as mean and standard deviation, whereas, qualitative data were expressed as frequency and percentage. Student t-test was used to compare continuous variables while Chi-square test was used to compare qualitative variables. Multivariate regression analysis was done to find out association of relevant independent variables with LA thrombus. Receiver operating characteristics (ROC) curve was used to derive the optimum cut-off value of D-dimer for diagnosing LA thrombus. A probability (p) value of < 0.05 was considered significant, while p>0.05 was considered insignificant.

Results

Demographic and clinical characteristics of both groups are summarized in Table I. Most of the parameters did not have any statistically significant difference between the two groups. However, pulse rate was higher in group I than in group II (99.2±14.9 vs 87.6±14.5, p=<0.05). Similarly, patients with AF were more predominant in group I than group II (72% vs 28%), and it was significant statistically (p< 0.05).

It has also been observed that patients with LA thrombus tend to have higher NYHA class than those without LA thrombus. Most patients in group II were in NYHA class II (56%), whilst the majority in group I were in NYHA class III (64%), and the difference was statistically significant ($p < 0.05$). (Table I)

Among the echocardiographic parameters, LA diameter in group with LA thrombus was significantly higher than that of group without LA thrombus (48.2±4.9 vs 43.8±4.2; $p < 0.05$). On the other hand, it has been observed that patients with LA thrombus had lower mitral valve pressure half time (285.5±32.4) than patients without LA thrombus (337.9±86.2), and it was statistically significant. Other echocardiographic parameters were more or less similar between the two groups without any statistically significant difference. (Table II)

Comparison of D-dimer levels between two groups revealed mean D-dimer level in group I (2.8± 1.9 µg/ml) was significantly higher than group II (0.43 ± 0.13 µg/ml, $p < 0.05$). (Table III)

Receiver operating characteristics (ROC) curve was plotted to derive the optimum cut-off value of D-dimer to predict LA thrombus. It showed largest area under the curve (AUC) was 0.86, with confidence interval 0.748-0.972, p <0.001. D-dimer level >0.6 ìg/ml has sensitivity 84%, specificity 88%, positive predictive value (PPV) (87.5%) and negative predictive value (NPV) (84.6%) with the relation of LA thrombus which indicates a good trade. (Figure 01)

Variables that showed significant association with LA thrombus, underwent multivariate logistic regression analysis. Among the 6 variables, higher D-dimer level >0.6 µg/ml was found to be independent predictor of LA thrombus with OR being 3.92. (Table IV)

Table I: Demographic and clinical characteristics of study population

Variables	Group I (n=25)	Group II (n=25)	*p* value
Age (years)	33.6 ±7.9	33.6 ±7.9	0.20
Males	7 (28%)	5 (20%)	0.51
Females	18 (72%)	20 (80%)	0.51
Pulse (bpm)	99.2±14.9	87.6±14.5	<0.05
Systolic Blood Pressure(mmHg)	95.6±7.7	99.2±10.7	0.18
Diastolic Blood Pressure (mmHg)	65.6±5.8	64.4±5.8	0.47
AF (%)	72	28	<0.05
NYHA II	5 (20%)	14 (56%)	<0.05
NYHA III	16 (64%)	7 (28%)	<0.05
NYHA IV	4 (16%)	4 (16%)	1.00

Table II: Echocardiographic parameters of study population

Echocardiographic characteristics	Group I (n = 25) Mean ± SD	Group II (n = 25) Mean ± SD	*p* value
LVEF (%)	52.8±4.8	58.2±5.6	0.11
Mean Mitral Valve Gradient (mmHg)	10.3±1.6	10.4±3.4	0.92
Mitral Valve Area (cm^2)	0.74±0.19	0.77±0.28	0.68
LA diameter (mm)	48.2±4.9	43.8±4.2	<0.05
Miral Valve Pressure Half Time (ms)	285.5±32.4	337.9±86.2	<0.05
Pulmonary Artery Systolic Pressure (PASP) (mmHg)	55.5±24.9	55.3±32.4	0.98

Table III: Comparison of D-dimer levels among study population.

	Group I (n = 25)	Group II (n = 25)	*p* value
	Mean ± SD	Mean ± SD	
D-dimer level (µg/ml_	2.8 ± 1.9	0.43 ± 0.13	<0.05

Table IV: Multivariate logistic regression analysis of different variables in relation with LA thrombus.

Variables of interest	Regression Coefficient	*p* value	Odds Ratio (OR)	95% CI
Increased pulse	0.055	0.11	1.01	0.011-1.475
AF	0.104	0.06	1.41	0.072 – 6.915
LA diameter (mm)	0.207	0.09	1.23	0.107-7.03
Low Mitral Valve Pressure Half Time	-0.013	0.11	0.99	0.978-1.997
Higher NYHA class	0.217	0.06	1.57	0.107-9.807
Elevated D-dimer level	1.651	<0.05	3.92	1.681-26.9

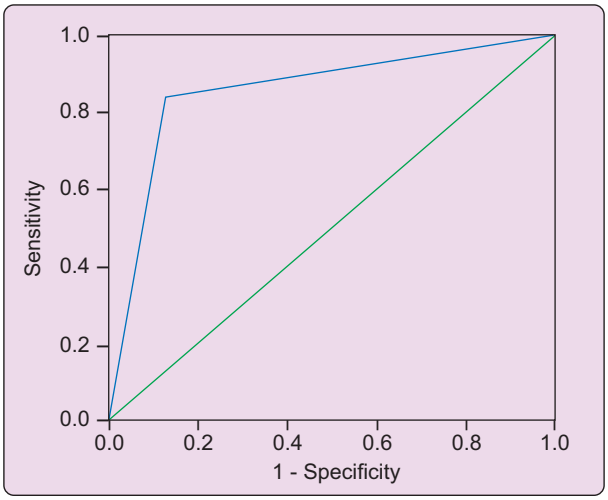

Figure 1: ROC curve analysis of D-dimer for prediction of LA thrombus.

Discussion

In this study we have compared clinical, echocardiographic and biochemical parameters between patients with and without LA thrombus.

In terms of clinical parameters, incidence of AF was higher in group with LA thrombus (72% vs 28%, $p<0.05$), which can explain significantly higher pulse rate in the same group. This finding is similar to that of Sukulal et al, (2020), which showed there is significant association of AF with LA thrombus.[10]

Among other clinical parameters, NYHA class was higher in group I than group II. Majority of patients of group I were in NYHA class III (64%), while majority were in NYHA class II (56%) in group II, this was statistically significant ($p<0.05$). In his study Kurakula et al,(2016)[11], also found patients with LA thrombus had higher NYHA class than patients without LA thrombus. This can be explained by CHF, as higher percentage of CHF was found in patients with LA thrombus in other studies.[12,13]

In terms of echocardiographic characteristics, LA diameter was significantly higher among patients with LA thrombus, (48.2±4.9mm vs 43.8±4.2mm, $p<0.05$). This finding is similar to study done by Kurakula et al, (2016)[11], which also showed larger LA diameter is associated with LA thrombus.

We measured D-dimer level in both groups, and D-dimer level was significantly higher in group I than in group II (2.8±1.9µg/ml vs 0.43±1.3µg/ml, $p<0.001$). Receiver Operator Characteristic (ROC) curve was constructed to analyze predictive value of D-dimer to detect LA thrombus. The largest area under the curve (AUC) was 0.86 CI; 0.748-0.972, ($p<0.05$). D-dimer >0.6 µg/ml has sensitivity of 84% and specificity of 88% which is a good trade. Kurakula et al, (2016) showed D-dimer >0.510µg/ml can predict LA thrombus with 70% sensitivity and 98% specificity.[11] Similarly, Rajappa et al, (2013) also showed D-dimer value >4µg/ml can predict LA thrombus with 66.67% sensitivity and 100% specificity.[14]

Conclusion

Elevated D-dimer level can predict LA thrombus in patients with rheumatic severe MS. D-dimer level >0.6 µg/ml has sensitivity of 84% and specificity of 88% to detect LA thrombus. Systemic thromboembolism is one of the life-threatening complications of rheumatic MS. TEE is considered gold standard to detect LA thrombus, however it is not widely available in a resource-poor country like Bangladesh. Therefore D-dimer along with TTE has the potential to be a noninvasive marker which can be used to rule out LA thrombus in patient with MS.

Acknowledgement

I am delighted to express my deepest regards and gratitude to Professor Dr. Mir Jamal Uddin, Director and Professor of Cardiology, NICVD, for his constant support and valuable suggestions in carrying out this thesis work.

I would also like to thank Professor Dr . Abdul Wadud Chowdhury, Professor of Cardiology, Dhaka Medical College Hospital and Professor Md Mozammel Hoque, Professor of Biochemistry, Bangabandhu Sheikh Mujib Medical University for their critical review of this paper.

Conflict of Interest: There was no conflict of interest.

Funding: Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Ethical approval: Ethical Review Committee of National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh.

Submitted: 21 July 2022

Final revision received: 14 November 2022

Accepted: 20 November 2022

Published: 01 December 2022

References

1. Coffey S, Cairns BJ and Iung B. The modern epidemiology of heart valve disease. *Heart* 2016; 102: 75-85. DOI: 10.1136/heartjnl-2014-307020
2. Thomas JD and Bonow RO. Mitral Valve Disease. In: Zipes DP, Libby P, Bonow RO, Mann D L, Tomaselli G F, Braunwald E. (eds) *Braunwald's heart disease: A Textbook of Cardiovascular Medicine*. 11 ed. Philadelphia, PA: Elsevier, 2019, pp. 1415-44. ISBN: 0323463428
3. Manning WJ, Weintraub RM, Waksmonski CA, Haering J M, Rooney P S, Maslow A D et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995; 123: 817-22. DOI: 10.7326/0003-4819-123-11-199512010-00001
4. D'Angelo A, D'Alessandro G, Tomassini L, Pittet J L, Dupuy G, Crippa L. Evaluation of a new rapid quantitative D-dimer assay in patients with clinically suspected deep vein thrombosis. *Thromb Haemost* 1996; 75: 412-16. PMID: 8701399.
5. Stein PD, Hull RD, Patel KC, Olson R E, Ghali W A, Brant R et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med* 2004; 140: 589-602. DOI: 10.7326/0003-4819-140-8-200404200-00005
6. Habara S, Dote K, Kato M, Sasaki S, Goto K, Takemoto H, et al. Prediction of left atrial appendage thrombi in non-valvular atrial fibrillation. *Eur Heart J* 2007; 28: 2217-22. DOI: 10.1093/eurheartj/ehm356
7. Somlói M, Tomcsányi J, Nagy E, BodÓ I, Bezzegh A. D-dimer determination as a screening tool to exclude atrial thrombi in atrial fibrillation. *Am J Cardiol* 2003; 92: 85-87. DOI: 10.1016/s0002-9149(03)00476-4.
8. Nozawa T, Inoue H, Hirai T, Iwasa A, Okumura K, Lee J et al. D-dimer level influences thromboembolic events in patients with atrial fibrillation. *Int J Cardiol* 2006; 109: 59-65. DOI: 10.1016/j.ijcard.2005.05.049.
9. Sadanaga T, Sadanaga M and Ogawa S. Evidence that D-dimer levels predict subsequent thromboembolic and cardiovascular events in patients with atrial fibrillation during oral anticoagulant therapy. *J Am Coll Cardiol* 2010; 55: 2225-31. DOI: 10.1016/j.jacc.2009.12.049.
10. Sukulal K, Mohanan Nair KK, Sasidharan B, Valaparambil A, Ganapathi S, Sivasubramanian S et al. Implication of d-dimer in rheumatic severe mitral stenosis - A tertiary centre study. *Indian Heart Journal* 2020; 72: 101-6. DOI: 10.1016/j.ihj.2020.04.002.
11. Kurakula N, Durgaprasad R, Velam V, Akula V S, Kasala L, Muvva K V. Predictive Value of D-Dimer Levels and Tissue Doppler Mitral Annular Systolic Velocity for Detection of Left Atrial Appendage Thrombus in Patients with Mitral Stenosis in Sinus Rhythm. *Echocardiography* 2016; 33: 264-75. DOI: 10.1111/echo.13026
12. Krishnamoorthy KM. Incidence and predictors of left atrial thrombus in patients with rheumatic mitral stenosis and sinus rhythm: a transesophageal echocardiographic study. *Echocardiography* 2012; 29: 876-77. PMID: 22882614.
13. Salam K, Zaky M and Sebaie M. Predictive Value of D-dimer Levels and Tissue Doppler Mitral Annular Systolic Velocity for Detection of Left Atrial Thrombus in Patients with Mitral Stenosis in Sinus Rhythm. Journal of the Saudi Heart Association 2013; 25: 141-2. DOI: 10.1016/j.jsha.2013.03.105
14. Rajappa M, Sunil Roy TN, Raj A, Trehan V, Mallika V. D-Dimer assay as a non invasive test for the diagnosis of left atrial Thrombi in Indian patients with Rheumatic MS. *Afr Health Sci* 2013; 13: 584-9. DOI: 10.4314/ahs.v13i3.9.