Usefulness of Novel Hematologic Inflammatory Parameter: Neutrophil to lymphocyte ratio in patients with rheumatic valve diseases

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Abstract

Background: the role of Neutrophil to lymphocyte ratio in predicting the presence and severity of rheumatic valve diseases has not been well studied in contemporary practice. **Methods:** this is a case control cross sectional study included four hundred patients who referred to the cardiology department of Benha university hospitals and National heart institute. The study population divided into two groups; Group A included 300 patients (as a case group diagnosed to have RHD) and Group B included 100 participants as a control group. Case group were further divided into four groups Group I included patients with isolated rheumatic mitral valve stenosis, Group II included patients with isolated rheumatic mitral valve regurgitation, Group III included patients with severe mixed rheumatic mitral valve lesions enrolled and group IV included patients with multivalvular RHD. **Results:** The NLR were higher in case group than control group (3.32±1.39 vs 1.57± 0.28) p=0.001. the mean NLR count was higher among severe multi valvular cases (4.35± 1.27) than less severe cases (3.58± 1.1in severe combined mitral valve cases, 3.41± 0.99 in severe MS, 2.84± 0.77 in severe MR) p=0.001. **Conclusion:** The presence and severity of ongoing chronic inflammation affecting the progression of chronic RHD could be predicted by measuring the NLR count, which is an inexpensive, readily available marker of persistent chronic inflammation.

Keywords: RHD, Neutrophil to lymphocyte ratio, inflammation

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Introduction

Rheumatic fever is a multifactorial disease that follows group A beta hemolytic streptococcal (GAS) pharyngitis **(the agent)** in a susceptible individual **(the host)** who lives under deprived social conditions **(the environment).** The theory of molecular mimicry holds that GAS pharyngitis triggers an autoimmune response to epitopes in the organism that cross-react with similar epitopes in the heart, brain, joints, and skin, and repeated episodes of rheumatic fever lead to rheumatic heart disease[(1)]. Chronic RHD is one of the latest sequels of ARF occurring in approximately 30% of patients with rheumatic fever. In case of ARF, several inflammatory cells, such as neutrophils, macrophages, and T and B lymphocytes, infiltrate both the myocardium and the valves. The healing process of rheumatic carditis results in varying degrees of fibrosis and valve damage. Inflammatory process plays a key role in RHD [(2)].

A blood marker that could discriminate patients who are at high risk to develop RHD would be beneficial to decreasing the morbidity and mortality of this disease. Previous studies have shown that patients with RHD have continuous (persistent) chronic inflammation [(2-7)]. Since RHD is a disease of underdeveloped countries with limited resources and technical facilities, inflammatory markers are rarely used in daily practice. Therefore, there is a need for simple, inexpensive, and easily obtainable biochemical markers that can be used in daily practice.

Recently, it was reported that the neutrophil–lymphocyte ratio (NLR) is an important marker of inflammation in several disorders, especially cardiovascular diseases [(8, 9)] and cancer [(10)].

Since it has been hypothesized that the NLR may reflect ongoing inflammation, we sought to investigate the relationship between NLR as a marker of systemic inflammation and rheumatic valve diseases, and to provide an inexpensive, readily available marker of persistent, chronic inflammation, that may be useful in predicting the presence and severity of rheumatic valve diseases.

Patients and methods

Case control cross sectional study included 400 participants who referred to the cardiology department of Benha university hospitals and National heart institute. The study population divided into two groups; Group A included 300 patients (as a case group

diagnosed to have RHD) and Group B included 100 participants as a control group. Case group were further divided into four groups Group I included patients with isolated rheumatic mitral valve stenosis, Group II included patients with isolated rheumatic mitral valve regurgitation both subgroups were further subdivided according to severity into mild, moderate and severe Group III included patients with mixed rheumatic mitral valve lesions (mixed mitral stenosis and regurgitation). In these group only patients with severe mixed rheumatic mitral valve lesions enrolled in the study (severe MS& severe MR) other non severe stenotic or regurgition lesions were excluded. Group IV included patients with multivalvular RHD (mixed rheumatic mitral and aortic valve affection). In these group only patients with severe rheumatic mitral valve affection either stenosis or regurgitation and severe rheumatic aortic valve affection enrolled in the study. In group III & IV the exclusion aimed to define a cut off value for progression of RHD from single mitral valve disease or combined severe mitral valve disease to severe multivalvular RHD. All patients had review of their medical history, underwent a clinical examination, ECG, and transthoracic echocardiography. The following patients were excluded; Chronic rheumatic heart disease with mixed mitral valve affection less than severe of both stenosis and regurgitation, Chronic rheumatic heart disease with multivalvular affection of both mitral and aortic valve less than severe, Acute rheumatic fever and acute infections, Chronic inflammatory disease (systemic lupus, rheumatoid arthritis) and malignancy, Patients with recent trauma, Pregnant and Patients with (diabetes mellitus, hypertension, coronary artery disease (CAD), chronic renal diseases and hepatic diseases).

Echocardiography assessment

Two-dimensional and Doppler echocardiography was performed. Echocardiographic changes that meet the criteria for ‘definite RHD’ are considered to be rheumatic in origin, provided that other etiologies have been excluded by echocardiography and clinical context.Morphological features of rheumatic mitral valve disease include; anterior mitral valve leaflet thickening ≥3 mm (age specific), chordal thickening, restricted leaflet motion, excessive leaflet tip motion during systole [(11)]. Morphological features of rheumatic aortic valve disease include; irregular or focal thickening, coaptation defect and restricted leaflet motion [(11)].

Biochemical measurements

Venous blood samples will be drawn in the morning from the antecubital vein . Total and differential leukocyte counts were measured by an automatic blood counter. Glucose, creatinine, and liver function tests will be assessed by standard methods. The base line NLR was measured by dividing the neutrophil count by the lymphocyte count.

Statistical Analysis

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 16.

Descriptive statistics were calculated for the data in the form of; mean and standard deviation for quantitative data, frequency and distribution for qualitative data.

In the statistical comparison between the different groups, ANOVA test was used to compare mean of more than two groups of quantitative data.Inter-group comparison of categorical data was performed by using chi square test (*X2*-value) and fisher exact test (FET).Correlation coefficient was used to find relationships between variables. Receiver–operating characteristic (ROC) curve analysis was used to determine the optimum cutoff levels of NLR that would predict the severity of RHD.

Results

A total of 400 participants (300 patients as case group and 100 participants as control group) were enrolled in this study. The case group was further categorized into four subgroups and the percentage of distribution of different case subgroups was illustrated in Figure 1.

Subgroup I enrolled 67 patients (22.33%) with rheumatic MS, and further subdivided into mild (12 patients), moderate (19 patients) and severe sub groups (36 patients).Subgroup II enrolled 69 patients (23%) with rheumatic MR, and further subdivided into mild (15 patients), moderate (20 patients) and severe sub groups (34 patients).Subgroup III enrolled 64 patients (21.33%) with combined severe rheumatic mitral stenosis and regurgitation. Subgroup IV enrolled 100 patients (33.33%) with severe mixed rheumatic mitral and aortic valve affection.

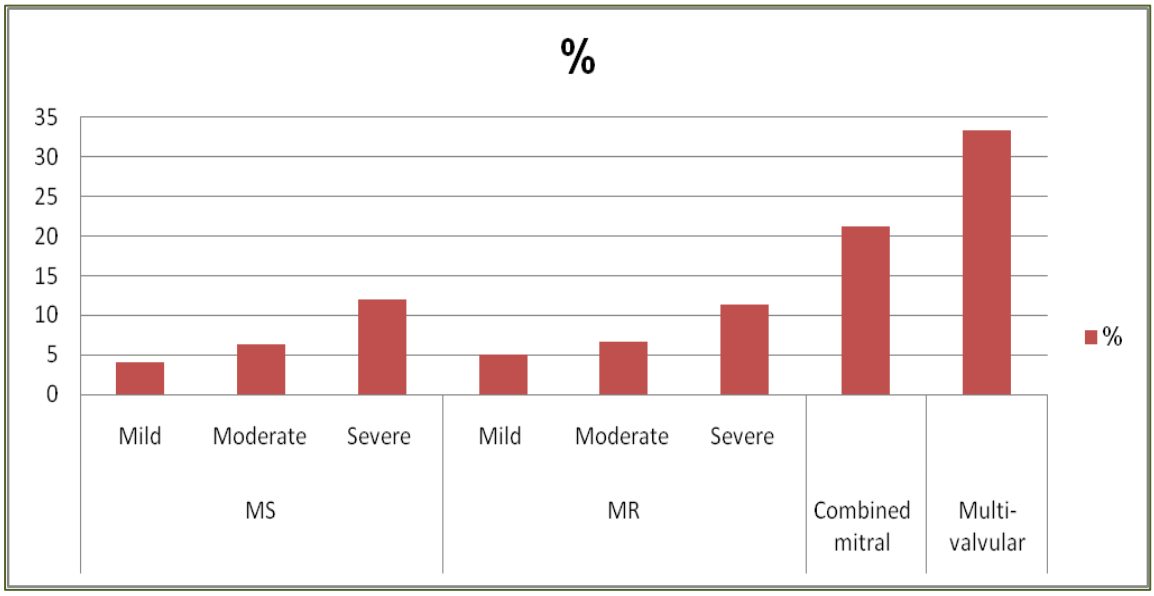

Figure (1): percentage of distribution of different case subgroups.

1-Age and Gender

The mean age of the whole participants was 36.78±10.17 years range from 13 years to 60 years, while as regard gender there were 46.2% males and 53.8% females (table 1).

There was no significant difference in the mean age and gender distribution between both case and control groups; the mean age of case group was 37.16± 10.6 years vs. 35.61± 8.7 years in control group, p value = 0.186) and as regard gender there was 47.0 % males and 53.0% females in case group while in the control participant; there was 44% males and 56% females with p value 0.524) (figure 2&table 1).

There were significant difference between different groups of valve diseases as regard the mean age (p = 0.022), However as regard gender distribution there was no significant difference between different groups (p value 0.107) (table 2).

Table (1): Comparison between case and control groups regarding personal data

	Age **mean ±SD**	**Gender**	
		Male n (%)	**Female** n (%)
Total Population (n=400)	36.78±10.17 (13-60 years)	185(46.2%)	215(53.8%)
Case group(n=300)	37.16± 10.6	141(47.0%)	159(53.0%)
Control group (n=100)	35.61± 8.7	44(44.0%)	56(56.0%)
St t test	1.32	X^2= 0.272	
P value	0.186	0.602	

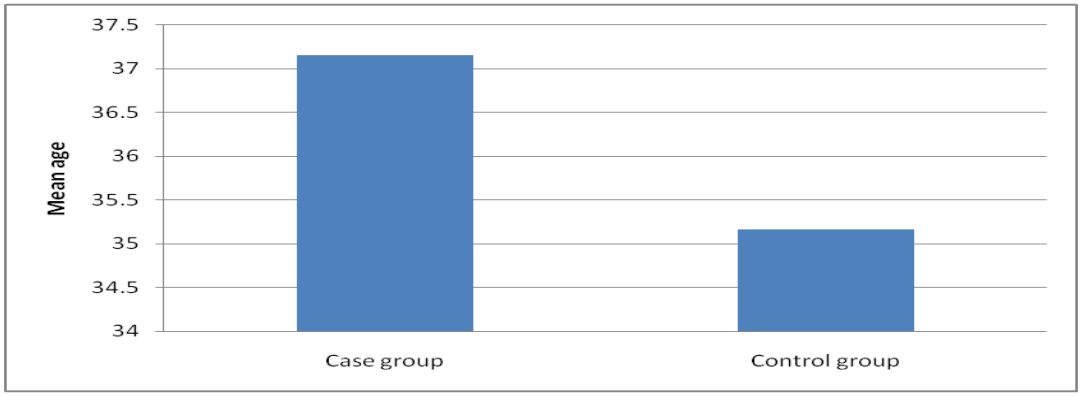

Figure (2): Comparison between case and control groups as regard mean age.

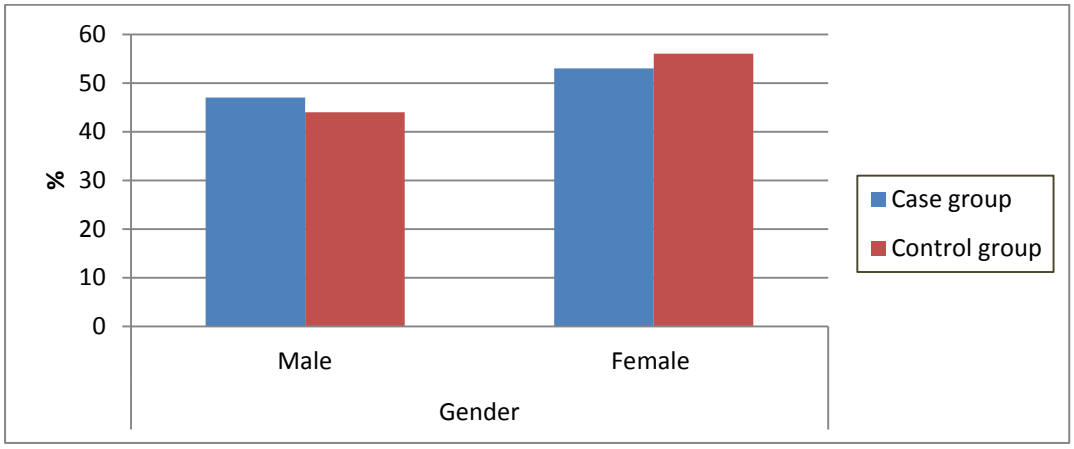

Figure (3): Comparison between case and control groups as regard gender.

Table (3): Comparison between different groups regarding personal data

	Age mean ±SD	Gender	
		Male n (%)	**Female** n (%)
Mild MS (n=12)	34.33± 6.31	5(41.7)	7(58.3)
Moderate MS (n=19)	37.63± 11.41	9(47.4)	7(52.6)
Severe MS (n=36)	36.89± 11.15	14(38.9)	22(61.1)
Mild MR (n=15)	26.73± 9.68	9(60.0)	6(40.0)
Moderate MR (n=20)	39.5± 10.81	10(50.0)	10(50.0)
Severe MR(n=34)	35.76± 13.3	10(29.4)	24(70.6)
Severe MS+ Severe MR (n=64)	39.72± 8.64	20(31.2)	44(68.8)
Multivalvular (n=100)	37.45± 10.08	64(64.0)	36(36.0)
Test (P)	3.88(0.022)	13.14(0.107)	

2-Rhythm distribution

In the whole study population; 203(50.8) Patients suffered from AF while 123(42.12%) participants had NSR.

In the Case group; 203(67.7) Patients suffered from AF and 97(32.3) patients had NSR while in control group all patients (100) had NSR (Table 4).

The majority of cases with severe MS (88.9%), severe MR (70.6%), severe combined mitral valve affection (84.4%) and severe multivalvular affection (72.0%) suffered from AF while the majority of cases with mild MS (66.7%) and mild MR (93.3%) had NSR (Table 5).

Table (4): Comparison between case and control groups regarding rhythm

	Rhythm	
	NSR n (%)	**AF n (%)**
Study group	197(49.2)	203(50.8)
Case group	97(32.3)	203(67.7)
Control group	100 (100)	0
Test	X^2=137.4	
P value	0.001	

Table (5): Rhythm distribution among different groups of valve diseases

	Rhythm	
	NSR n (%)	AF n (%)
Mild MS	8(66.7)	4(33.3)
Moderate MS	9(47.4)	10(52.6)
Severe MS	4(11.1)	32(88.9)
Mild MR	14(93.3)	1(6.7)
Moderate MR	12(60.0)	8(40.0)
Severe MR	10(29.4)	24(70.6)
Severe MS+ Severe MR	10(15.6)	54(84.4)
Multivalvular	30(30.0)	70(70.0)
Test	FET=46.35	
P Value	0.01	

Rhythm distribution regarding NLR in RHD Group

Regarding rhythm distribution in RHD group There were significant difference in NLR between different groups; the mean NLR was 3.52±1.20in patients suffered from AF while in patients with NSR the mean NLR was 2.74± 1.18 and the p value = 0.001(Table 6 &figure 4).

Table (6): Rhythm distribution regarding NLR in RHD Group

		(n) Mean± SD	t test	P value
NLR	NSR	(97) 2.74± 1.18	5.31	0.001
	AF	(203) 3.52±1.20		

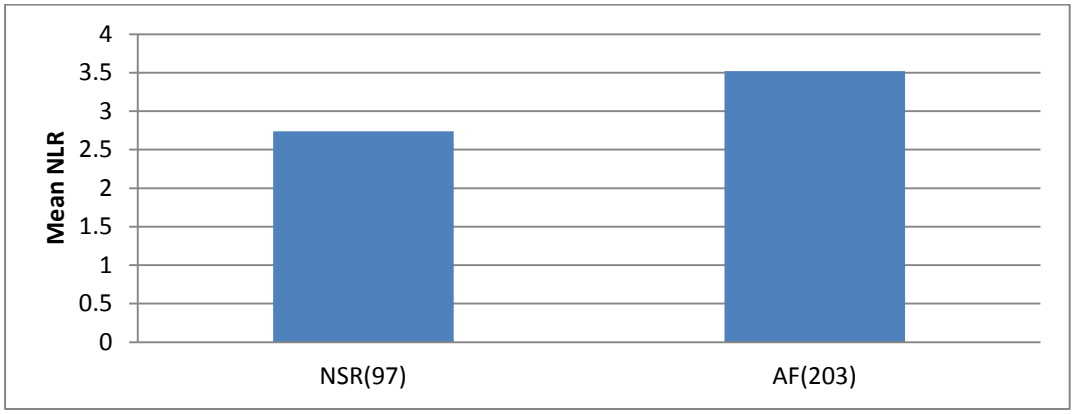

Figure (4): Rhythm distribution regarding NLR in RHD Group.

3-Laboratory data

There was significant difference in the mean TLC, Neutrophil, lymphocyte, NLR counts between case and control groups

The mean TLC, Neutrophil counts and NLR were higher in case group than control group (7.06±1.54 vs 6.44±1.29, 4.91±1.36vs 3.44±0.88, 3.32±1.39vs 1.57± 0.28) respectively. While the mean lymphocytes count was lower among case group than control group (1.61±0.52 vs 2.24±0.60) respectively (table 7&figure 5).

Table (7): laboratory data among case and control groups

	Case group(300)	Control group(100)	St t test	P value
TLC mean ±SD	7.06±1.54	6.44±1.29	3.42	0.001
Neutrophil mean ±SD	4.91±1.36	3.44±0.88	9.73	0.001
Lymphocytes mean ±SD	1.61±0.52	2.24±0.60	8.98	0.001
NLR mean ±SD	3.32±1.39	1.57±0.28	12.4	0.001

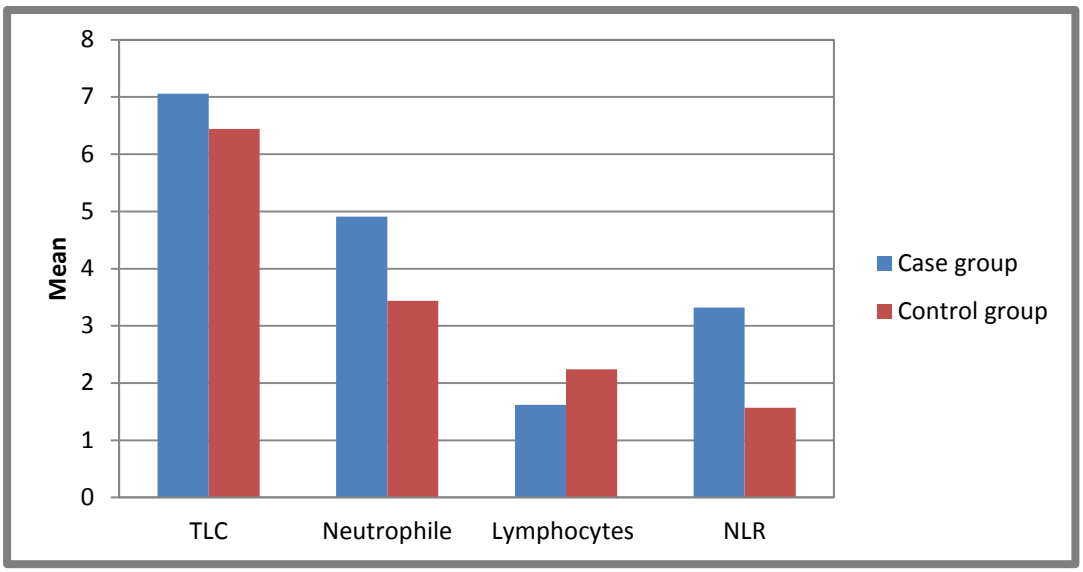

Figure (5): Comparison between case and control groups as regard TLC, Neutrophil count, Lymphocyte Count and NLR

Table (8): laboratory data among different groups

	TLC mean ±SD	Neutrophil mean ± SD	Lymphocytes mean± SD	NLR mean ± SD
Mild MS	5.53± 1.43	3.26± 0.87	1.83± 0.5	1.79± 0.21
Moderate MS	5.74± 0.84	3.78± 0.65	1.64± 0.31	2.37± 0.50
Severe MS	7.46± 1.5	5.24± 1.17	1.63± 0.45	3.41± 0.99
Mild MR	5.88± 1.6	3.84± 0.98	2.46± 0.67	1.61± 0.40
Moderate MR	6.22± 1.65	4.15± 0.99	2.06± 0.73	2.17± 0.58
Severe MR	6.94± 1.45	4.7± 1.18	1.7± 0.36	2.84± 0.77
Severe MS + Severe MR	7.11± 1.52	5.11± 1.28	1.48± 0.36	3.58± 1.1
Multivalvular	7.64± 1.31	5.67± 1.2	1.36± 0.29	4.35± 1.27
Control group	6.44± 1.29	3.44± 0.88	2.24± 0.60	1.57± 0.28
Test	7.12	29.41	22.56	70.14
P value	0.001	0.001	0.001	0.001

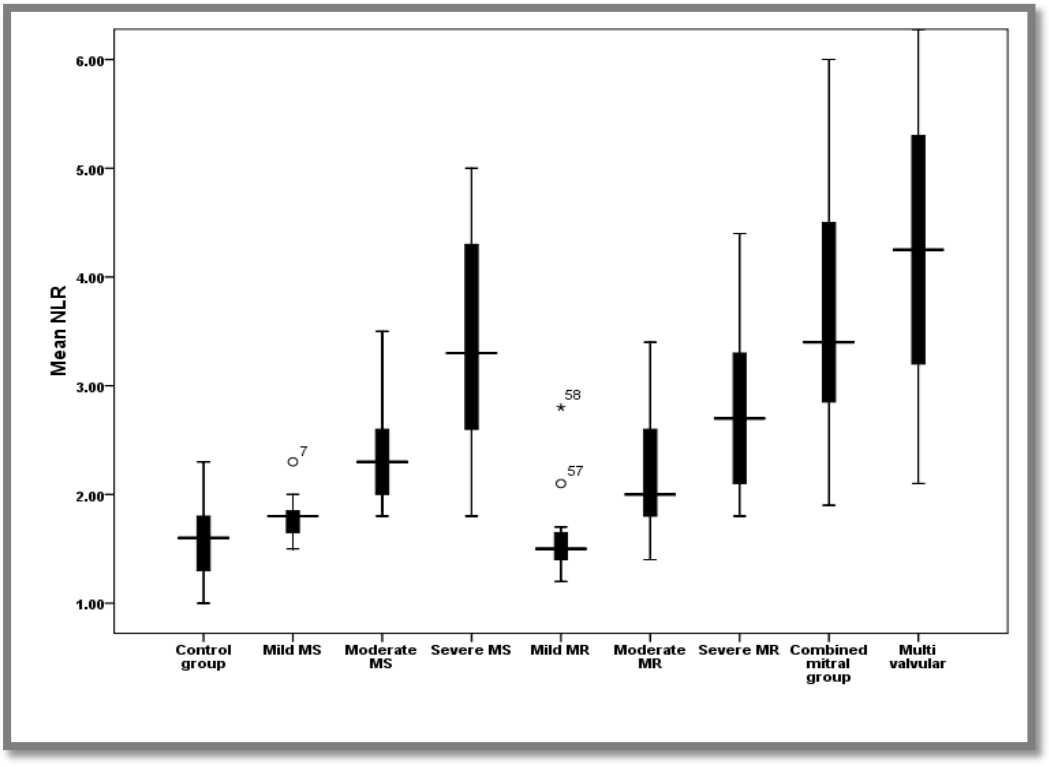

Figure (6): Box plot curve show distribution of NLR among different groups.

Table 8 and figure 6 illustrated that there was significant difference in the mean TLC, Neutrophil, lymphocyte, NLR counts between different groups of RHD.

In patients with MS; The mean TLC, Neutrophil and NLR Count was higher in severe MS than moderate and mild cases (TLC count 7.46± 1.5, 5.74± 0.84, 5.53± 1.43; Neutrophil count 5.24± 1.17, 3.78± 0.65, 3.26± 0.87; NLR Count 3.41± 0.99, 2.37± 0.50, 1.79± 0.21) respectively, however the mean lymphocyte count was lower in severe MS than moderate and mild cases (1.63± 0.45, 1.64± 0.31, 1.83± 0.5) respectively.

Also in patients with MR, The mean TLC, neutrophil count and the mean NLR count were higher in severe MR than moderate and mild cases (TLC count 6.94± 1.45, 6.22± 1.65, 5.88± 1.6; Neutrophil count 4.7± 1.18, 4.15± 0.99, 3.84± 0.98; NLR count 2.84± 0.77, 2.17± 0.58, 1.61± 0.40) respectively, however the mean lymphocyte count was lower in severe MR than moderate and mild cases (1.7± 0.36, 2.06± 0.73, 2.46± 0.67) respectively.

Moreover the mean NLR count was higher among severe multivalvular cases (4.35± 1.27) than less severe cases (3.58± 1.1in severe combined mitral valve cases, 3.41± 0.99 in severe MS, 2.84± 0.77 in severe MR).

4-Validity of NLR

a. Using a cutoff level of 2.25, the NLR could predict RHD with a sensitivity of 78.7%specificity of 99.0 % (figure 7).
b. Using a cutoff level of 2.55, the NLR could predict severe MS with sensitivity of 77.8 % specificity of 77.4% % among rheumatic MS group (figure 8).
c. Using a cutoff level of 2.55, the NLR could predict combined severe rheumatic mitral valve disease with a sensitivity of 78.1 % specificity of 47.8%% in patients with rheumatic Mitral stenosis disease (figure 9).
d. Using a cutoff level of 2.55, the NLR could predict severe multivalvular RHD with a sensitivity of 88.0% specificity of 47.8% in patients with rheumatic MS (figure 10).
e. Using a cutoff level of 2.45, the NLR could predict severe rheumatic MR with a sensitivity of 64.7 % specificity of 82.9% in patients with mild to moderate rheumatic MR (figure 11).
f. Using a cutoff level of 2.55, the NLR could predict combined severe rheumatic mitral disease with a sensitivity of 78.1 % specificity of 59.4% in patients with rheumatic MR (figure12).
g. Using a cutoff level of 2.55, the NLR could predict severe rheumatic multivalvular disease with a sensitivity of 88.0%, specificity of 59.4% in patients with rheumatic MR (figure13).
h. Using a cutoff level of 3.65, the NLR could predict severe rheumatic multivalvular disease with a sensitivity of 54.0% specificity of 59.4%in patients with severe combined rheumatic mitral valve disease (figure14).

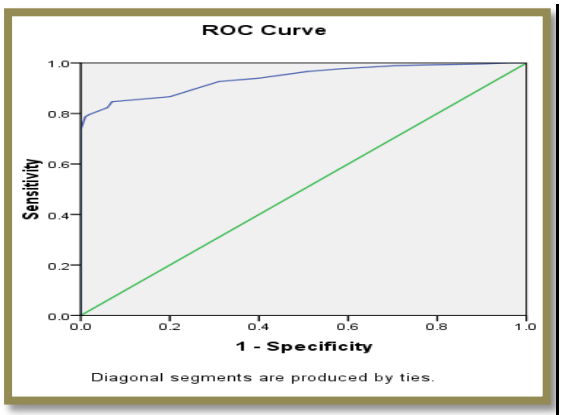

Figure (7): The receiver–operating characteristic (ROC) curve analysis of neutrophil to lymphocyte ratio for predicting RHD

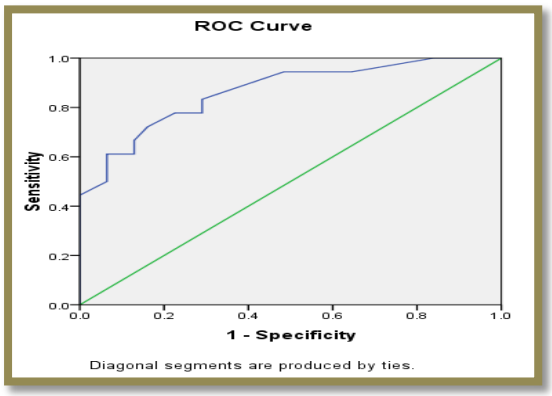

Figure (8): ROC curve analysis of NLR in predicting severe rheumatic MS among rheumatic MS group

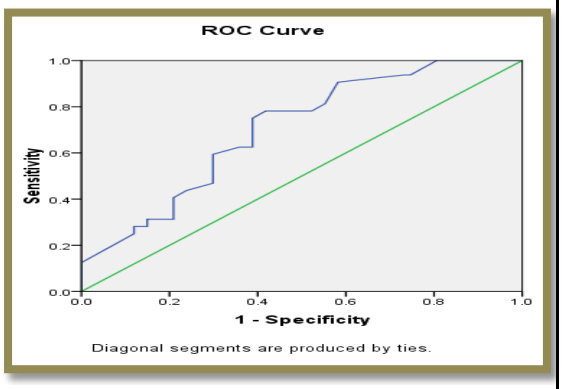

Figure (9): ROC curve analysis of NLR in predicting severe rheumatic multivalvular disease among rheumatic MS group

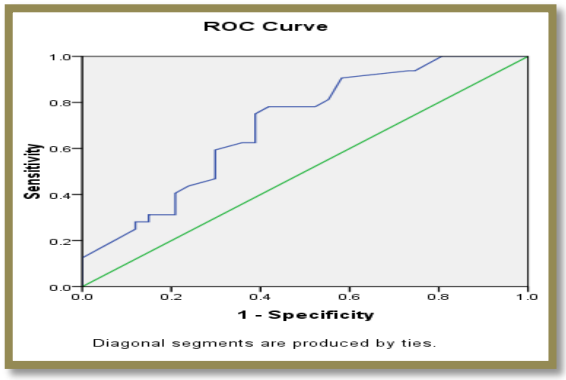

Figure (10): ROC curve analysis of NLR in predicting severe rheumatic multivalvular disease among rheumatic MS group

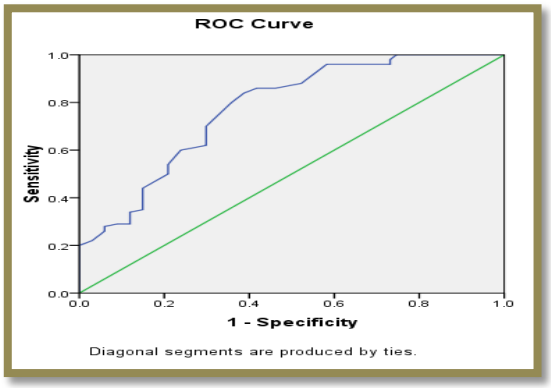

Figure (11): ROC curve analysis of NLR in predicting severe rheumatic MR among rheumatic MR group

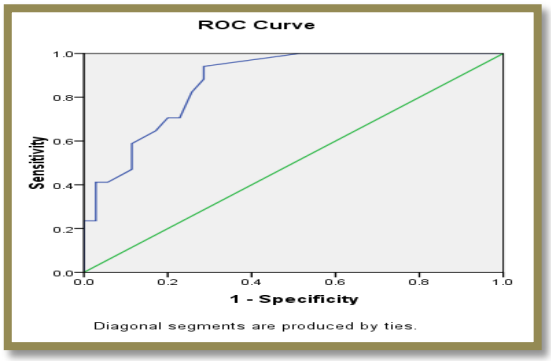

Figure (12): ROC curve analysis NLR in predicting combined severe rheumatic mitral disease among rheumatic MR group.

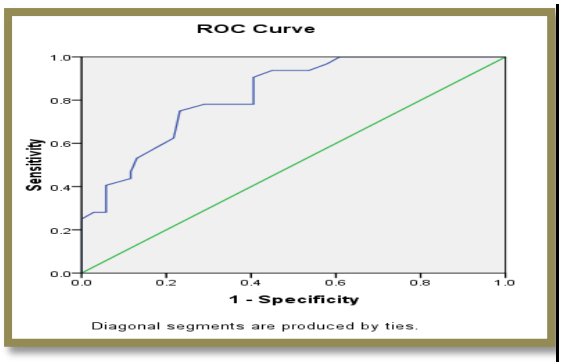

Figure (13): ROC curve analysis of NLR in predicting severe rheumatic multi valvular disease among rheumatic MR group

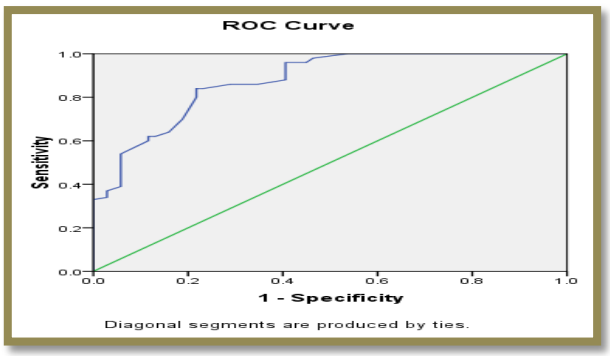

Figure (14): ROC curve analysis of NLR in predicting severe rheumatic multi-valvular disease among severe combined rheumatic mitral group

Table (9): progression of RHD

Progression of RHD		Cut off point	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV	Accuracy
From	To							
Normal	RHD	2.25	0.94 (0.918-0.961)	78.7%	99.0%	99.6%	60.7%	83.8%
Mild and moderate MS	Severe MS	2.55	0.865 (0.78-0.949)	77.8%	77.4%	80.0%	75.0%	77.6%
MS	CSRMVD	2.55	0.701 (0.613-0.79)	78.1%	47.8%	58.8%	69.6%	62.6%
MS	SMRD	2.55	0.774 (0.701-0.847)	88.0%	47.8%	71.5%	72.7%	71.9%
Mild and moderate MR	Severe MR	2.45	0.872 (0.79-0.954)	64.7%	82.9%	78.6%	70.7%	73.9%
MR	CSRMVD	2.55	0.826 (0.758-0.894)	78.1%	59.4%	64.1%	74.5%	68.4%
MR	SMRD	2.55	0.875 (0.823-0.927)	88.0%	59.4%	75.9%	77.4%	76.3%
CSRMVD	SMRD	3.65	0.602 (0.513-0.691)	54.0%	59.4%	67.5%	45.2%	56.1%

RHD: Rheumatic heart disease, **MS:** Mitral stenosis, **MR:** Mitral regurgitation, **CSRMVD:** Combined severe Rheumatic mitral valve disease, **SMRD:** Severe multivalvular Rheumatic disease, **AUC:** area under curve; **CI:** confidence interval, **PPV**: Positive Predictive Value, **NPV:** Negative Predictive Value

Discussion

The NLR is significantly higher in patients with RHD than control group and is highest among severe combined aortic and mitral rheumatic heart diseases; cut off values was taken to predict the progression of RHD from mild cases to severe cases among different groups.

The hepatocyte-derived acute phase reactant C-reactive protein was the subject of intense researches over the last two decades. Many authors reported high levels of high sensitivity C-reactive protein either in acute or chronic rheumatic heart disease. In a study by Golbasi et al, levels of high-sensitivity C-reactive protein (hsCRP) were higher in patients with chronic rheumatic valvular disease than in healthy participants and patients with valve replacement which may indicate that the inflammatory response persists in the chronic phase of rheumatic heart disease [(7)]**.** In addition, hs CRP levels were higher in children with RHD compared to the control group, and hs CRP levels were correlated with the degree and severity of the valve involvement [(6)].

Similarly, in a study conducted on patients with rheumatic mitral stenosis, hs CRP levels were significantly higher in patients with RMS than in the control group, and hsCRP values correlated with the Wilkins valve score and its components [(12)].Kaya et al detected a significant positive correlation between the hs CRP and the NLR in patients with Rheumatic MS. In this study, only patients with Rheumatic MS were included, and patients with and without spontaneous echo contrast were compared in terms of NLR [(13)]**.**In accordance with the aforementioned studies, the NLR had a positive and significant correlation with hs CRP.

In current study, we found that the mean TLC, Neutrophil counts and NLR were higher in case group than control group (7.06±1.54 vs 6.44±1.29, 4.91±1.36 vs 3.44±0.88, 3.32±1.39 vs 1.57± 0.28) respectively. While the mean lymphocytes count was lower among case group than control group (1.62±0.52 vs 3.44± 0.88) respectively.

In a retrospective study among patients with Rheumatic MS. Lymphocyte count was lower in the Rheumatic MS group as compared to the control group [1.8 (0.4-4.6) vs. 2.2 (0.8-4.0), $p<0.001$]. NLR was significantly higher in the Rheumatic MS group [2.9 (0.6-13.0) vs. 2.1 (0.7-5.8), $p<0.001$] [(14)].

In our study there was significant difference in the mean TLC, Neutrophil, lymphocyte, NLR counts between case and control groups. The mean TLC, Neutrophil

counts and NLR were higher in case group than control group (7.06±1.54 vs 6.44±1.29 p =0.001, 4.91±1.36 vs 3.44±0.88 p =0.001, 3.32±1.39 vs 1.57± 0.28 p =0.001) respectively.

While the mean lymphocytes count was lower among case group than control group (1.62±0.52 vs 3.44± 0.88 p =0.001) respectively (table 18&figure 14).

Using a cutoff level of 2.25, the NLR could predict RHD with a sensitivity of 78.7 % specificity of 99.0 % (figure 16&table 21).

Polat et al detected that the NLR was significantly higher in patients with severe MS when compared to those with mild to moderate MS (P = .002) while lymphocyte count was lower (P = .034). Neutrophil and lymphocyte counts were significantly different between patients with severe RMS and those with mild to moderate MS, while the total WBC counts were similar (Neutrophil count 6.43 + 1.95 vs 5.56 + 1.86, z = 2.038, P = .042; lymphocyte count 1.87 + 0.66 vs 2.26 + 0.64, z = 2.119, P = .034; respectively). Also Patients with severe Rheumatic MS had significantly higher NLR levels than those with mild to moderate Rheumatic MS (3.72 + 1.35 vs 2.66 + 1.24, z = 3.067, P = .002; respectively). Using a cutoff level of 2.56, the NLR predicted severe Rheumatic MS with a sensitivity of 75% and specificity of 74% [(15)].

Results of current study were also in accordance with previous study on association of NLR with rheumatic mitral stenosis. Neutrophil and NLR Count was higher in severe MS than moderate and mild cases (Neutrophil count 5.24± 1.17, 3.78± 0.65, 3.26± 0.87; NLR Count 3.41± 0.99, 2.37± 0.50, 1.79± 0.21) respectively, also the mean lymphocyte count was lower in severe MS than moderate and mild cases (1.63± 0.45, 1.64± 0.31, 1.83± 0.5) respectively.

However the mean TLC was significantly higher in severe MS than moderate and mild cases (7.46± 1.5, 5.74± 0.84, 5.53± 1.43) respectively.

Using a cutoff level of 2.55, the NLR could predict severe MS with sensitivity of 77.8 % specificity of 77.4 % among rheumatic MS group.

We also defined a cutoff level 2.55 to predict combined severe rheumatic mitral valve disease and severe multivalvular RHD with a sensitivity of 78.1 % &88.0 % respectively and specificity of 47.8% to both among patients with rheumatic MS.

We further studied association of NLR with rheumatic mitral regurgitation The mean TLC, neutrophil count and the mean NLR count were higher in severe MR than moderate and mild cases (TLC count 6.94± 1.45, 6.22± 1.65, 5.88± 1.6; Neutrophil count 6.8± 1.45, 3.78± 0.65, 3.26± 0.87; NLR count 2.84± 0.77, 2.17± 0.58, 1.61± 0.40) respectively, however the mean lymphocyte count was lower in severe MR than moderate and mild cases (1.7± 0.36, 2.06± 0.73, 2.46± 0.67) respectively.

Using a cutoff level of 2.45, the NLR could predict severe rheumatic MR with a sensitivity of 64.7 % specificity of 82.9 % in patients with mild to moderate rheumatic MR. we also defined a cutoff level 2.55 to predict combined severe rheumatic mitral valve disease and severe multivalvular RHD with a sensitivity of 78.1 % &88.0 % respectively specificity of 59.4 % to both.

In Combined severe mitral stenosis and regurgitation The Mean Neutrophil Count was 5.11± 1.28. The Mean Lymphocyte count was 1.48± 0.36. The Mean NLR was 3.58± 1.1. Using a cutoff level of 3.65, the NLR predicted severe rheumatic multivalvular disease with a sensitivity of 54.0 % specificity of 59.4 %.

In addition to that the mean NLR count was higher among severe multi valvular cases (4.35± 1.27) than less severe cases (3.58± 1.1in severe combined mitral valve cases, 3.41± 0.99 in severe MS, 2.84± 0.77 in severe MR).

Many previous studies had shown that higher levels of NLR were associated with increased inflammation in various cardiovascular diseases. High NLR levels have been found to be independent predictors of the severity of coronary artery disease [(16)], slow coronary flow phenomenon [(17)], arterial stiffness, and coronary calcium scores [(18)].

In a review that included more than 34 000 patients, the NLR was shown to be a simple, readily available inflammatory marker for the risk stratification of patients with acute coronary syndrome or for whom revascularization was performed [(19)].

In addition, higher NLR levels were associated with an increased risk of long-term mortality in patients admitted with acute decompensated heart failure [(20)].Also Turak et al found a significant relationship between the NLR and the in-hospital mortality and cerebrovascular events in patients with infective endocarditis [(21)].

In addition to other parameters used for risk stratification in various cardiovascular diseases, a recent review has shown the NLR to be a simple, easily obtainable marker of inflammation [8].

Similarly, in patients with chronic renal failure, the NLR was found to be correlated with the standard inflammatory markers hsCRP and IL-6 [22].

The NLR was significantly increased in patients with pulmonary arterial hypertension, for which inflammation plays a key role in the pathophysiology [23].The NLR was also increased in certain types of cancer in which inflammation is prominent. In a review including a large number of patients (>37 000) with various types of cancers, the NLR anticipated the clinical prognosis, and it was associated with other markers of inflammation, in particular with hsCRP. Elevation in the NLR is associated with hypoalbuminemia, suggesting that the NLR may be able to demonstrate the malnutrition status of patients with cancer [10].

High levels of neutrophil in patients with chronic rheumatic valve disease indicate the persistence of inflammation in the chronic phase. In current study, patients with RHD had significantly lower lymphocyte counts. The main cause of lymphopenia was probably the decreased production of lymphocytes as a result of increased steroid levels due to RHD-induced stress conditions. The other probable cause may be the increased apoptosis of lymphocytes triggered by the increased inflammatory status in RHD [14], or may be due to malnutrition; and therefore, further studies should include tests to determine malnutrition status [15].

Conclusion

Patients with RHD showed significantly higher levels of NLR count than normal population and patients with multivalvular RHD showed significantly higher levels of NLR count than less severe cases.

According to these findings, the presence and severity of ongoing chronic inflammation affecting the progression of chronic RHD could be predicted by measuring the NLR count, which is an inexpensive, readily available marker of persistent chronic inflammation.

Recommendations

Levels of inflammatory markers as N/L ratio should be routinely checked in all patients presenting with chronic RHD.

Further studies needed to investigate the role of NLR in prediction and prognosis of ARF and its value after ballon valvulopalasty or surgical treatment.

Randomized controlled trials are required to determine the value of anti-inflammatory therapy like Aspirin, steroid and statin in the chronic phase of RHD.

Study limitations

The limited number of patients and the use of data from a single center could limit the strength of conclusions reached from this study.

A spot NLR value for our analysis was used rather than long term follow up to show the outcome on long term basis.

Measurement of other inflammatory markers while measuring NLR could provide stronger evidence of the results of current study.

References

1-Carapetis J, McDonald M, Wilson NJ: Acute rheumatic fever. Lancet. 2005; 366:155-168.

2-Davutoglu V, Celik A, Aksoy M: Contribution of selected serum inflammatory mediators to the progression of chronic rheumatic valve disease, subsequent valve calcification and NYHA functional class. J Heart Valve Dis Mar. 2005; 14(2): 251–256.

3. Krasuski RA, Bush A, Kay JE, et al. C-reactive protein elevation independently influences the procedural success of percutaneous balloon mitral valve commissurotomy. Am Heart J. 2003; 146(6): 1099-1104.

4. Yetkin E, Erbay AR, Ileri M, et al. Levels of circulating adhesion molecules in rheumatic mitral stenosis. Am J Cardiol. 2001; 88(10):1209 1211.

5. Guilherme L, Cury P, Demarchi LM, et al. Rheumatic heart disease: proinflammatory cytokines play a role in the progression and maintenance of valvular lesions. Am J Pathol. 2004;165(5): 1583-1591.

6. Habeeb NM, Al Hadidi IS. Ongoing inflammation in children with rheumatic heart disease. Cardiol Young. 2011;21(3):334-339.

7. Golbasi Z, Ucar O, Keles T, et al. Increased levels of high sensitive C-reactive protein in patients with chronic rheumatic valve disease: evidence of ongoing inflammation. Eur J Heart Fail. 2002;4(5):593-595.

8. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11(1):55-59.

9. Kaya MG. Inflammation and coronary artery disease: as a new biomarker neutrophil/lymphocyte ratio [in Turkish]. Turk Kardiyol Dern Ars. 2013;41(3):191-192.

10. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88(1):218-230.

11-Reményi B, Wilson N, Steer A, et al: World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease: An evidence-based guideline. Nat Rev Cardiol. 2012; 9:297-309.

12-Alyan O, Metin F, Kacmaz F, et al: High levels of high sensitivity C-reactive protein predict progression of chronic rheumatic mitral stenosis. J Thromb Thrombolysis. 2009; 28(1): 63–69.

13-Kaya MG, Akpek M, Elcik D, et al. Relation of left atrial spontaneous echocardiographic contrast in patients with mitral stenosis to inflammatory markers. Am J Cardiol. 2012;109(6): 851-855.

14- Akboğa M K, Akyel A, Şahinarslan A, et al: Neutrophil-to-lymphocyte ratio is increased in patients with rheumatic mitral valve stenosis?. Anatol J Cardiol. 2015; 15(5):380-384.

15-Polat N, Yildiz A, Yuksel M, et al: Association of Neutrophil–Lymphocyte Ratio With the Presence and Severity of Rheumatic Mitral Valve Stenosis. Clinical and Applied Thrombosis/Hemostasis. 2014; 20(8): 793-798.

16. Kaya H, Ertaş F, İslamoğlu Y, et al: Association between Neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost. 2014; 20(1): 50-54.

17. Doğan M, Akyel A, Çimen T, et al: Relationship between Neutrophil to lymphocyte ratio and slow coronary flow. Clin Appl Thromb Hemost. 2015 ;21(3): 251-254.

18-Park BJ, Shim JY, Lee HR, et al: Relationship of neutrophil–lymphocyte ratio with arterial stiffness and coronary calcium score. Clin. Chim. Acta. 2011; 412(11–12): 925–929.

19-Guasti L, Dentali F, Castiglioni L et al: Neutrophils and clinical outcomes in patients with acute coronary syndromes and/or cardiac revascularisation. A systematic review on more than 34,000 subjects. Thromb. Haemost. 2011; 106(4): 591–599.

20-Uthamalingam S, Patvardhan EA, Subramanian S, et al: Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol. 2011; 107(3): 433–438.

21-Turak O, Özcan F, Isleyen A, et al: Usefulness of Neutrophil-to-Lymphocyte Ratio to Predict In-hospital Outcomes in Infective Endocarditis. Canadian Journal of Cardiology. 2013; 29: 1672-1678.

22-Okyay G U, İnal S, Öneç K, et al: Neutrophil to Lymphocyte Ratio in Evaluation of Inflammation in Patients with Chronic Kidney Disease. Renal Failure. 2013; 35(1): 29–36.

23-Yildiz A, Kaya H, Ertas F, et al: Association between Neutrophil to lymphocyte ratio and pulmonary arterial hypertension. Turk Kardiyol Dern Ars. 2013; 41(7): 604-609.