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STUDY OF RELATIONSHIP BETWEEN PRESENCE OF LEFT ATRIAL THROMBUS IN PATIENTS WITH MITRAL STENOSIS WITH PLATELET LYMPHOCYTE RATIO TO IDENTIFY AT RISK PATIENT

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ABSTRACT :

Objective: LA thrombus in Rheumatic Heart Disease -Mitral Stenosis cannot be explained only with the slowdown of blood flow and stasis in the left atrium associated with rheumatic mitral valve stenosis (RMVS) ; seen in around 20% of these with only valvular obstruction. In addition to LA stasis, inflammation, oxidative stress, platelet size, and an increase in activation have been found to be associated with thrombus formation . Recently, the platelet-to-lymphocyte ratio (PLR), known to be an inflammatory marker, has been found to be associated with various cardiovascular diseases. This study is done with the **objective** to examine relationship between presence of LA thrombus in Rheumatic mitral stenosis and platelet-lymphocyte ratio and to identify at risk patients

METHODS: The study included 85 (Eighty five) paients who presented to the Department of Cardiology, NEIGRIHMS, Shillong with Rheumatic heart disease Mitral stenosis . All patients were evaluated using transthoracic and transesophageal echocardiography was divided into 2 groups: those with and without LA thrombus. In addition to echocardiographic and biochemical parameters, platelet lymphocyte ratio (PLR) was compared between the groups

A ROC curve was generated to relate the platelet- lymphocyte ratio with presence or absence of thrombus by TOE. PLR was compared between the groups. Student's t-test, Mann–Whitney U test ; Sensitivity, specificity and positive predictive value was estimated for platelet- lymphocyte ratio in comparison to TOE for presence or absence of thrombus

RESULTS : The **platelet lymphocyte ratio** was found to be significantly higher (**P= 0.004)** In the LA thrombus group **;** The **mean platelet lymphocyte ratio** in patients with LA clot was 132.41 ± 16.19 and in patients without LA clot was 118.34 ± 4.7 . ROC curve analysis showed that the optimal PLR cut-off value for predicting LA thrombus was 118.81, with a sensitivity of 78.4% and specificity of 69.8% (AUC = 0.809, 95% CI: 0.77–0.86)

CONCLUSION : The platelet lymphocyte ratio is a simple low cost test which provides relevant information regarding the risk of left atrial thrombus in patients of RHD MS . The PLR is a CBC index, which presents inflammatory status. The PLR were higher in patients who has been diagnosed with left atrial thrombus in RHD MS. The PLR is a better predictor for LA thrombus in RHD MS than isolated leucocyte subtypes.

INTRODUCTION

Problem statement : Rheumatic valve diseases are an important cause of morbidity and mortality, particularly in developing and undeveloped countries . The slowdown of blood flow and stasis in the left atrium associated with rheumatic mitral valve stenosis (RMVS) causes the formation of thrombus However, it is not possible to explain the development of left atrial (LA) thrombus in patients with MS, and the major embolic events seen in around 20% of these with only valvular obstruction. Rheumatic carditis-induced mitral valve disease is associated with a chronic inflammatory process. The close relationship between inflammation and prothrombotic processes is known. *Rationale* : In addition to LA stasis, inflammation, oxidative stress, platelet size, and an increase in activation have been found to be associated with thrombus formation . Recently, the platelet-to-lymphocyte ratio (PLR), known to be an inflammatory marker, has been found to be associated with various cardiovascular diseases.

Novelty : PLR is a cheap and easily reproducible parameter that is obtained by complete blood count analysis and is analyzed in nearly every patient

Echocardiography in mitral stenosis :

Echocardiography has proved to be both sensitive and specific for MS, when adequate studies are done. The echocardiography findings of MS reflect the loss of normal valve function. The fusion of commissures results in movementof the anterior and posterior leaflets anteriorly in parallel during diastole. In patients in sinus rhythm, there is an absence of further opening of valve that is normally seen with atrial contraction. Other findings include, Increased EF slope, Decreased mitral valve leaflet excursion and Multiple echoes indicating thickening or calcification of the valve. LA enlargement is seen. When transthoracic echocardiography is unsatisfactory, transoesophageal echocardiography is a useful technique to assess the LA thrombus, the anatomy of the mitral valve and subvalvular apparatus and to assess the suitability of the patient for catheter balloon commissurotomy or surgical valve repair.[1]

Left atrial thrombus:

Rheumatic MS is associated with LA thrombus in patients in sinus rhythm (3%–13%)[2, 3] and markedly increases in AF (~33%).[4] The presence of LA thrombus carries a risk of systemic embolization and neurologic morbidity. TEE is a sensitive diagnostic modality to detect LA thrombus, particularly in the LAA.[5] It has a 97% sensitivity, 100%specificity, positive predictive value of 100%, and a negative predictive value of 99.6% to detect a thrombus.[6] Small thrombus can be detected using contrast echocardiography which provides contrast opacification within the cardiac chambers to delineate the “filling defect” of the thrombus.[7]

Manjunath *et al*.[8] proposed an echocardiographic classification of LA thrombus based on its location, extension, and mobility as follows:

- Type Ia: LA appendage clot confined to appendage (most common)
- Type Ib: LA appendage clot protruding into LA cavity
- Type IIa: LA roof clot limited above the plane of fossa ovalis
- Type IIb: LA roof clot extending below the plane of fossa ovalis
- Type III: Layered clot over the IAS
- Type IV: Mobile clot which is attached to LA free wall or roof or IAS
- Type V: Ball valve thrombus (free floating).

The incidence of LA thrombus according to types has been reported in a few small studies as Type Ia (64%–76%), Type Ib (9%–32%), Type IIa (3.6%–12.5%), and Type IIb (2%).[8,9] However, in this case, the LA thrombus shared characteristics of both Types IIb and III with Grade 0–1+ spontaneous echo contrast (SEC). The risk factors for LA thrombus formation in MS include AF, previous embolic episodes, age >40 years, LA dimension >4.5 cm, and LAA emptying velocity <20 cm/s.[8] However, MS patients in sinus rhythm are also at risk of LA clot formation with an inferosuperior LA dimension >6.9 cm, mean mitral gradient >18 mmHg, and SEC Grade >3.[9]

Study hypothesis : An increased platelet lymphocyte ratio is associated with higher incidence of LA thrombus in Rheumatic mitral stenosis.

Aims and objectives: To examine relationship between presence of LA thrombus in Rheumatic mitral stenosis and platelet-lymphocyte ratio and to identify at risk patients

METHODOLOGY: An hospital based observational study was carried out in the Department of Cardiology, NEIGRIHMS, Shillong in the period between .The project was approved by the Institutional scientific advisory committee as well as the Institutational Ethics committee. Consecutive recruiting was carried out after the research was duly explained and Informed consent duly signed.

Study Participants: 85 (Eighty five) paients who presented to the Department of Cardiology, NEIGRIHMS, Shillong with Rheumatic heart disease Mitral stenosis were considered. All patients satisfying the inclusion and exclusion criteria and having given an informed consent to participate in the study were selected for the study.

Inclusion criteria: consecutive patients determined to have RMVS as a result of transthoracic echocardiography (TTE) mitral valve area (MVA): <2 cm2] following presentation at the cardiology outpatient clinic with various complaints

Exclusion criteria:

- Significant valvular heart disease except mitral valve disease (moderate and severe aortic valve disease, severe mitral regurgitation);
- Heart failure;
- Presence of acute coronary syndrome;
- Previous cardiac surgery and/or percutaneous balloon valvuloplasty;
- Hematologic disorders; anemia (defined according to the world health organization as hemoglobin levels of <12 g/dl in women or <13 g/dl in men);
- Active infectious or inflammatory diseases;
- Rheumatologic diseases;
- Current therapy with corticosteroids, non-steroidal anti inflammatory drugs, cytotoxic drugs, thrombolytic therapy, and glycoprotein iib/iiia inhibitors;
- Thyroid disease;
- Smoking;
- Chronic kidney disease [estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m2] or abnormal liver function (elevation of transaminases levels to >3 times the upper limit of normal); and
- Malignancy.

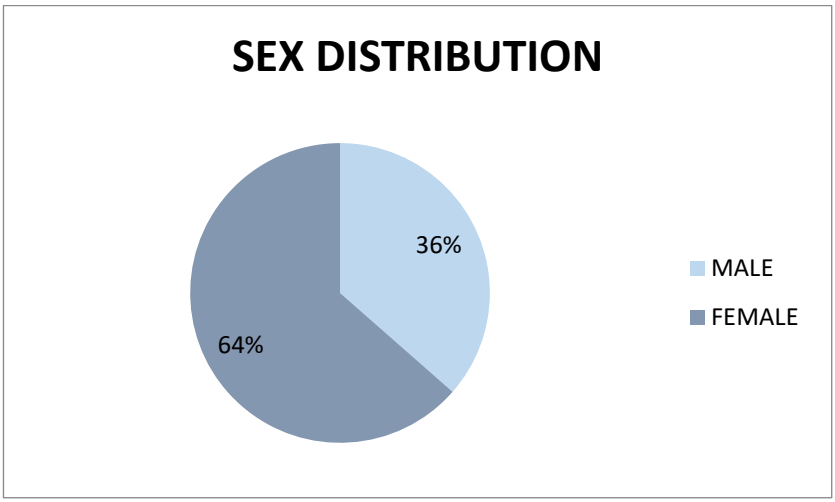
Study procedure: Consecutive patients determined to have RMVS as a result of transthoracic echocardiography (TTE) [mitral valve area (MVA): <2 cm2] following presentation at the cardiology outpatient clinic with various complaints was included in the study
. All patients evaluated using transthoracic and transesophageal echocardiography was divided into 2 groups: those with and without LA thrombus. In addition to echocardiographic and biochemical parameters, platelet lymphocyte ratio (PLR) was compared between the groups.

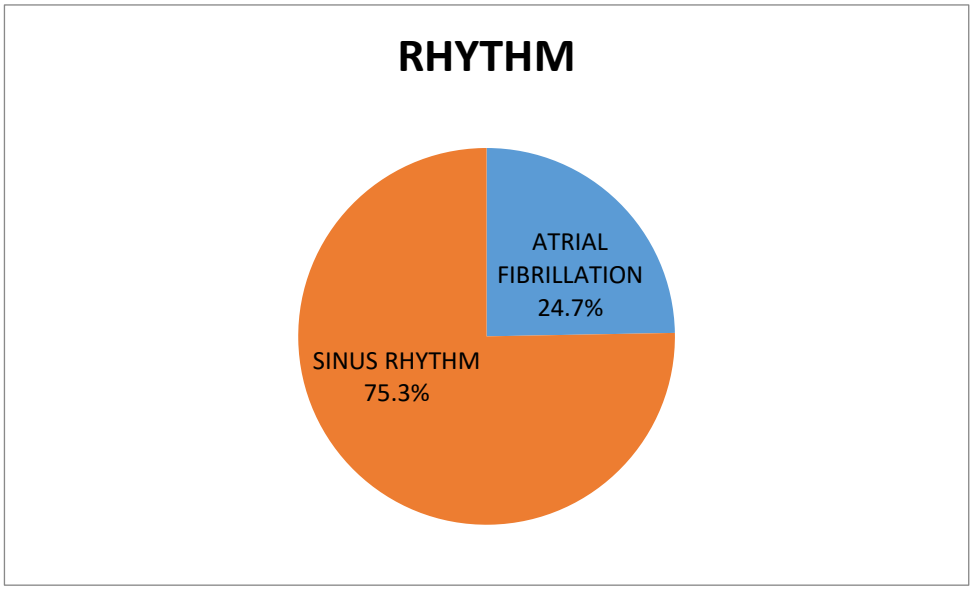
Statistical analysis:
Descriptive analysis was used to describe the socio - demographic characteristics of the study subjects in frequency and percentage . Continuous variables were expressed as mean standard deviation and percentages were used for categorical behaviours. A ROC curve was generated to relate the platelet-lymphocyte ratio with presence or absence of thrombus by TOE. . PLR was compared between the groups - Student's t-test, Mann–Whitney U test Sensitivity, specificity and positive predictive value was estimated for platelet- lymphocyte ratio in comparison to TOE for presence or absence of thrombus Statistical significance was defined as a p value less than 0.05. Data entry and analysis was done on SSPS version 22.0 Benefit and risk of the study : This study may help other people in the future by contributing to the field of research in the area of risk of LA thrombus and subsequent ischemic stroke and thereby help in formulating guidelines for its future management. There was no risk associated with the study.

RESULTS
A total number of 85 patients of RHD MS presenting to the Department of Cardiology , NEIGRIHMS during the 1 year study period were evaluated in this study.

Age and Sex Distribution of cases:-
The mean age of the patients enrolled in the study was 40.5±9.1 yrs. Most of the patients were in 3rd and 4th decade of life .
31 (36.4 %) patients were male and 54 (63.6%) were female .
Atrial fibrillation was present in 21(24.7%) of the patients while 64 patients had sinus rhythm

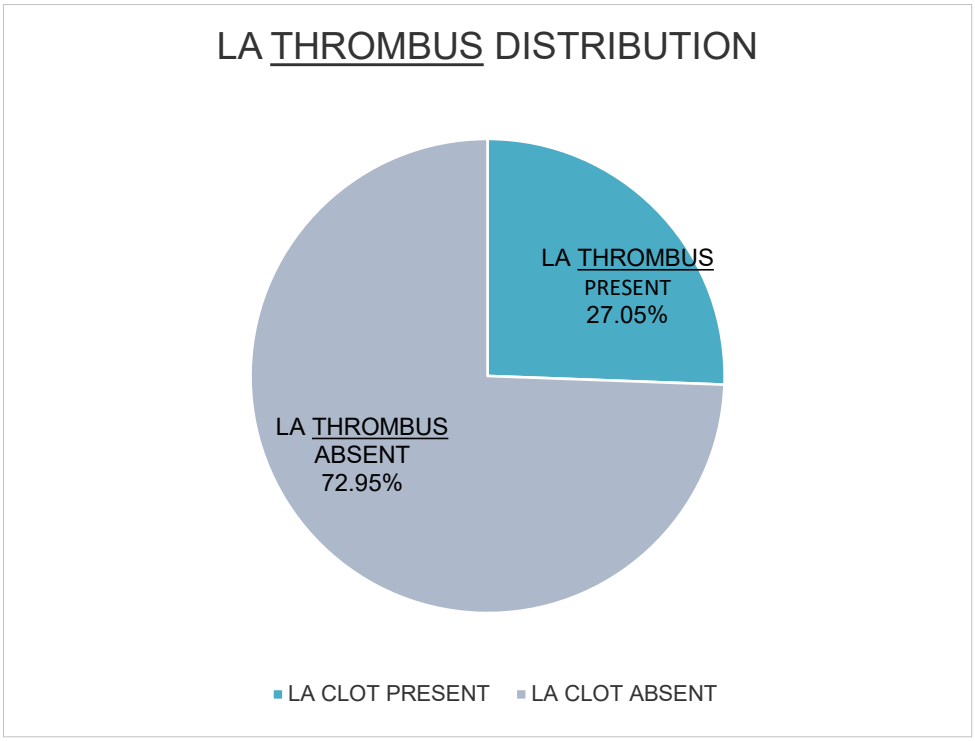
CHARACTERISTICS	**N=85**	
Age(yrs), mean±SD	40.5±9.1	
SEX	Males - 31 (36.4 %)	Females -54 (63.6%)
RHYTHM	Atrial fibrillation : 21(24.7%)	Sinus Rhythm : 64 (75.3%)
Mitral valve area cm^2(mean±SD)	1.06±0.15	
Mean Gradient across MV mm HG (mean±SD)	10.64±1.7	
LA AP Diameter mm(mean±SD)	43.03±5.09	





LA THROMBUS

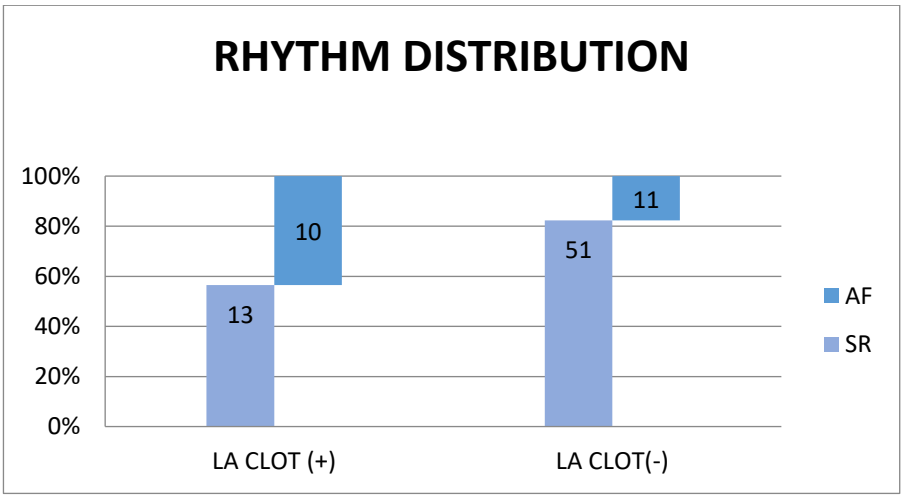
LA thrombus was present in 23 (27.05%) of 85 patients.



RHYTHM DISTRIBUTION ACCORDING TO LA THROMBUS

Atrial fibrillation was present in 10(43.4%0 out of 23 patients with LA Clot . 11(17.74%) of 62 patients without LA clot had AF.

RHYTHM	LA CLOT (+)	LA CLOT(-)	
AF	10	11	
SR	13	51	P=0.0228
TOTAL	23	62	



ASSOCIATION OF AGE WITH LA THROMBUS

The age in patients with LA clot was 40.24±9.06 yrs and in patients without LA clot was 41.52 ±9.11 $mm^{2.}$. No significant association was noted between age and LA threombus(p = 0.58)

ASSOCIATION OF MITRAL VALVE AREA WITH LA THROMBUS

The mean mitral valve area in the study population was 1.06 ±0.15 $mm^{2.}$ The **mean mitral valve area** in patients with LA clot was 1.13±0.126 $mm^{2.}$ and in patients without LA clot was 0.90 ±.09 $mm^{2.}$

	LA CLOT (+)$mm^{2.}$	**LA CLOT(-)** $mm^{2.}$	
mean mitral valve area	0.90 ±.09	1.13±0.126	**P< 0.001**

In the LA thrombus group **mitral valve area** was found to be lower with statistical significance(**P< 0.01)[CI : 1.098- 1.162 ;CI: 0.8661-0.9389**

ASSOCIATION OF MEAN GRADIENT (MG) ACROSS MITRAL VALVE WITH LA THROMBUS

The mean MG across mitral valve in the study population was 10.649 ± 1.70 mm HG. The **mean MG across mitral valve** in patients with LA clot was 12.56±0.75 and in patients without LA clot was 9.94 ± 1.38 mm HG

	LA CLOT (+)mm HG	**LA CLOT(-)** mm HG	
mean MG across mitral valve	12.56±0.75	9.94 ± 1.38	**P< 0.001**

In the LA thrombus group **mean MG across mitral valve** was found to be higher with statistical significance(**P< 0.001)[CI : 12.23- 12.884 ;CI: 9.59-10.29)**

ASSOCIATION OF LEFT ATRIAL AP DIAMETER WITH LA THROMBUS

The mean left atrial AP diameter in the study population was 43.03 ± 5.09 mm . The **mean left atrial ap diameter** in patients with LA clot was 49.47±04.65 and in patients without LA clot was 40.64 ± 2.61 mm .

	LA CLOT (+)mm	**LA CLOT(-)** mm	
mean left atrial AP diameter	49.47±04.65	40.64 ± 2.61	**P< 0.001**

In the LA thrombus group **mean left atrial AP diameter** was found to be higher with statistical significance(**P< 0.001)[CI : 47.459- 51.48 ;CI: 39.97-41.30)**

PLATELET DISTRIBUTION

The mean platelet count in the study population was 240.576471 ±20.15 (x $10^{3)}$) / $mm^{3.}$ The mean platelet count in patients with LA clot was 253.69 ±32.04 and in patients without LA clot was 235.70 ±9.54.

	LA CLOT (+) (x10^3)	**LA CLOT(-) (x10^3)**	
Platelet count	**253.69** ±32.04	235.70 ±9.54.	**P< 0.01**

In the LA thrombus group platelet count was found to be higher with statistical significance(**P< 0.01) [CI : 239.85- 267.53 ;CI: 233.28-238.12)**

LYMPHOCYTE DISTRIBUTION

The mean lymphocyte count in the study population was 1970.8235±41.31 / $mm^{3.}$ The mean platelet count in patients with LA clot was 1914.17 ± 33.82 and in patients without LA clot was 1991.83 ±16.83

	LA CLOT (+) (x10^3)	**LA CLOT(-) (x10^3)**	
Mean lymphocyte count	**253.69** ±32.04	235.70 ±9.54.	**P =0.01**

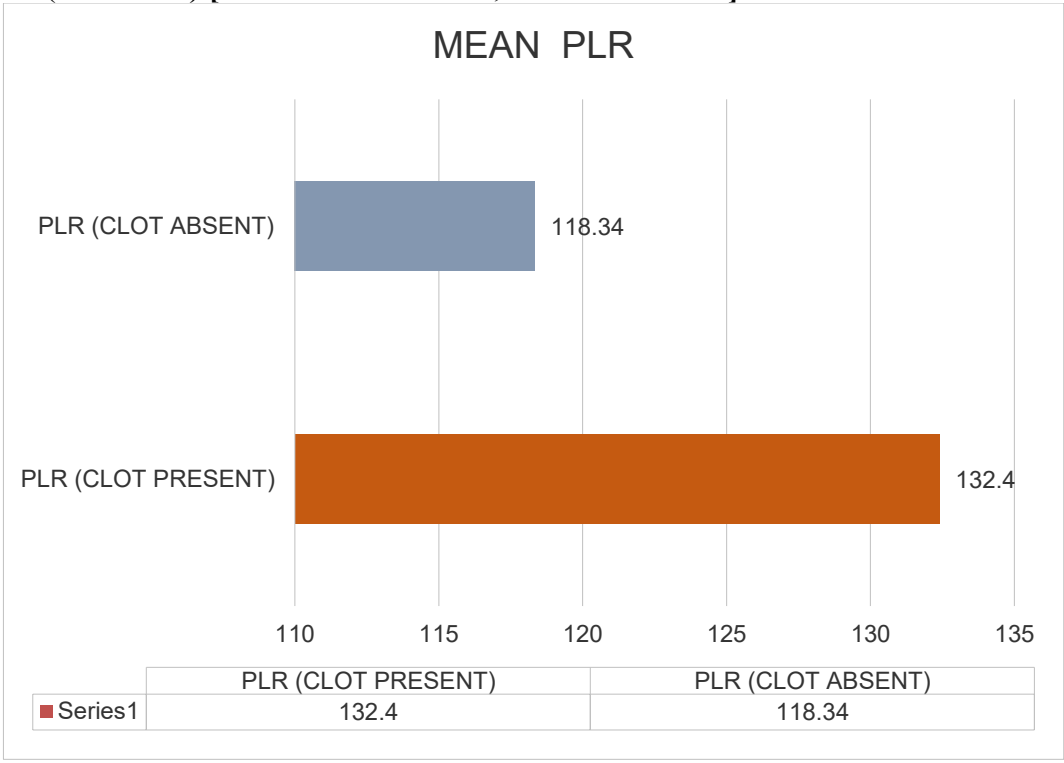
In the LA thrombus group lymphocyte count was found to be lower with statistical significance(**P= 0.01) [CI : 1896.3- 1932.0 ;CI: 1987.6-1996.1]**

ASSOCIATION BETWEEN PLATELET LYMPHOCYTE RATIO AN LA THROMBUS

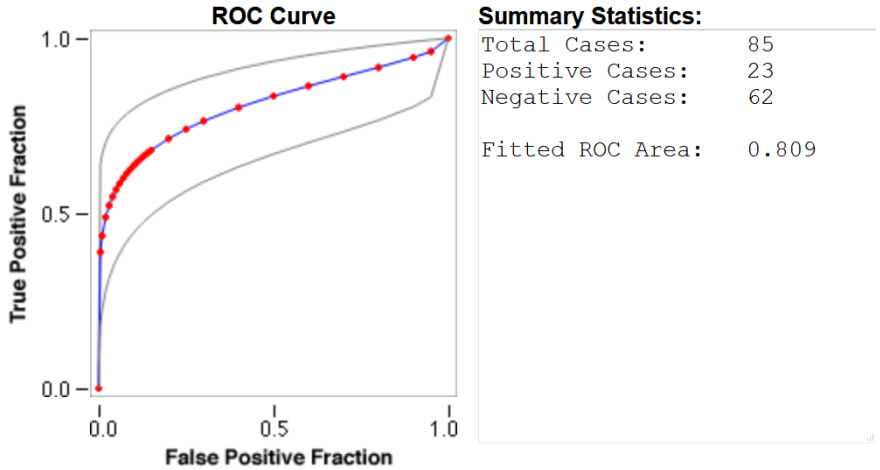
The mean platelet lymphocyte ratio the study population was 122.16 ±11.12 / $mm^{3.}$ The **mean platelet lymphocyte ratio** in patients with LA clot was 132.41 ± 16.19 and in patients without LA clot was 118.34 ± 4.7

	LA CLOT (+)	**LA CLOT(-)**	
Platelet Lymphocyte Ratio	132.41 ± 16.19	118.34 ± 4.7	**P =0.004**

In the LA thrombus group **platelet lymphocyte ratio** was found to be higher with statistical significance(**P= 0.004) [CI : 125.41- 139.41 ;CI: 117.6-119.53]**



ROC curve analysis showed that the optimal PLR cut-off value for predicting LA thrombus was 118.81, with a sensitivity of 78.4% and specificity of 69.8% (AUC = 0.809, 95% CI: 0.77–0.86)



DISCUSSION

A total number of 85 patients of RHD MS presenting to the Department of Cardiology , NEIGRIHMS during the 1 year study period were evaluated in this study.

Age and Sex Distribution of cases:-

The mean age of the patients enrolled in the study was 40.5±9.1 yrs. Most of the patients were in 3rd and 4th decade of life .
31 (36.4 %) patients were male and 54 (63.6%) were female .
Atrial fibrillation was present in 21(24.7%) of the patients while 64 patients had sinus rhythm

LA THROMBUS

LA thrombus was present in 23 (27.05%) of 85 patients rhythm distribution according to la thrombus Atrial fibrillation was present in 10(43.4%) out of 23 patients with LA Clot . 11(17.74%) of 62 patients without LA clot had AF.
The association between presence of AF with LA clot in patients with RHD MS was found to be significant. (p =0.0228 , CI 1.210 -4.540) In the LA thrombus group **mitral valve area** was found to be lower with statistical significance(**P< 0.01)[CI : 1.098- 1.162 ;CI: 0.8661-0.9389) ;** The **mean mitral valve area** in patients with LA clot was 1.13±0.126 $mm^{2.}$ and in patients without LA clot was 0.90 ±.09 $mm^{2.}$ In the LA thrombus group **mean MG across mitral valve** was found to be higher with statistical significance(**P< 0.001)[CI : 12.23- 12.884 ;CI: 9.59-10.29) ;** The **mean MG across mitral valve** in patients with LA clot was 12.56±0.75 and in patients without LA clot was 9.94 ± 1.38 mm HG The **platelet lymphocyte ratio** was found to be significantly higher (**P= 0.004)** In the LA thrombus group **;** The **mean platelet lymphocyte ratio** in patients with LA clot was 132.41 ± 16.19 and in patients without LA clot was 118.34 ± 4.7 ROC curve analysis showed that the optimal PLR cut-off value for predicting LA thrombus was 118.81, with a sensitivity of 78.4% and specificity of 69.8% (AUC = 0.809, 95% CI: 0.77–0.86)

There are a very few studies assessing the platelet lymphocyte ratio in LA thrombus in patients with mitral stenosis.

Erdal Belen et al found that PLR was significantly higher in patients with thrombus than in those without (133±38 vs. 119±31, p=0.001). Higher PLR was identified as independently associated with the presence of LA thrombus (odds ratio: 1.03, 95% confidence interval: 1–1.06, p=0.016).
PLR is an easy-to-obtain parameter that can be used as a marker for inflammation at the clinical level (10). Platelets, which are acute phase reactants, increase in number with stimulus such as systemic infection and inflammation and lead to overproduction of inflammatory cytokines (11, 12). The increase in platelets due to the proliferation of megakaryocytes through the stimulation of inflammatory mediators may reflect the underlying inflammatory state In a previous study, the neutrophil-tolymphocyte ratio, an indicator of inflammation, was found to be higher in patients with RMVS when compared with the control group (13)

CONCLUSION

The platelet lymphocyte ratio is a simple low cost test which provides relevant information regarding the risk of left atrial thrombus in patients of RHD MS .The PLR is a CBC index, which presents inflammatory status. The **platelet lymphocyte ratio** was found to be significantly higher (**P= 0.004)** In the LA thrombus group **;** The **mean platelet lymphocyte ratio** in patients with LA clot was 132.41 ± 16.19 and in patients without LA clot was 118.34 ± 4.7 . ROC curve analysis showed that the optimal PLR cut-off value for predicting LA thrombus was 118.81, with a sensitivity of 78.4% and specificity of 69.8% (AUC = 0.809, 95% CI: 0.77–0.86). The PLR is a better predictor for LA thrombus in RHD MS than isolated leucocyte subtypes.

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