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Relationship Between Neutrophil-Lymphocyte Ratio Value and Severity of Mitral Stenosis Due to Rheumatic Heart Disease in Outpatients at H. Adam Malik General Hospital Medan

Aziz Achmad[1*], Zainal Safri[1], Teuku Bob Haykal[1], Abdullah Afif Siregar[1], Nizam Zikri Akbar[1], Tengku Winda Ardini[1], Cut Aryfa Andra[1], Anggia Chairuddin Lubis[1]

[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*
[1]*cardiology Department, Faculty of Medicine, Universitas Sumatera Utara*

***Corresponding Author**: Aziz Achmad, E-mail: dr.azizachmad@gmail.com

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ABSTRACT

Introduction: Mitral stenosis (MS) is a heart valve disease characterized by narrowing of the mitral valve, commonly caused by rheumatic heart disease. Accurate evaluation of MS severity is crucial for management, with echocardiography being the gold standard. The Neutrophil-Lymphocyte Ratio (NLR), reflecting inflammation, may correlate with MS severity. This study aims to assess the relationship between NLR values and MS severity due to rheumatic heart disease.

Method: This cross-sectional study was conducted at H. Adam Malik General Hospital Medan from January 2023 until the required sample size was achieved. Patients diagnosed with MS by echocardiography based on the American Society of Echocardiography (ASE) criteria were included. Echocardiographic parameters such as mitral valve area (MVA) and mean pressure gradient (MV mean PG), along with blood NLR values, were analyzed for associations. Statistical significance was set at $P < 0.05$.

Results: Significant differences in NLR values were observed between mild-to-moderate MS (1.93; 0.82–10.64) and severe MS (3.56; 1.81–13.08) ($P = 0.0001$, Mann-Whitney test). An NLR threshold of 2.91 predicted severe MS with 82% sensitivity and 81.8% specificity ($P = 0.0001$; AUC 0.856; 95% CI 0.772–0.940).

Conclusion: NLR strongly correlates with MS severity and serves as a reliable predictor for severe MS in patients with rheumatic heart disease. NLR offers a simple, cost-effective tool for assessing MS severity, complementing echocardiography in clinical practice.

Keywords

Neutrophil to Lymphocyte Ratio, Mitral Stenosis, Rheumatic Heart Disease

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INTRODUCTION

Rheumatic fever is a multifactorial disease caused by Streptococcus β-hemolytic group A (Group A Streptococcus/GAS), which is the etiology of pharyngitis (agent) in susceptible individuals (hosts) living in socially deprived conditions (environment). The molecular mimicry theory states that pharyngitis by GAS triggers an autoimmune response to epitopes in the organism that cross-react with similar epitopes in the heart, brain, joints, and skin in repeated episodes of rheumatic fever, thus causing rheumatic heart disease.[1]

Chronic rheumatic heart disease is one of the latest sequelae of acute rheumatic fever occurring in approximately 30% of patients with rheumatic fever. The inflammatory process is the basic pathophysiology of rheumatic heart disease. In cases of acute rheumatic fever, several inflammatory cells, such as neutrophils, macrophages, and T and B lymphocytes will infiltrate the myocardium and heart valve leaflets. The healing process of rheumatic carditis results in fibrosis and damage to the heart valve leaflets. One of the damage to the heart valve leaflets that can occur is mitral stenosis. Mitral stenosis (MS) is a form of heart valve disease characterized by narrowing of the mitral valve opening.[2,3]

Mitral stenosis is evaluated using noninvasive and invasive measures. Echocardiogram (one of the noninvasive evaluations) is useful for assessing the etiology of mitral stenosis, morphology, severity, and treatment interventions. Morphological analysis of the mitral valve apparatus includes mobility and flexibility of the leaflets, leaflet thickness, leaflet calcification, subvalvular fusion, and the appearance of commissures. The Wilkins score assesses each component of the mitral apparatus (leaflet mobility, thickness, calcification, and subvalvular apparatus damage) from grade 1 to 4.[3]

Another examination that plays a role in the diagnosis of mitral stenosis is a blood laboratory examination that can distinguish patients at high risk for rheumatic heart disease which will be useful in reducing the morbidity and mortality of this disease. Previous studies have shown that patients with persistent rheumatic heart disease will experience a chronic inflammatory process. 2 Because rheumatic heart disease is a disease that commonly occurs in developing countries with limited resources and health access, inflammatory markers are rarely used in daily practice. Therefore, a simple, inexpensive, and easily available biochemical marker is needed for use in daily practice.[4]

Recently, it has been reported that the neutrophil-lymphocyte ratio (NLR) is an important biomarker as a marker of inflammation in several disorders, especially cardiovascular diseases.[5] and cancer.[6] Neutrophils and lymphocytes play an important role in the infection process compared to other leukocyte subpopulations. In the infection process, an increase in neutrophils is a typical response of leukocytes to microbes entering the body. Therefore, the neutrophil-lymphocyte ratio (NLR) is more sensitive to indicate systemic inflammation than other leukocyte subpopulations.[7] Moreover, several studies have stated that NLR is also significantly related to the severity of mitral stenosis.[8]

Based on the above description, it has been hypothesized that NLR may reflect ongoing inflammation. Therefore, this study aims to investigate the relationship between NLR as a marker of systemic inflammation with the severity of rheumatic valve disease as a cheap and readily available examination, which is certainly very much needed in our country which is one of the developing countries.

METHOD

This study is an observational analytical study with a cross-sectional study design to see the relationship between the neutrophil-lymphocyte ratio variable and the severity of mitral stenosis due to rheumatic heart disease in outpatients at H. Adam Malik General Hospital, Medan. This study was conducted from January 2023 to September 2024. The research sample waspatients suffering from mitral stenosis due to rheumatic heart disease on outpatient basis undergoing echocardiography examination. The unpaired comparative numerical analytical research formula was used to determine the sample size with a total of 88 samples divided into two groups.

The inclusion criteria for the sample were patients with mitral stenosis due to rheumatic heart disease in the outpatient clinic of H. Adam Malik General Hospital Medan who had supporting examination data such as laboratory and echocardiography and were in stable clinical condition with NYHA functional class I-II. The exclusion criteria included patients with mitral stenosis due to rheumatic heart disease who were not examined according to research needs, patients who had other moderate-severe organic valve abnormalities, congenital diseases, other acute infectious diseases, increased ESR andpoor echo window.This research has been approved by the Health Research Ethics Committee of the University of North Sumatra.

The subjects who became the research sample were all patients with a diagnosis of mitral stenosis due to rheumatic heart disease in the outpatient clinic who had undergone echocardiography and basic laboratory

examinations on patients who met the inclusion criteria. Basic data, subject identity, anamnesis, physical examination, ECG, chest X-ray, basic laboratory examinations and echocardiography were recorded completely. For patients who were treated before the time of the study, all anamnesis, physical examinations and supporting examinations were recorded through medical record data. For the healthy population as a control group, volunteers will be taken, then anamnesis, physical and laboratory examinations will be carried out without echocardiography.

Neutrophil-lymphocyte ratio was obtained through blood examination in the pathology laboratory of Haji Adam Malik General Hospital using the Architech C4000/C8000 device. ECG was assessed with Bionet Cardiotouch 3000 at a speed of 25mm/s and an amplitude of 10 mV and echocardiography was performed using GE Vivid S60N/E95 (heart probe 3.25 MHz) with blindassessmentagainst mitral stenosis.The severity of mitral stenosis is calculated based on the MVA obtained from planimetry. In the short axis section, MVA is calculated using planimetry during mid-diastolic. From the results of MVA planimetry, the severity of mitral stenosis is grouped.

After the data was collected, analysis was carried out using SPSS to test for significant differences in the values of each parameter. Data processing used SPSS. Categorical data are presented in frequency (%) and numerical data in mean ± SD for normal distribution or median with interquartile range for non-normal distribution. Normality tests were performed using Kolmogorov-Smirnov (n> 50) or Shapiro-Wilk (n <50). The relationship between the neutrophil-lymphocyte ratio and mitral stenosis was tested using the t-test or Mann-Whitney. Comparisons of three groups were tested using ANOVA or Kruskal-Wallis, with $p<0.05$ considered significant. ROC analysis was used to determine the cut-off for the neutrophil-lymphocyte ratio with AUC, sensitivity, and specificity.

RESULTS

A total of 89 samples were successfully obtained in this study. A total of 27 (30.3%) samples were male samples, while 62 (69.7%) were female samples. A total of 43 (48.3%) samples were samples with sinus rhythm ECG, while 46 (51.7%) were samples with atrial fibrillation ECG. All samples were samples with rheumatic etiology as the cause of mitral stenosis. A total of 45 (50.5%) samples were samples with severe MS severity, 44 (49.5%) with mild-moderate MS severity. (Table 1).

Table 1. Basic Characteristics of Categorical Data Research Samples

Parameter	n (%) (n total = 89)
Gender	
Man	27 (30.3)
Woman	62 (69.7)
ECG	
Sinus Rhythm	43 (48.3)
Atrial Fibrillation	46 (51.7)
Severity of MS	
Light-Moderate	44 (49.5)
Heavy	45 (50.5)

In this study, the median age of the research sample was 43 (18 - 73), the median height of the research sample was 158 (145 - 180), the median weight of the research sample was 56 (36 - 91), the median BMI of the research sample was 22.2 (14.6 - 37.1), the median LVEF of the research sample was 58 (27 - 77), the median TAPSE of the research sample was 18 (9 - 26), the median MVA of the research sample was 1.5 (0.4 - 2.2), the median Mean PG of the research was 8.8 (3.3 - 21.73), the median ESR of the research was 10 (4 - 20), the median absolute Neutrophil of the research was 5.45 (1.5 - 14.73), the median absolute Lymphocyte of the research was 1.91 (0.47 - 4.35), the median absolute NLR of the research was 2.93 (0.82 – 13.08). In this study, the average Neutrophil% (62.83 ± 11.35), and the average Lymphocyte% (23.06 ± 8.02) were obtained (Table 2). In terms of the differences in parameters based on the severity of mitral

stenosis, there were significant differences in the mean and median in both groups of mitral stenosis severity (Table 3).

Table 2. Basic Characteristics of Numerical Data Research Samples

Parameter	Mean ± SD / Median (min-max)
Age	43 (18 – 73)
Body height	158 (145 – 180)
Body weight	56 (36 – 91)
BMI	22.2 (14.6 – 37.1)
LVEF	58 (27 – 77)
TAP	18 (9 – 26)
MVA	1.5 (0.4 – 2.2)
MVMeanPG	8.8 (3.3 – 21.73)
LAVi	41 (36 – 82)
ESR	10 (4 – 20)
Neutrophils%	62.83 ± 11.35
Lymphocytes%	23.06 ± 8.02
Absolute neutrophils	5.45 (1.5 – 14.73)
Absolute lymphocyte	1.91 (0.47 – 4.35)
NLR	2.93 (0.82 – 13.08)

Table 3. Differences in Sample Baseline Characteristic Values Based on Mitral Stenosis Severity

Parameter	Severity of Mitral Stenosis		p value
	Light-Moderate	Heavy	
Gender			
Male	10 (22.7%)	17 (37.8%)	0.189[a]
Female	34 (77.3%)	28 (62.2%)	
ECG			
Sinus Rhythm	22 (50%)	14 (31.1%)	0.110[a]
Atrial Fibrillation	22 (50%)	31 (68.9%)	
Age	46 (24 – 73)	41 (18 – 69)	0.231[b]
TB	155 (145 – 180)	160 (145 – 172)	0.038[b]
BB	60 (36 – 83)	55 (42 – 91)	0.472[b]
BMI	23.75 (14.6 – 37.1)	21.3 (15.4 – 33.4)	0.208[b]
LVEF	58 (27 – 77)	56 (28 – 74)	0.681[b]
TAP	18.5 (12 – 19)	17 (9 - 26)	0.031[b]
MVA	1.7 (1.5 – 2.2)	0.8 (0.4 – 1.4)	0.0001[b]
MVMeanPG	6.81 (3.3 – 12.65)	11.4 (3.52 – 21.73)	0.0001[b]
LAVi	39 (36 – 67)	46 (36 – 82)	0.005[b]
ESR	8 (4 – 20)	11 (6 – 20)	0.040[b]
Neutrophils%	56.68 ± 11.5	68.85 ± 7.34	0.0001[c]
Lymphocytes%	27.39 ± 8.01	18.82 ± 5.37	0.0001[c]
Absolute neutrophils	4.85 (1.5 – 8.2)	6.58 (3.04 – 14.73)	0.001[b]
Absolute lymphocyte	2.03 (0.77 – 4.35)	1.8 (0.47 – 2.59)	0.065[b]
NLR	1.93 (0.82 – 10.64)	3.56 (1.81 – 13.08)	0.0001[b]

a, Chi Square test; b, Mann-Whitney Test cStudent; T Test dFisher Exact test

In this study, ROC curve analysis was also carried out to see the value.cut offNLR in mitral stenosis patients to predict the severity of mitral stenosis. ROC curve analysis showed good ability of NLR value, with P value = 0.0001, AUC 0.856, and 95% CI 0.772 - 0.940. The NLR threshold value of 2.91 has a sensitivity of 82% and a specificity of 81.8% to predict severe mitral stenosis severity. AUC values above 0.5 are considered to have significant predictive ability, where the closer to 1 the stronger the predictor power. In the ROC curve model of this study, an AUC value of 0.856 was obtained so that it can be concluded that the NLR value has strong predictive ability in detecting the severity of mitral stenosis (Table 4 and Figure 1).

Table 4. Analysis of AUC Values, Sensitivity, Specificity of NLR

Para-Meter	Threshold Valu	AUC	p value	Sensitivity	Specificity	95% ci
NLR	2.91	0.856	0.0001	82%	81.8%	0.772 - 0.940

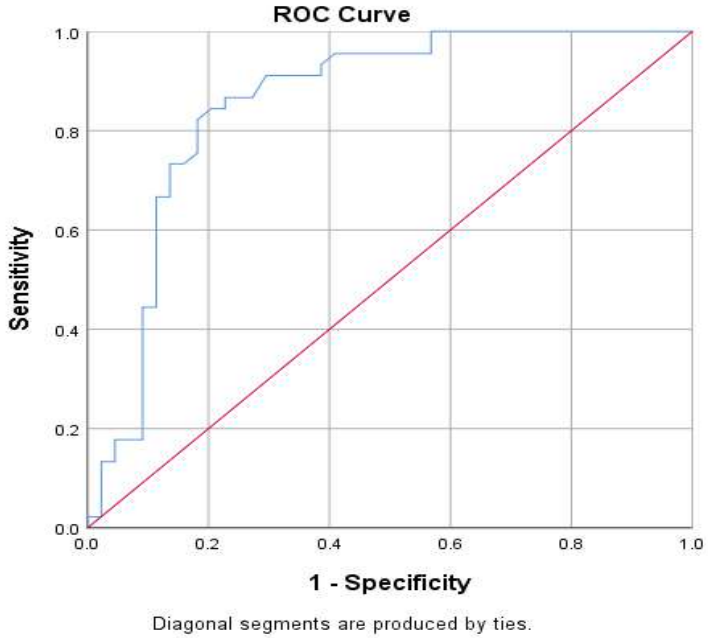

Figure 1. ROC curve of NLR value to assess the severity of mitral stenosis

From the Spearman correlation analysis, there was a moderate correlation between NLR and MVA (Spearman Coeff r = -0.545; P = 0.001) and NLR with MV mean PG (Spearman Coeff r = 0.489; P = 0.001). This shows that the greater the NLR, the smaller the MVA value, while the MV mean PG value will be greater. This is in line with the hypothesis that the NLR value is closely related to the severity of mitral stenosis (Figures 2 and 3).

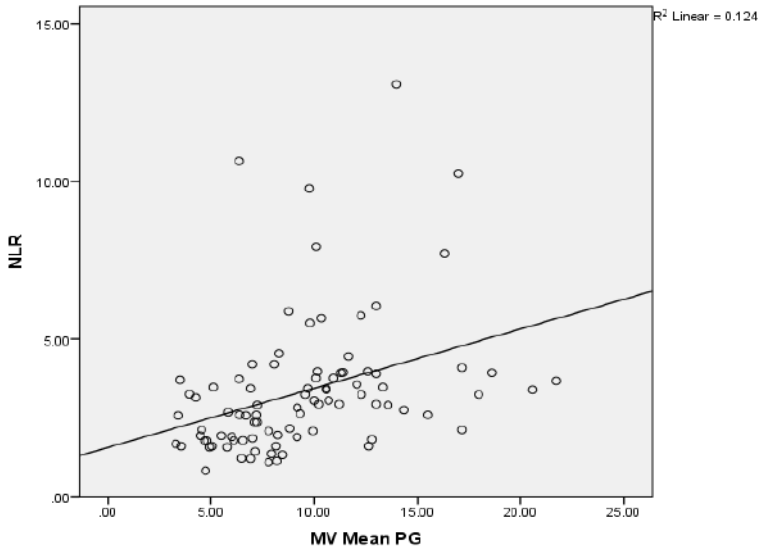

Figure 2. Relationship between NLR value and MV Mean PG

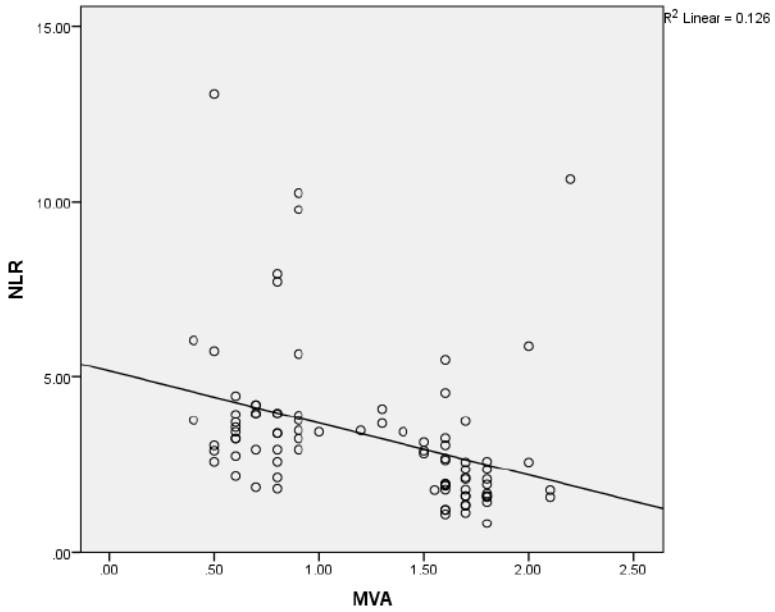

Figure 3. Relationship between NLR and MVA values

DISCUSSION

In this study, 89 samples with mitral stenosis and 10 control samples were obtained. This figure is quite representative considering the still high number of rheumatic heart disease, especially in developing countries. The endemic pattern of rheumatic heart disease is very visible in low- and middle-income countries, especially in Southeast Asia, sub-Saharan Africa, and Oceania. 1 China, India, Pakistan, and Indonesia were the countries with the highest number of rheumatic heart disease cases in 2015. Data show that the prevalence of heart failure worldwide due to rheumatic heart disease increased from 1990 to 2015.[9]

A hospital-based retrospective study conducted at the Harapan Kita National Cardiovascular Center, Indonesia in 2012-2018 showed that 279 patients were diagnosed with rheumatic heart disease, 108 of whom were children (mean age 12.02 ± 3.36 years) and 171 young adults (mean age 24.9 ± 3.84). Rheumatic heart disease is more common in young adult women than in young adult men (1.5:1). Hospitalization due to complications of rheumatic heart disease such as congestive heart failure occurred in 11.11% of cases in children, while pulmonary hypertension occurred in 19.95% of cases in young adults. Reactivation of rheumatic heart disease occurred in 17.2% (48/279) cases, significantly in children (P <0.001). Overall, the mitral valve (either isolated or combined) was the most affected organ in children (39.13%) and young adults (44.81%). Isolated mitral stenosis was more common in young adults (19/47, 40.42%).[10] This also explains the prevalence of female samples found in this study.

In this study, all etiologies of mitral stenosis were rheumatic heart disease. Rheumatic disease is the number one cause of mitral stenosis.[11-13] Uncommon causes of mitral stenosis are mitral valve calcification and congenital heart disease. Other causes of mitral stenosis include infective endocarditis, mitral annular calcification, endomyocardial fibroelastosis, malignant carcinoid syndrome, systemic lupus erythematosus,Whipple, diseaseFabry, and rheumatoid arthritis.[14]

In this study, there were also more samples with atrial fibrillation ECG rhythm in patients with severe mitral stenosis. Atrial fibrillation (AF) is the most common complication in patients with mitral valve stenosis, occurring in approximately 40% of patients. Mitral valve stenosis causes progressive left atrial pressure overload, which in turn causes atrial cardiomyopathy with electrical and structural remodeling. These changes can be demonstrated even in patients with mitral valve stenosis with normal sinus rhythm and are considered precursors to the development of AF. In patients with mitral valve stenosis, the left atrium not only shows pathologically increased volume, but also reduced systolic flow and pump dysfunction due to atrial wall stiffness, which can worsen when AF occurs.[15,16]

In this study, the mitral valve area was found to be smaller in severe mitral stenosis. The mean mitral valve inflow pressure was also higher in patients with severe mitral stenosis severity. This is in line with the pathophysiological explanation that has been discussed in previous publications. One of the criteria to indicate the severity of mitral stenosis is a severe mitral valve area when below 1.5 cm2 and the mean mitral valve inflow pressure exceeds 5 mmHg.[11-13]

In this study, TAPSE values were found to be much worse in line with the severity of mitral stenosis. Previous studies have shown changes in echocardiographic parameters of right heart function along with increasing severity of mitral stenosis. TAPSE values, FAC (fractional area change), S', and RVFWS (RV free wall strain) were substantially decreased in MS cases compared to healthy controls. In addition, PAP values were markedly increased in MS subjects. Furthermore, S and TAPSE values were significantly lower in very severe MS patients compared to severe mitral stenosis patients.[17] As the severity of MS increases, the increaseafterloadRV occurs. Right ventricular-pulmonary circulation coupling is an important physiological phenomenon. The RV is capable of pumping against a pressure of 30 mm Hg, which is one-fourth that of the LV. The RV free wall thickness is thinner than the LV wall thickness. Thus, compared with LV systolic function, RV systolic function is more easily affected and deteriorates with increasing afterload.[18]

In cases of mitral stenosis due to rheumatic heart disease, the inflammatory process plays a major role in the pathophysiology of changes and calcification of the involved mitral valve. Inflammatory markers, as well as inflammatory cells lymphocytes, monocytes and other cells play an active role in the pathogenesis, and are often found to be increased in this condition.[19-22] In this study, absolute neutrophil and lymphocyte values were higher and lower in patients with severe mitral stenosis, respectively. This will result in higher NLR values in severe mitral stenosis, as evidenced by the results of this study. In line with previous studies, which mentioned a strong association between NLR values and the severity of mitral stenosis, this study found similar results. Polat et al. also showed that the NLR threshold value of 2.56 can predict the occurrence of severe rheumatic mitral stenosis with a sensitivity of 75% and a specificity of 74%.[8] In this study, it was obtained through ROC curve analysis that the NLR value, with a P value = 0.0001, AUC 0.856, and 95% CI 0.772 - 0.940, and the NLR threshold value of 2.91 had a sensitivity of 82% and a specificity of 81.8% in predicting severe mitral stenosis.

In previous studies, a weak correlation was found between NLR values and MVA and a moderate correlation between NLR and mean MV PG.[23] However, in this study, a strong correlation was found between NLR values and MVA (Spearman Coeff r = -0.545; P = 0.001) and NLR with mean MV PG (Spearman Coeff r = 0.489; P = 0.001). This is in line with the hypothesis that NLR values are closely related to the severity of mitral stenosis.

This study also clearly found that the mean LAVi value was higher in patients with more severe mitral stenosis. Previous studies have shown that LAVi has no less important prognostic value in patients with progressive MS. One study found that LAVI >57 mL/m2 was independently associated with poor outcomes in patients with progressive MS.[24] Another study found that preoperative left atrial volume index, age, body mass index, and atrial fibrillation were independently associated with the degree of left atrial reverse remodeling during the follow-up period after primary mitral valve surgery. The greatest reverse remodeling was found in patients with higher baseline left atrial volume index (P < .001), but less reverse remodeling was observed in patients with older age (P < .001).[25]

A correlation has also been shown to occur between increased NLR and mitral annular calcification (p < 0.001; r = 0.58); NLR was higher in patients with mitral annular calcification (3.3 ± 1.8 vs 1.6 ± 0.4, p < 0.001) compared to control individuals.[26] In another recent study, Öztürk et al reported that higher NLR was associated with spontaneous echocardiographic contrast in rheumatic mitral stenosis.[27] However, in the present study, the analysis was limited to the association between NLR values and the severity of mitral stenosis itself.

Furthermore, another study showed that inflammation also plays a role as a predictor of mortality in valve patients undergoing valve replacement surgery. The study showed that patients with NLR >3.5 had a

higher incidence of death within 30 days after surgery (5.3% vs 1.2%, P <0.001). The study concluded that CRP levels >5 mg / L and NLR >3.5 can effectively predict postoperative heart failure and death within 30 days after surgery. This further provides the basis that the inflammatory process plays a very important role in the occurrence of rheumatic heart disease and can even be used as a prognosis of mortality after surgical heart valve replacement.[28]

CONCLUSION

There was a significant relationship between neutrophil-lymphocyte ratio (NLR) and the severity of mitral stenosis due to rheumatic heart disease in outpatients at H. Adam Malik General Hospital Medan. Significant differences were found in the mean and minimum-maximum values of NLR between mild-moderate mitral stenosis (1.93; 0.82–10.64) and severe (3.56; 1.81–13.08). Statistical analysis showed that these results were statistically significant (P = 0.0001; Mann-Whitney test). NLR values can predict severe mitral stenosis, with a threshold value of 2.91 which has a sensitivity of 82% and a specificity of 81.8% (P = 0.0001; AUC 0.856; 95% CI 0.772–0.940).

In further studies, it is recommended to consider multivariate tests to compare predictive factors of severe mitral stenosis, as well as evaluate NLR in predicting rehospitalization and mortality risk in patients with severe mitral stenosis, including those undergoing valve replacement or PTMC.

DECLARATIONS

The authors would like to thank the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara

CONSENT FOR PUBLICATION

This study was approved by Ethical Committee of Universitas Sumatera Utara, Medan, Indonesia, on Agustus 23, 2023. No : 911/KEPK/USU/2023. The sampels provided the consent to participated in the study.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest in this report.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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