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# Romatizmal Mitral Darlığı Olan Hastalarda Wilkins Ekokardiyografik Skor ve Nötrofil Lenfosit Oranı Arasındaki İlişki

## Relationship Between Wilkins Echocardiographic Score and Neutrophil to Lymphocyte Ratio In Patients with Rheumatic Mitral Stenosis

Zehra Erkal, Nermin Bayar

Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Antalya, Türkiye

**Öz**

**AMAÇ**: Romatizmal mitral darlığı (RMS) olan hastalarda Wilkins ekokardiyografik skoru (WS) perkütan mitral balon valvuloplastiye (PMBV) uygunluğu değerlendirmede yaygın olarak kullanılmaktadır. WS 11'den yüksek olanlar PMBV için uygun kabul edilmemektedir. Daha önceki çalışmalarda RMS' un ilerlemesinde inflamasyonun rolü gösterilmiştir. Bu çalışmada inflamasyonun göstergelerinden olan nötrofil/lenfosit oranının (NLR) yüksek WS' nu göstermedeki rolü araştırıldı.

**GEREÇ ve YÖNTEMLER**: Bu retrospektif çalışmaya orta-ciddi RMS olan hastalar alındı. Hastaların transtorasik ve transözefageal ekokardiyografik görüntüleri incelendi. Hastalar WS' na göre iki gruba ayrıldı; grup 1'de WS≤ 11 olanlar, grup 2'de WS>11 olanlar. Grupların ekokardiyografik ve hematolojik parametreleri karşılaştırıldı.

**BULGULAR**: Çalışmaya 93'ü kadın (%80) 115 hasta alındı. Grup 1'de 72 hasta (ortalama yaş 43.7±12.0) ve grup 2'de 43 hasta (ortalama yaş 52.7±11.3) vardı. Grup 1'de ortalama WS 7.4±2.0 iken grup 2'de 12.4±0.7 idi. NLR değeri grup 2'de grup 1'den anlamlı olarak daha yüksek saptandı (sırasıyla 3.8±0.5 ve 2.6±0.9, p<0.001). NLR için 3.09 sınır değeri yüksek WS' nu göstermede %100 duyarlılık ve %78 özgüllüğe sahip bulundu.

**SONUÇ**: RMS' lu hastalarda NLR değeri WS>11 olması ile bağımsız ilişkilidir.

**Anahtar Kelimeler:** Biyometrik parametreler, Cerrahi süresi, Fakoemülsifikasyon, Nükleer Skleroz, Ultrason süresi

**Abstract**

**OBJECTIVE**: Wilkins echocardiography score (WS) is commonly used for patients with rheumatic mitral stenosis (RMS) to evaluate their eligibility for percutaneous mitral balloon valvuloplasty (PMBV) treatment. Patients with WS of higher than 11 are not eligible for PMBV treatment. Previous studies demonstrated that inflammation might play a role in RMS progression. The purpose of this study was to investigate the role of neutrophil/lymphocyte ratio (N/L ratio), which is an indicator of inflammation in predicting high WS.

**MATERIALS and METHODS**: In this retrospective study, we investigated 115 patients (93 females, 22 males) with moderate to severe RMS. Transthoracic and transesophageal echocardiography reports were analysed. Patients were divided into two groups according to their Wilkins scores. Patients with a WS ≤ 11 were included in Group 1 and those with a WS >11 were included in Group 2. The echocardiographic and haematological parameters of the groups were compared.

**RESULTS**: Group 1 consisted of 72 patients (mean age 43.7±12.0) and group 2 consisted of 43 patients (mean age 52.7±11.3). In Group 1, the mean WS was 7.4±2.0 while it was 12.4±0.7 in Group 2. The N/L ratio was 3.8±0.5 in Group 2 and it was significantly higher than that of Group 1, which was 2.6±0.9 (p<0.001). The N/L ratio cut-off point was 3.09 with a sensitivity of 100% and specificity of 78% in predicting RMS patients with high WS.

**CONCLUSION**: The N/L ratio was independently associated with WS>11 in patients with RMS.

**Keywords:** Biometric parameters, Nuclear sclerosis, Phacoemulsification, Surgery time, Ultrasound time

## INTRODUCTION

Rheumatic mitral stenosis (RMS) is a late sequela of acute rheumatic fever [1]. Mitral valve is the most commonly affected part of the heart in rheumatic heart disease. It is widely accepted that molecular mimicry between the antigens of mitral valve and streptococcus M protein induces autoimmunity and inflammation, which leads to progressive deformation [2]. Studies demonstrate that high-sensitive C-reactive protein (hsCRP) and interleukin-1β (IL-1 β) levels and systemic inflammatory activity markers are higher in these patients compared to normal

**İletişim Bilgisi / Correspondence**
Uzm. Dr. Zehra Erkal, Antalya Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği, Antalya - Türkiye
**E-mail:** zehraerkalkard@hotmail.com
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population. Moreover, levels of these inflammatory markers decrease after percutaneous mitral balloon valvuloplasty (PMBV) treatment while the level of hsCRP is correlated with the severity of disease [3, 4].

Neutrophil to lymphocyte ratio (N/L ratio) is a marker of subclinic inflammation, various studies have demonstrated the correlation between N/L ratio and many diseases such as inflammatory disease, cardiovascular disease, cancer and type 2 diabetes 5-6)

Percutaneous mitral balloon valvuloplasty is commonly performed in patients with RMS who have suitable valvular morphology. Wilkins echocardiographic score (WS) is a common method to select the patients eligible for PMBV treatment (7) Studies have shown that patients with WS<8 benefit more from PMBV treatment. However, higher success rates can be obtained at an early stage in patients with scores higher than 11, but surgical treatment is recommended for these patients as the long-term cardiovascular mortality risk increases gradually [8, 9].

In this study, in addition to clinical and echocardiographic parameters, we aimed at investigating the efficacy of N/L ratio, which is a systemic inflammatory marker in selecting patients who are not eligible for PMBV treatment due to their high WS scores.

## MATERIALS and METHODS

In this retrospective study, we investigated 115 patients (93 females (80.9%); 22 males (19.1%)) (with moderate-severe RMS (mitral valve area ≤1.5cm2) who underwent PMBV between 2011 and 2016 in our clinic. The study was approved by the local ethics committee. All experiments were conducted following the criteria of Declaration of Helsinki. Clinical features, laboratory parameters and echocardiograms of the patients were retrieved from the patient files. All patients gave their written informed consent prior to the study. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) records were reviewed.

The exclusion criteria were left atrial thrombus formation, moderate or severe mitral regurgitation, other moderate or severe valvular diseases, history of malignancy, renal/liver failure, previous history of any inflammatory disease, current therapy with corticosteroids or anticoagulant agents, connective tissue disease, thyroid disease, history of coronary artery disease, other haematological diseases and acute infectious diseases. The past medical histories of the patients were recorded from patient anamnesis form.

The results of the blood tests performed in the past month were examined. Complete blood count (CBC) including white blood cell (WBC), neutrophil and lymphocyte counts was measured using an automated CBC device (Abbott Cell Dyn, IL, USA). The N/L ratio was calculated using the data obtained from the CBC results.

Transthorasic echocardiography and TEE records of the patients were analysed (EPIQ 7 Cardiac Ultrasound, Philips, Amsterdam, Netherlands). All echocardiographic findings were carefully evaluated by two independent cardiologists. All measurements were performed according to the recommendations of the American Society of Echocardiography [8]. An average of 3 to 7 measurements were performed for each patient with sinus rhythm and atrial fibrillation, respectively. Routine echocardiographic findings were recorded. Left atrial diameter and left ventricular end-systolic and end-diastolic diameters were measured in the parasternal long axis view by M-mode echocardiography. Ejection fraction was measured by modified Simpson's rule. Mitral valve area was calculated by planimetric method in the parasternal short axis. The WS was calculated through morphological evaluation of the mitral valve with TEE. To estimate the WS, scores from 0 to 4 were given

according to leaflet mobility, leaflet thickening, calcification and the severity of subvalvular thickening [5]. Based on the Wilkins scores, the patients were divided into two groups: Group 1 consisted of 72 patients (mean age 43.7±12.0) with WS≤ 11 and Group 2 consisted of 43 patients (mean age 52.7±11.3) with WS>11.

**Statistical analysis**

The data was analysed with the SPSS software version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean±SD, while the categorical variables were expressed as percentage. The $\chi 2$ test and Fisher's exact test were used to compare the categorical variables. The Kolmogorov–Smirnov test was performed to assess the distribution of the continuous variables. Student's t-test was used for those variables with normal distribution and the values were presented as mean ± SD. The continuous variables without normal distribution were analysed using Mann-Whitney U test and the resulting values were presented as median (50th) values and interquartile ranges (25th and 75th). The odds ratios (OR) and 95% confidence intervals (CI) were calculated. Receiver–operating characteristic (ROC) curve analysis was performed to determine the optimum cut-off levels of the N/L ratio in association with high WS. A two-tailed p-value of <0.05 was considered as statistically significant.

## RESULTS

A total of 115 patients with moderate to severe RMS were included in the study. The baseline characteristics of the patients are given in Table 1. There was no significant difference between the two groups in terms of hypertension, hyperlipidemia and gender. No difference was found between the groups in terms of permanent atrial fibrillation (p=0.179).

The CBC parameters are given in Table 2. No significant difference was found in the white blood cell count and the haemoglobin levels between the groups. However, neutrophil levels (5.0±1.3 vs 6.6±1.4, p<0.001) were significantly higher in Group 2, and lymphocyte levels (2.1±1.1 vs 1.7±0.5) were significantly higher in the Group 1 (p=0.02). The N/L ratio (2.6±0.9 vs 3.8±0.5, p<0.001) and platelet count (220.7±67.0 vs 254.2±50.2 p=0.004) were significantly higher in Group 2. ROC curve analysis revealed an N/L ratio>3.09, which had a sensitivity of 100% and specificity of 78% in predicting RMS patients with high WS (area under the curve 0.923, p<0.001) (Figures 1 and 2).

Among the echocardiographic parameters; left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, planimetric mitral valve area, transmitral mean and peak gradient and systolic pulmonary artery pressure were not significantly different between two groups. The mean WS in Group 1 was 7.4±2.0 while it was 12.4±0.7 in Group 2. However, left atrial diameter was significantly greater in Group 2 (48.0±2.1 vs 45.0±2.4, p<0.001) (Table 3).

Factors leading to a high WS were evaluated with univariate and multivariate logistic regression analysis (Table 4). Univariate analysis for high WS demonstrated significant differences in age, N/L ratio, left atrial diameter, platelet count and diabetes mellitus. Multivariate analysis showed that left atrial diameter was an independent predictor of WS>11 (OR=1.625; 95% CI:1.197 – 2.204, p=0.002) and N/L ratio was an independent predictor of WS>11 (OR=13.545; 95% CI:4.144-44.272, p<0.001). We found that WS and N/L ratio were highly and significantly positively correlated (r=0.866; p<0.001).

## DISCUSSION

In this study, we demonstrated that the N/L ratio, which is a marker of inflammatory status, was statistically and independently associated with RMS in patients with WS>11. An N/L ratio>3.09 on admission had a sensitivity of 100% and specificity of 78% in predicting WS>11 in patients

with RMS according to the ROC curve analysis.

Rheumatic mitral stenosis is still an important public health problem in developing countries. Mitral valve is the most commonly affected valve in rheumatic heart disease [11]. Although its pathophysiology is not understood well, it is well known that inflammation and autoimmunity are important factors in its pathogenesis. The antigenic similarity between streptococcal M5 protein and cardiac myosin leads to inappropriate cross-reaction in patients with RMS [2, 12]. The main reason of valvular damage in RMS patients is inflammatory response while pathological examination of the excised valvular tissues has revealed infiltration of T cells specific for streptococcic M protein [13]. Despite the lack of infectious agents; inflammation persists and valvular destruction continues during the chronic phase of the disease [2]. As a result, it leads to thickening of mitral valve leaflets, commissural fusion, shortening of chordae and mitral stenosis [14]. Furthermore, it has been shown that RMS patients with calcification have lower levels of fetuin-A, which is an inhibitor of ectopic calcification, in comparison to the normal population [15].

Since PMBV is a less invasive method, it is highly preferred in patients with RMS who have an appropriate valvular morphology. WS is the most widely used parameter to evaluate valvular morphology. In this scoring system; leaflet mobility, leaflet thickening, valvular calcification and subvalvular disease are given a value from 1 to 4, resulting in a total maximum WS of 16 [7]. Most of the studies reported in the literature included TTE measurements for estimating WS [9]. In this study, however, we evaluated the TEE records for estimating WS, which enabled more accurate evaluation of subvalvular structures. In a similar study conducted by Nunes et al, a newer classification was reported to be superior to WS in estimating long-term outcomes after PMBV treatment. The new classification has been used to assess the planimetric measurement of the largest and smallest mitral valve areas, asymmetry of commissural thickening and measurement of maximal opening of the leaflets from anulus during diastole [16]. However, planimetric measurements may be harder to perform for RMS patients with prominent calcification.

The WS is an important predictor of early and long-term results of PMBV. Several studies suggest that PMBV treatment provides optimal results in patients with WS scores of lower than 8. Patients with a score from 9 to 11 are in the grey zone with moderate success, whereas surgical treatment is recommended for patients with a score higher than 12 [8, 9]. The inpatient and follow-up mortality rates have been found to be lower in patients with a WS lower than 8 who underwent PMBV treatment [17]. It has also been reported that patients with a WS of 9-11 have better and more favourable outcomes if they are operated with more experienced surgeons. [18]. Even though it is likely to obtain promising short-term results after a successful PMBV procedure in patients with WS>11, long-term cardiovascular risk is higher and surgery should be recommended to such cases [9]. Our study confirmed that N/L ratio could be safely and effectively used in patients with a WS greater than 11, who are considered as ineligible for PMBV treatment.

Rheumatic mitral stenosis patients were found to have higher levels of systemic inflammatory markers, including hsCRP, N/L ratio, and IL-1β levels compared to the normal population [3, 4, 19, 20]. These findings suggest that there is an ongoing inflammation in RMS patients [21]. The N/L ratio as an indicator of systemic inflammation has been investigated in numerous epidemiologic studies. It has been reported that the N/L ratio is higher in various cardiovascular diseases and it is an adverse prognostic indicator [22-24]. In a recent similar study, patients with RMS and non-stenotic rheumatic heart disease and normal controls were analysed; the NLR value was found

to be higher in the stenotic group and rheumatic heart disease group as compared to the healthy individuals. Similarly, in this study, the N/L ratio>2.56 had a sensitivity of 75% and specificity of 75% for severe mitral valve stenosis [17]. These results showed that the N/L ratio might be an important parameter to demonstrate the presence of RMS. In another study, hsCRP level, which is another inflammatory marker, was found to be correlated with WS [3]. WS is the most important parameter to decide if PMBV should be performed, which is why these correlations are important. In our study, CRP levels were not associated with WS, but this might be attributed to the low level of sensitivity in our kits. However, WS was found to be independently associated with NLR. Higher levels of WS in patients with NLR higher than 3.09 can be explained by higher level of systemic inflammatory response.

**Study Limitations**

This was a retrospective study. Another limitation was that it was also a single-centre experience, which included a small number of patients. We did not evaluate the impact of N/L ratio on prognosis. We also did not assess inflammatory markers other than N/L ratio and CRP in this study.

Consequently, neutrophil to lymphocyte ratio, which is an inexpensive, readily available marker of systemic inflammation, it may be useful in predicting the level of WS in patients with RMS. Future studies may further consolidate the importance of N/L ratio in medical treatment and anti-inflammatory treatment in patients with RM.

**Statement of Ethics:** This research was conducted in accordance with the World Medical Association Declaration of Helsinki. The local ethics committee approved the study.

**Informed Consent:** Written consent was obtained from the participants.

**Conflict of Interest:** Authors declared no conflict of interest.

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