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The Relationship Between Platelet and Lymphocyte Ratios and Left Atrial Thrombus Formation in Patients with Severe Mitral Stenosis due to Rheumatic Heart Disease at Haji Adam Malik Hospital Medan

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ABSTRACT

Introduction: Rheumatic heart disease is an immune disease condition that often causes damage to the structure of the heart valves, such as mitral stenosis. One of the complications of severe mitral stenosis is thrombus in the left atrium. This condition is closely related to inflammation, so inflammatory cells such as lymphocytes and platelets are closely related to their severity and complications. Therefore, this study aims to see the ability of mitral platelet and lymphocyte ratios to the incidence of left atrial thrombus.
Methods: This study is an analytical descriptive study with a cross-sectional research design, conducted at the Integrated Heart Center of Haji Adam Malik Hospital, from November 2024. The parameters of echocardiography, blood laboratory, as well as thrombus in the left atrium data were acquired. A statistical analysis test will be was done to assess the difference in the average ratio of platelets and lymphocytes based on the presence of thrombus in the left atrium, as well as the ability of the predictor of the ratio.
Results: There are a total of 175 samples in this study. A total of 45 (25.7%) of the sample had thrombus in the left atrium. The median value and interquartile range of the Platelet/Lymphocyte Ratio (PLR) were higher in the thrombus group in the left atrium compared to the group without thrombus in the left atrium (P = 0.0001). The ROC curve analysis showed PLR parameters, with P = 0.0001, AUC 0.713, and 95% CI 0.620 – 0.806. The threshold value of PLR 132.5 has a sensitivity of 71.1% and a specificity of 61.0% has the ability to predict the presence of thrombus in the left atrium.
Conclusion: The PLR ratio has a significant association with the occurrence of thrombus in the left atrium, in the condition of severe mitral stenosis due to rheumatic heart disease.

Keywords

Mitral stenosis, Rheumatic heart disease, LA thrombus, Platelet/lymphocyte ratio (PLR)

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INTRODUCTION

Rheumatic heart disease (RHD) is a significant cause of morbidity and mortality, particularly in developing countries such as India. One of the key complications of rheumatic mitral valve stenosis (RMVS) is the formation of a thrombus in the left atrium due to slowed blood flow and stasis. These thrombi can enter the circulatory system and cause embolic complications, with cerebrovascular involvement being the most serious. However, understanding the process of thrombus formation in patients with mitral valve stenosis remains challenging, as embolic events occur in only approximately 20% of such cases, often in the absence of valve obstruction. [1,2]

Rheumatic heart disease, an autoimmune condition following streptococcal throat infection, leads to inflammation of the heart valves, often causing mitral valve stenosis (MVS). This disease continues to present

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critical health challenges worldwide, with an estimated decline of 47.8% in age-standardized mortality rates between 1990 and 2015. However, significant discrepancies in incidence remain between endemic and non-endemic regions, with the highest mortality rates observed in Oceania, South Asia and sub-Saharan Africa. In countries with a high incidence of rheumatic heart disease, including Indonesia, mitral stenosis is a common complication. The chronic inflammatory response triggered by streptococcal infection leads to valve damage and stenosis.[3,4]

Mitral stenosis impedes blood flow to the left ventricle by preventing the mitral valve from fully opening during the diastole. This obstruction causes blood stasis in the left atrium, resulting in elevated atrial pressure and inflammation. Over time, these changes cause the left atrium to dilate, leading to fibrosis and disorganization of the atrial muscle fibers. Such alterations increase the risk of atrial fibrillation and decreased atrial contraction, which in turn leads to thrombus formation and systemic embolism.[5]

Lymphocytes and neutrophils, both types of white blood cells, have recently been identified as markers of inflammation and thrombosis, with several studies linking their presence to the severity and prognosis of cardiovascular diseases. The Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) have emerged as valuable diagnostic tools for assessing thrombosis. PLR is a cost-effective diagnostic marker that has been studied in various diseases, including cancer, chronic kidney disease, and coronary artery disease. Platelets, which are crucial for thrombosis, play a key role in its development and progression. [6,7,8]

Thrombus formation in the left atrium, particularly in the left atrial appendage (LAA), is frequently associated with atrial fibrillation, stroke, and blood stasis. The presence of mitral valve stenosis contributes to this condition. A high PLR may indicate underlying inflammatory conditions or ischemic stress, which contribute to thrombus formation. However, the relationship between PLR and thrombus formation in the left atrium is not always direct or specific. Thus, PLR is often used in conjunction with clinical evaluation and other diagnostic tests to assess the risk and management of patients with cardiovascular conditions, particularly those with rheumatic valvular disease. [2,10]

METHOD

This retrospective, cross-sectional study aimed to explore the relationship between the Platelet-Lymphocyte Ratio (PLR) and the incidence of left atrial thrombus in patients with mitral stenosis due to rheumatic heart disease at Haji Adam Malik Hospital. The research will be conducted from January 2022 to December 2024. All patients diagnosed with rheumatic heart disease and mitral stenosis who fulfill the inclusion criteria will be included in the study, while those with incomplete medical records, other valvular heart diseases, acute coronary syndrome, or a history of cardiac surgery or percutaneous balloon valvuloplasty will be excluded.

The sample size calculation for this study was determined using an analytical numerical formula for non-paired data. With a confidence level of 95% ($Z\alpha = 1.96$) and a standard deviation ($S = 312$), the required sample size was calculated to be at least 77 participants per group, totaling 154 samples. This nonrandom sampling method ensured the inclusion of patients with comprehensive medical data and a diagnosis of severe mitral stenosis due to rheumatic heart disease.

The primary independent variable for this study was the Platelet-Lymphocyte Ratio (PLR), calculated through laboratory tests, while the dependent variable was the presence of left atrial thrombus, assessed using echocardiography (both transthoracic and transesophageal). Other variables, including hemoglobin levels, platelet counts, and lymphocyte counts, will be measured to support the analysis.

The procedural steps for this study are as follows: Upon approval from the Research Ethics Committee of the Faculty of Medicine, University of North Sumatra, and obtaining written informed consent from all participants, data collection will commence. First, eligible patients with confirmed rheumatic heart disease and mitral stenosis will be identified. Their medical records will be reviewed to ensure that they meet the inclusion criteria and to gather relevant baseline data. Participants will then undergo both transthoracic and transesophageal echocardiography to determine the presence or absence of a left atrial thrombus. Blood samples will be collected to measure platelet and lymphocyte counts, as well as other relevant parameters,

such as hemoglobin. The Platelet-Lymphocyte Ratio will be calculated by dividing the platelet count by the lymphocyte count.

All patients who meet the inclusion criteria and consent to participate in the study will be categorized based on the presence or absence of a left atrial thrombus. The platelet and lymphocyte ratio was then calculated for each participant. Data will be processed using the SPSS version 24. Descriptive statistics will be presented as frequencies and percentages for categorical variables, and measures of central tendency (mean or median) will be used for continuous variables. For comparisons, the Mann-Whitney U test will be applied for non-normally distributed variables, and independent t-tests will be used for variables that approximate a normal distribution. The significance level will be set at 5% ($P < 0.05$).

Ethical approval for this study will be obtained from the Research Ethics Committee of the Faculty of Medicine, University of North Sumatra. Written informed consent will be obtained from all participants before their inclusion in the study.

RESULTS

A total of 175 samples were successfully included in this study. Of the participants, 51 (29.1%) were men and 124 (70.9%) were women. Regarding cardiac rhythm, 64 (36.6%) participants exhibited sinus rhythm, whereas 111 (63.4%) presented with atrial fibrillation. All participants were diagnosed with severe mitral stenosis attributed to rheumatic heart disease. Regarding medication usage, 164 (93.7%) patients were prescribed loop diuretics in the form of furosemide, 157 (89.7%) received Mineralocorticoid Receptor Antagonists (MRA) in the form of spironolactone, 131 (74.9%) were administered beta-blockers, 91 (52%) were taking digoxin, and 127 (72.6%) were on warfarin. Additionally, 45 (25.7%) patients had left atrial thrombi. The basic characteristics of the participants are summarized in Table 1.

Table 1. Basic Characteristics of the Study Samples (Categorical Data)

Parameter	N (%) (N total = 175)
Gender	
Male	51 (29.1%)
Female	124 (70.9%)
ECG Rhythm	
Sinus Rhythm	64 (36.6%)
Atrial Fibrillation	111 (63.4%)
Medications	
Loop Diuretics	164 (93.7%)
MRA (Spironolactone)	157 (89.7%)
Beta-blockers	131 (74.9%)
Digoxin	91 (52%)
Warfarin	127 (72.6%)
Left Atrial Thrombus	
Yes	45 (25.7%)
No	130 (74.3%)

For numerical data analysis, the mean and standard deviation were employed for normally distributed data, whereas the median and interquartile range (IQR) were used for data that did not conform to a normal distribution. The mean hemoglobin level of the sample was 13.03 ± 2.07 g/dL, mean hematocrit was 38.96 ± 5.96%, mean platelet count was 242,340 ± 69,513.71 cells/mm^3, and mean lymphocyte count was 1,936.80 ± 838.30 cells/mm^3. The median white blood cell count was 8,719 (3,940 – 25,030) cells/mm^3, while the median International Normalized Ratio (INR) was 1.6 (0.89 – 7.11). The median Platelet-Lymphocyte Ratio (PLR) was 157 (range, 13 – 679), and the median left atrial volume index (LAVi) was 68.7 (range, 12.18 – 233) mL/m^2. The detailed numerical data are presented in Table 2.

Table 2. Basic Characteristics of the Study Samples (Numerical Data)

Parameter	Mean ± SD / Median (min-max)
Age (Years)	42.03 ± 10.63
Laboratory Parameters	
Hemoglobin (g/dL)	13.03 ± 2.07
Hematocrit (%)	38.96 ± 5.96
Leukocyte (cells/mm³)	8,690 (3,940 – 25,030)
INR	1.6 (0.89 – 7.11)
Platelets (cells/mm³)	242,340 ± 69,513.71
Lymphocytes (cells/mm³)	1,936.80 ± 838.30
PLR	157 (13 – 679)
Echocardiography Parameters	
Ejection Fraction (%)	58 (50 – 89)
MVA (cm²)	0.75 (0.2 – 1.5)
MVMeanPG (mmHg)	10.53 ± 4.65
LAVi (mL/m²)	68.7 (12.18 – 233)
Wilkin Score	7 (4 – 13)
TAPSE (mm)	18.14 ± 4.95

This study further investigated the variations in both categorical and numerical parameters contingent on the presence of a left atrial thrombus. Significant differences were observed in several parameters. The median and interquartile range of the Platelet-Lymphocyte Ratio (PLR) was higher in patients with left atrial thrombus (149 [71 – 679]) than in those without (122 [13 – 462]), with this difference being statistically significant (P = 0.0001). Similarly, the median and interquartile range for the Mitral Valve Area (MVA) were reduced in patients with left atrial thrombus (0.6 [0.3 – 1]) compared to those without thrombus (0.79 [0.2 – 1.5]), also demonstrating a significant P-value of 0.0001. No significant differences were observed in any other parameters between the two groups. Furthermore, 35 (77.8%) patients with atrial fibrillation exhibited left atrial thrombi, whereas 76 (58.5%) patients without atrial fibrillation did not. Conversely, 10 (22.2%) patients with sinus rhythm had a left atrial thrombus, whereas 54 (41.5%) patients without sinus rhythm did not. This difference was statistically significant (P = 0.043). The findings are presented in Table 3.

Table 3. Differences in the Basic Characteristics of Samples Based on the Presence of Left Atrial Thrombus

Parameter	Left Atrial Thrombus	No Left Atrial Thrombus	P-Value
Gender			
Male	13 (28.9%)	38 (29.2%)	0.965a
Female	32 (71.1%)	92 (70.8%)	
ECG Rhythm			
Sinus Rhythm	10 (22.2%)	54 (41.5%)	0.032a
Atrial Fibrillation	35 (77.8%)	76 (58.5%)	
Age (Years)	42.4 ± 9.9	41.91 ± 10.9	0.790c
Laboratory Parameters			
Hemoglobin (g/dL)	13.16 ± 1.76	12.99 ± 2.17	0.643c
Hematocrit (%)	39.4 ± 4.81	38.8 ± 6.31	0.556c
Leukocyte (cells/mm³)	9,190 (3,960 – 20,030)	8,517 (3,940 – 20,470)	0.343d
INR	1.66 (0.89 – 5.19)	1.64 (0.89 – 7.11)	0.627
Platelets (cells/mm³)	230,222.22 ± 69,065.80	246,534.62 ± 69,439.40	0.176c
Lymphocytes (cells/mm³)	1,848 ± 784.09	1,967.54 ± 857.03	0.411c
PLR	226 (71 – 679)	133 (13 – 462)	0.0001d
Echocardiographic Parameters			
Ejection Fraction (%)	56 (50 – 74)	58 (50 – 89)	0.123d
MVA (cm²)	0.6 (0.3 – 1)	0.79 (0.2 – 1.5)	0.0001d
MVMeanPG (mmHg)	11.31 ± 4.31	10.27 ± 4.76	0.198c
LAVi (mL/m²)	75 (14.3 – 183)	68.6 (12.18 – 233)	0.956d
Wilkin Score	7 (4 – 13)	7 (4 – 13)	0.778d
TAPSE (mm)	16.95 ± 4.56	18.56 ± 5.04	0.061c

Noted: a, Chi-Square test; b, Mann-Whitney Test; c, Student T Test; d, Fisher Exact Test

Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the predictive efficacy of the Platelet-to-Lymphocyte Ratio (PLR) in identifying the presence of left atrial thrombus in patients with mitral stenosis. The analysis demonstrated a moderate predictive capability for PLR, with a P-value of 0.0001, an Area Under the Curve (AUC) of 0.713, and a 95% Confidence Interval (CI) ranging from 0.620 to 0.806. The optimal PLR cutoff value of 132.5 yielded a sensitivity of 71.1% and specificity of 61.0% for predicting the presence of left atrial thrombus. An AUC value exceeding 0.5 signifies a meaningful predictive ability, with values approaching 1 indicating a stronger predictive power. In this study, an AUC of 0.713 indicates that PLR has a moderate capacity to predict the presence of left atrial thrombus.

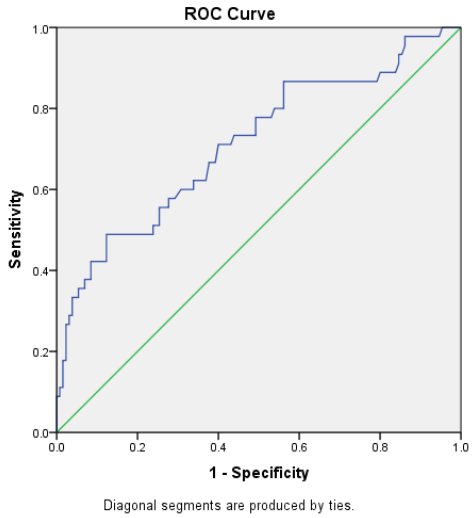

Figure 1. ROC Curve for PLR to Predict the Presence of Left Atrial Thrombus

Table 4. AUC Analysis of PLR

Parameter	Cutoff Value	AUC	P-Value	Sensitivity	Specificity	95% CI
PLR	132.5	0.713	0.0001	71.1%	61.0%	0.620 – 0.806

DISCUSSION

In this study, 175 patients with mitral stenosis were analyzed. The high prevalence of rheumatic heart disease (RHD) continues to burden healthcare systems, particularly in developing countries. Asian countries, including China, India, Pakistan, and Indonesia, were identified as having the highest RHD rates in 2015. The global trend of increasing heart failure prevalence due to RHD from 1990 to 2015 reflects this growing public health concern. A retrospective study at the National Cardiovascular Center Harapan Kita in Indonesia from 2012 to 2018 revealed that of 279 patients diagnosed with RHD, 108 were children (average age 12.02 ± 3.36 years), and 171 were young adults (average age 24.9 ± 3.84 years). RHD was more common in females than males, with an incidence ratio of 1.5:1. In this study, the mean age was 42.03 ± 10.63 years, indicating inadequate screening and detection of RHD in Indonesia, as the disease is often diagnosed only in adulthood. [11]

Not all patients with Acute Rheumatic Fever (ARF) present with symptoms, and not all symptomatic cases are correctly diagnosed by healthcare providers. Hence, more reliable discriminators of subclinical RHD are needed. Recent studies have highlighted the superiority of echocardiographic screening over auscultation in detecting RHD. [12-14] In this study, mitral stenosis due to RHD was more prevalent among females, consistent with previous studies. Negi et al. (2020) reported that mitral and tricuspid valve involvement is significantly lower in males compared to females, with an odds ratio (OR) of 0.55 (95% CI 0.44–0.61), while the aortic valve is more frequently affected in males (OR 1.36, 95% CI 1.14–1.62). RHD prevalence was more than twice as high in females than in males (71.4% vs. 29.6%, $p < 0.0001$). [15]

In this study, 159 (90.9%) mitral stenosis cases were due to RHD. RHD remains the leading cause of mitral stenosis, with less frequent causes, including mitral valve calcification and congenital heart disease. [16-18] Other causes include infective endocarditis, mitral annular calcification, endomyocardial

fibroelastosis, malignant carcinoid syndrome, systemic lupus erythematosus, Whipple's disease, Fabry disease, and rheumatoid arthritis. [19]

The study found that most patients had atrial fibrillation (AF), the most common supraventricular arrhythmia in patients with mitral valve stenosis, occurring in approximately 40% of patients. Mitral stenosis causes progressive left atrial pressure elevation, leading to atrial cardiomyopathy with electrical and structural remodeling. Even in patients with sinus rhythm, this remodeling can precede the development of AF. In patients with mitral stenosis, the left atrium exhibits pathological dilation, reduced systolic flow, and pump dysfunction due to atrial wall stiffness, which worsens with AF. [20,21]

Regarding the relationship between the Platelet-Lymphocyte Ratio (PLR) and left atrial thrombus, the study found significant results. The median and interquartile range of PLR was higher in the left atrial thrombus group (226 [71 – 679]) than in the no thrombus group (133 [13 – 462]), with a statistically significant p-value of 0.0001. These findings support the use of PLR as a predictor of left atrial thrombus formation in patients with mitral stenosis. Belen et al. (2016) reported similar findings, noting significant differences in blood cell parameters and C-reactive protein levels in patients with left atrial thrombus. Elevated PLR was identified as an independent factor associated with left atrial thrombus presence (odds ratio: 1.03, 95% CI: 1–1.06, p = 0.016).[2]

Zhou et al. (2023) found several inflammatory markers that correlated positively with C-reactive protein levels. The study identified indices, including the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio (MLR), and platelet-related ratios, as independent predictors of left atrial thrombus. [22] This aligns with the results of the present study, where PLR was significantly associated with left atrial thrombus formation.

The ROC curve analysis demonstrated PLR's predictive capability of PLR for left atrial thrombus, with a P-value of 0.0001, an Area Under the Curve (AUC) of 0.713, and a 95% Confidence Interval (CI) of 0.620 – 0.806. The cutoff PLR value of 132.5 exhibited a sensitivity and specificity of 71.1% and 61.0%, respectively. While previous studies reported higher AUC values and better sensitivity and specificity, the AUC of 0.713 in the current study still suggests a moderate ability of PLR to predict left atrial thrombus. [23]

The study confirmed that atrial fibrillation (AF) is closely associated with left atrial thrombi in patients with mitral stenosis. Similar findings were reported by Belen et al. (2015), who found that patients with AF had a higher incidence of left atrial thrombus, and PLR was a significant marker for thrombus presence, independent of AF. [2] The study found that the median MVA was lower in the thrombus group than in the non-thrombus group, supporting the notion that mitral valve area is critical in thrombus formation.

Virchow's triad states that thrombosis occurs due to disturbances in blood flow, endothelial injury, and increased coagulability. In patients with severe mitral stenosis, blood flow obstruction at the stenotic valve can lead to turbulent flow, whereas left atrial dilation is associated with blood stasis, both contributing to a higher risk of thromboembolism. Even with anticoagulant therapy, the risk of thrombus formation remains elevated, particularly in the presence of left atrial dilation. This prothrombotic environment significantly increases the likelihood of thrombus formation in the body. [24-27]

The median and interquartile range of ejection fraction (EF) did not differ significantly between the left atrial thrombus and non-thrombus groups. This finding contrasts with that of other studies, such as that by Kim et al. (1992), which identified left ventricular ejection fraction (LVEF) as an independent predictor of left atrial thrombus in patients with mitral stenosis. [28] The lack of a significant difference in EF could be due to the specific characteristics of the sample or the fact that mitral stenosis primarily affects the atrium rather than the left ventricle.

CONCLUSION

This study highlights a significant relationship between PLR and the presence of left atrial thrombi in patients with mitral stenosis. The findings show that PLR can serve as a useful predictor of left atrial thrombus occurrence. A higher thrombus prevalence was observed in patients with atrial fibrillation than in those with sinus rhythm. The PLR demonstrated a moderate ability to predict the presence of left atrial thrombus.

DECLARATIONS
Ethics approval and consent to participate were obtained. Permission for this study was obtained from the Ethics Committee of the Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION
The Authors agree to publication in the Journal of Society Medicine.

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The authors declare no conflicts of interest in this study.

AUTHORS' CONTRIBUTIONS
All authors significantly contributed to the work in terms of execution, data acquisition, analysis, interpretation, or all these areas. Contributed to drafting, revising, and critically reviewing the manuscript. Approved the final version for publication, agreed to the journal submission, and agreed to be accountable for all aspects of the work.

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