RESEARCH ARTICLE / *Araştırma Makalesi*

Capibility of Neuthrophil-lymphocyte Ratio to Predict Rheumatic Heart Valve Disease In Pregnant Women

Nötrofil-Lenfosit Oranının Hamile Kadınlarda Romatizmal Kalp Kapağı Hastalığını Öngörme Yeteneği

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Abstract

Objective	There is a role of inflammatory processes on the pathophysiology of rheumatic heart valve disease (RHVD). The neutrophil-lymphocyte ratio (NLR) as an inflammatory marker is associated with some clinical situations in pregnancy. In this study, we aimed to investigate the predictive role of NLR in pregnant women with NLR.
Materials and Methods	First-trimester pregnant women, who were referred to cardiology outpatient clinic and diagnosed with RHVD (n=24) were enrolled in this study and age-matched healthy pregnant women (n=24) were taken as control groups. The two groups were compared in terms of clinical characteristics, echocardiographic findings, and NLR. The role of NLO in predicting RKKH has been examined.
Results	Groups were similar in terms of demographic features. NLR was higher in pregnant women with RHVD than the control group (3.68 ±1.74 vs. 2.68±1.14, p=0.00239). NLR (OR: 0,597, p= 0,037, 95% CI: 0,343-0,921) and neutrophil count (OR: 0,609, p= 0.013, 95% CI: 0,390-0,863) were possible independent predictors of RHVD.
Conclusion	NLR was significantly higher among pregnant women with RHVD. As it is not possible to provide routine cardiac check-up to all pregnant women; markers for specific risk groups need to be defined to reduce the risks associated with heart diseases during pregnancy. According to these findings, pregnant women with high NLR may need extra attention in terms of CVD like RHVD. Further studies with large patient groups are needed to define the predictive value of NLR.

Keywords Pregnancy; neutrophil-lymphocyte ratio; rheumatic heart valve disease

Öz

Amaç	*Enflamatuar süreçlerin, romatizmal kalp kapağı hastalığı (RKKH) patofizyolojisi üzerinde bir rolü vardır. Enflamatuar bir belirteç olarak nötrofil-lenfosit oranı (NLO), gebelikte bazı klinik durumlarla ilişkilidir. Bu çalışmada, RKKH'li gebelerde NLO'nun prediktif rolünü araştırmayı amaçladık.*
Gereç ve Yöntemler	*Çalışmaya kardiyoloji polikliniğine sevk edilen ve RKKH tanısı alan (n = 24) birinci trimester gebeler alındı ve kontrol grubu olarak yaşları eşleşen sağlıklı gebeler (n = 24) alındı. İki grup klinik özellikler, ekokardiyografik bulgular ve NLO açısından karşılaştırıldı. NLO'nun RKKH'nı ön görmedeki rolü incelendi.*
Bulgular	*Gruplar demografik özellikler açısından benzerdi. NLO RKKH'lı kadınlarda kontrol grubuna göre daha yüksekti (3.68 ± 1.74 ve 2.68 ± 1.14, p = 0.00239). NLO (OR: 0,597, p= 0,037, 95% CI: 0,343-0,921) ve nötrofil sayısı (OR: 0,609, p= 0.013, 95% CI: 0,390-0,863) RKKH'nın olası bağımsız prediktörleriydi.*
Sonuç	*NLO RKKH olan gebe kadınlarda anlamlı olarak daha yüksekti. Tüm hamile kadınlara rutin kardiyak muayene sağlamak mümkün olmadığından; hamilelik sırasında kalp hastalıkları ile ilişkili riskleri azaltmak için spesifik risk grupları için belirteçlerin tanımlanması gerekir. Bu bulgulara göre, yüksek NLO'lı gebe kadınların RKKH gibi KVH açısından daha fazla dikkat göstermeleri gerekebilir. NLO'nın prediktif değerini tanımlamak için geniş hasta gruplarıyla daha ileri çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler *Gebelik; nötrofil-lenfosit oranı; romatizmal kalp kapak hastalığı*

INTRODUCTION

Rheumatic heart valve disease (RHVD) is the most common heart disease in developing countries and, is stil one of the major causes of cardiac morbidity and mortality among young women.[1] Although the exact mechanisms are not clearly defined, RHVD has the characteristics of inflammatory and autoimmune processes.[2] In previous studies, the role of systemic inflammation in the pathophysiology of RHVD is established.[3] White blood cells and their subtypes have been shown to be predictors of poor prognosis in many diseases that develops on the basis of inflammatory reaction. As a consequence of lymphocytopenia and increased neutrophils, the neutrophil-to-lymphocyte ratio (NLR) is increased in many inflammatory diseases.[4,5] In previous studies, it has been revealed that there is a close relationship between NLR and bad outcomes in cardiovascular diseases.[6,7] Neutrophils play an important role in inflammatory processes and they are the first blood cells responding to inflammation.[8] NLR also has a relationship with poor pregnancy outcomes, as an example; there are higher neutrophil counts in pre-eclamptic patients and NLR has also relationship with hyperemesis gravidarum and gestational diabetes mellitus.[9-13] To the best of our knowledge, there is no data regarding the relationship between NLR and RHVD in pregnant women. Since NLR is closely linked to inflammation and RHVD is associated with chronic and systemic inflammatory status, we aimed to investigate the predictive role of NLR in pregnant women with NLR.

MATERIALS and METHODS

This study was conducted in a tertiary delivery center in Ankara, Turkey. First-trimester pregnant women, who were referred to cardiology outpatient clinic between March – September 2017 and diagnosed with RHVD were enrolled in this study and age-matched healthy pregnant women were taken as control groups. A routine TTE (Vivid S5 System, GE Health-care, USA) was performed to all pregnant women by a single cardiologist. Medical history and demographic features, age, gravidity, parity, gestational week, height, weight and heart rate of patients were recorded. Patients with active infection signs (high leukocyte count, fever, positive urine or cervix culture) and symptoms, patients with a history of chronic systemic disease (hypertension, diabetes mellitus, thyroid disease, thrombophilia, and rheumatic disease), known history of cardiovascular disease and anemia were excluded from the study after evaluation of patient records. Multiple pregnancies were additionally excluded from the study. All echocardiography measurements were performed based on the American Society of Echocardiography guidelines. RHVD was defined according to heart valve disease literature.[14] Echocardiographic changes (valve thickening, chordal thickening, restricted leaflet motion) that meet the criteria for 'definite RHVD are considered to be rheumatic in origin, provided that other etiologies have been excluded by echocardiography and clinical context.[15] In the records, twenty-six pregnant women were diagnosed with RHVD. After evaluation according to the study exclusion criteria, 24 patients remained for further analysis. Twenty four age-matched individuals who had normal echocardiographic findings were randomly selected from the same echocardiography database as the control. The study protocol was approved by the local institutional review board with number 2020/126.

In the study population the following data were recorded; left ventricle end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), right atrium end-systolic diameter (RAESD), right ventricle end-diastolic diameter (RVEDD), left atrium end-systolic diameter (LAESD), mitral E wave velocity (m/s), mitral A wave velocity (m/s). Left ventricular dimensions were determined using two-dimensional directed M-Mode echocardiography in the long axis of the para-sternal view. Teicholz formula was used to asses the left ventricular ejection fraction. Left ventricular diastolic function was evaluated by trans-mitral Doppler using the pulsed-Doppler technique with 2D guidance in the apical four-chamber view. Laboratory parameters were recorded.

Statistical analysis was carried out with JMP®, Version 12.0. (SAS Institute Inc.,Cary, NC, 1989-2019). All the values were expressed as mean ± standard deviation. Shapiro-Wilk W test was performed for normality. Differences between two groups were assessed by t-tests for normally distributed data and Mann Whitney U test was used for non-normal distributions. P-values less than 0.05 were considered significant. Receiver operating characteristic (ROC) curves for NLR and neutrophil values were plotted to determine the optimal cut-off values for individual parameters in order to predict the probability of the existence of RHVD in pregnant women.

RESULTS

Twenty-four pregnant women with RHVD were compared with 24 age-matched controls. The demographic features of the study population are shown in Table 1. There were no statistically significant differences between pregnant women with RHVD and controls in terms of gravida, parity, gestational week, weight, height, BMI and heart rate. The laboratory and echocardiographic findings are shown in Table 2. NLR and neutrophil levels were significantly higher in pregnant women with RHVD than the control group (3.68±1.74 vs 2.68±1.14; p=0.00239) (6.93±2.25 vs 5.33±1,44; p=0,0057).

The diagnostic performance of NLR was evaluated by receiver operating characteristic (ROC). In the ROC curve analysis for NLR, an NLR level cut-off point of more than 3.31 predicted the presence of RHVD with a sensitivity of 50% and specificity of 83.3% (Fig. 1).

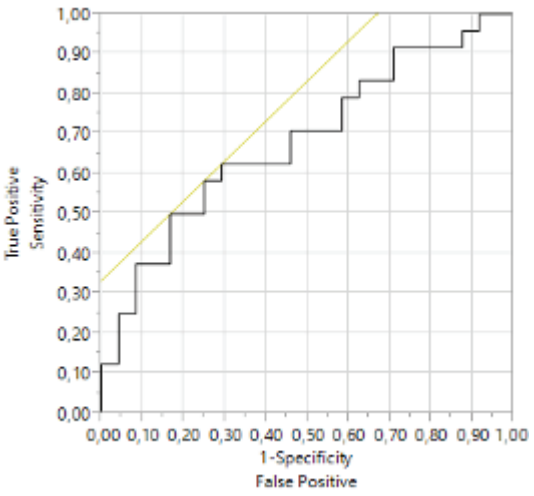

Figure1. ROC curve analysis for neutrophil-to-lymphocyte ratio as a predictor of rheumatic heart valve disease. The area under the ROC curve (AUC) of the NLR 0.68403. The best cutoff point of NLR was 3.31. Sensitivity=0.50, Specificity=0,833

Since low sensitivity and specificity were obtained from the ROC curve analysis for NLR; diagnostic performance of neutrophil count was evaluated. In the ROC curve analysis for neutrophil, a neutrophil level cut-off point of more than 6.91 predicted the presence of RHVD with a sensitivity of 50% and specificity of 87.5 % (Fig. 2). In the regression analysis, NLR (OR: 0,597, p= 0,037, 95% CI: 0,343-0,921) and neutrophil count (OR: 0,609, p= 0.013,

Table 1. Clinical and demographic features of the study population

Parameters	Pregnant women with RHVD (n=24)	Control Group (n=24)	P value*
Age (years)	28,00 (± 7,00)	28,54 (± 6,90)	NS
Gestational week	6.96 (±1.19)	7.32 (±1.62)	NS
Weight (kg)	66.07 (±12.22)	68,33 (± 13,59)	NS
Height (cm)	161.27 (±7.30)	161,29 (± 7,41)	NS
Heart Rate (bmp)	75.00 (±8.94)	78,80 (± 12,85)	NS
Gravidity (n)	2,00 (1,00 ; 6,00)	2,00 (1,00 ; 5,00)	NS
Parity (n)	0,50 (0,00 ; 3,00)	0,50 (0,00 ; 4,00)	NS

*P<0.05= significant, NS: Not significant, Continuous parameters are given as Mean (± SD) and ordinal parameters are given as Median (Min; Max)

Table 2. Laboratory and echocardiographic findings of the study population			
Parameters	**Pregnant women with RHVD (n=24)**	**Control group (N=24)**	**P value***
LVEF (%)	67.71 ±2.93	67,87 (± 2,20)	NS
E (m/sec)	1.01 ±0.17	1.00 ±0.13	NS
A (m/sec)	0.80 ±0.18	0.79 ±0.12	NS
E' (m/sec)	13.36 ±2.50	13 ±2.16	NS
A' (m/sec)	10.10 ±2.51	9.79 ±3.24	NS
LVEDD (cm)	4.47 ±0.21	4.43 ±0.16	NS
RAESD (cm)	2.88 ±0.36	3.05 ±0.30	NS
RVEDD (cm)	2.15 ±0.19	2.16 ±0.14	NS
LAESD (cm)	3.06 ±0.40	2.88 ±0.30	NS
Mean Platelet Volume (fl)	10.54 ±0.88	10.40 ±0.67	NS
Mean Corpuscular Volume (fl)	83.60 ±5.71	84.33 ±6.30	NS
Neutrophil (X10 3 /µL)	6.93 ±2.25	5.33 ±1.44	**<0.01**
Lymphocyte (X10 3 /µL)	2.05 ±0.56	2.16 ±0.60	NS
NLR (Neutrophil-to-lymphocyte ratio)	3.68 ±1.74	2.68 ±1.14	**0.048**

*p<0.05= significant
NS: Not significant; LVEF: left ventricle ejection fraction; LAEDD: Left atrium end-diastolic diameter; LVEDD: Left ventricular end-diastolic diameter; RVEDD: Right ventricular end-diastolic diameter; RAEDD: Right atrial end-diastolic diameter; E: peak velocity of early filling; A: peak velocity of atrial filling; E': early diastolic mitral annular velocity; A': late diastolic mitral annulus velocity

95% CI: 0,390-0,863) were possible independent predictors of RHVD.

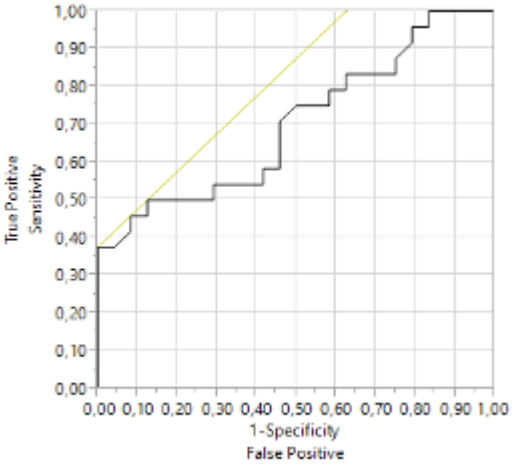

Figure 2.ROC curve analysis for the neutrophil count as a predictor of rheumatic heart valve disease. The area under the ROC curve (AUC) of the neutrophil 0.70052. The best cutoff point of NLR was 6.91. Sensitivity=0.50, Specificity=0,875

DISCUSSION

We have analyzed the NLR in first-trimester pregnant women diagnosed with RHVD, depending on the possible relationship on the inflammatory basis of the RHVD process and found a significant increase in NLR when compared with healthy pregnant women. Additionally, NLR and neutrophil count were independent predictors of the presence of RHVD in our study group. To the best of our knowledge, there are no data regarding the relationship between NLR and RHVD in pregnant women although there are limited studies investigating the association of NLR and RHVD.

Physiological changes happen in pregnancy and one of the systems majorly affected during this period is the cardiovascular system. There is a significant increase in blood volume and cardiac output; which may lead to decompensation in cardiac functions in patients even with mild and moderate.[16]

Cardiovascular diseases are the most common causes of

death during pregnancy. Cardiovascular complications are seen in 0.2-4% of pregnancies.[17] Registry of Pregnancy and Cardiac Disease [18] reported a mortality rate of 1.9% while heart failure rates were up to 50% in patients with severe mitral stenosis and 23% with significant mitral regurgitation due to RVHD.[18]

Rheumatic heart diseases are the most common CVD in developing countries; risk classification gains importance to refer the pregnant women to a cardiologist when they present with altered cardiac symptoms during pregnancy. In the literature, some algorithms have been developed about which pregnant women should be directed to routine heart evaluation.

The current guidelines do not recommend routine cardiac screening performed by a cardiologist to all pregnant women during pregnancy. Considering the risk factors, presentation signs and symptoms, vital sign abnormalities and physical examination findings of patients; The California Pregnancy-Associated Maternal Morbidity and Mortality Committee Cardiovascular Disease in Pregnancy and Postpartum Task Force (CAPREG) which included management strategies of women with the cardiac disease was developed.[19] ROPAC which included 2742 pregnant women (mean age = 29.2 ± 5.5 years) previously diagnosed with CVD was prepared from the registry of the European Society of Cardiology (ESC), based on the modified World Health Organization (mWHO) risk classification.[20] Risk classification according to the mWHO guide is useful for the management of pregnant women with CVD in developed countries but this seems less effective in developing countries because of the differences in CVD spectrum and undiagnosed patients especially because of lack of health services. CAPREG and ROPAC task forces also advise that women with previously diagnosed heart disease should see a cardiologist prior to pregnancy and receive pre-pregnancy counseling.

A recent clinical management guideline published by The American College of Obstetricians and Gynecologists (ACOG) in 2019 reported; CVD; the leading cause of maternal death during pregnancy and postpartum period with a rate of 4.23/100.000 live births was responsible for 26.5% of pregnancy-related deaths in the U.S.[15] This guide recommended the assessment of all pregnant women using the California Improving Health Care Response to Cardiovascular Disease in Pregnancy and referral of pregnant women with higher cardiac risk to tertiary care centers. According to ACOG; the four parameters: physical examination, vital signs and symptoms and risk factors should be evaluated to decide which pregnant women should be evaluated by a cardiologist.[15] For women with asymptomatic valve disease, monitoring by a cardiologist with appropriate frequencies indicated for the patient's mWHO classification was also advised.

In pregnant women, signs and symptoms of pregnancy may overlap with symptoms of the heart diseases so that it may be difficult to suspect a cardiovascular disease in pregnancy and it poses a particular problem especially in pregnant women, in whom the diagnosis is often delayed or missed. Therefore, it gains importance identification of the clinical predictors of CVD risk at the beginning of pregnancy to support the algorithms in the literature. We need to detect more clinical risk factors related to increased cardiac risk at the beginning of the pregnancy to determine the pregnant women who need a referral to a cardiologist for detailed cardiac examination.

RHVD is still the most important cause of maternal morbidity and mortality due to cardiovascular diseases in developing countries. In a previous study it was showed that ongoing inflammation in the chronic phase in RVHD may be the cause of valve scarring and valve calcification.[21] It was shown that levels of chronic inflammatory markers were higher in patients with rheumatic valve disease than control groups.[2] So, evaluating inflammatory markers may be a good option in pregnant women at cardiac risk in terms of RVHD.

Song at al. showed that the NLR was a novel and a useful predictive factor in patients with calcific aortic valve disease.[22] In another study that aimed to investigate NLR as a useful marker for all grades of degenerative aortic stenosis (AS), NLR in the severe AS group was significantly higher than that of the mild/moderate AS group.[23] Studies suggested that NLR was higher in patients with mitral annular calcification.[24] A study by Avci et al., a positive correlation with trans-valvular peak aortic gradient and the NLR was reported.[25] Unlike studies evaluating the relationship between NLR and the degree of valvular diseases; we evaluated the relationship between the presence of RVHD and NLR in pregnant women.

Our study excluded patients with diabetes mellitus, any other valvular diseases, hypertension, any active inflammation or coronary artery disease. Thus, this inflammation marker that we researched in RHVD was not affected by a secondary inflammation process.

Our results, as expected in line with previous studies, showed that pregnant women with RVHD have higher NLR values indicating increased inflammation compared to healthy pregnant women. Akboga et al.; investigated the relationship between NLR and RHVD and they demonstrated that NLR was significantly increased in rheumatic mitral valve stenosis.[26] According to their results the ROC curve analysis, an NLR level cutoff point of more than 2.3 predicted the presence of RMVS with a sensitivity of 60.8% and specificity of 77.2%.Similarly to their results; in our study, despite the meaningful statistical significance, we cannot say that NLR is a good predictor of RVHD because of low sensitivity and specificity observed with ROC curve analysis. Since NLR was investigated as a predictor in the literature, we first examined the prediction capability of NLR. But our results showed that instead of its ratio to lymphocyte, neutrophil count itself may be a better predictive marker. However, in ROC curve analysis for the neutrophil count, sensitivity and specificity are not still high enough to define it as a reliable predictor. Therefore, we suggest that the threshold value for NLR and also neutrophil should be determined with further studies including higher case numbers. So, NLR or neutrophil may be used also a parameter for the identification of cardiac risk in pregnancy.

Because of RHVD being the most common cardiac disease in developing countries, it is important to reveal the predictors of RHVD during pregnancy. NLR may be a cheap and easy defined risk factor especially in developing countries with a higher incidence of rheumatic heart diseases in young adult females. We suggest that predicting the presence of valvular heart disease with such an easy and inexpensive method in healthy pregnant women will contribute to the early detection of risky pregnant women and the determination of pregnancy follow-up.

Limitations

Valve pathologies were not classified according to their types and severity due to restricted number of patients because of including a special patient group. This was the main limitation of our study. The results of our study would enlighten future studies involving large patient groups to investigate the clinical significance of NLR among pregnant women with RHVD. Another limitation of our study was that since the patients were referred to the multidisciplinary hospital for the birth, there was no follow up data of the subject.

CONCLUSION

NLR as a good marker of ongoing inflammation was significantly increased in pregnant women with RHVD. We suggest that pregnant women with high NLR need extra attention in terms of CVD like RHVD. Because NLR is an available and cheap method, it can easily be used in daily clinical practice to detect pregnant women at cardiac risk.

Declarations

Conflicts of interest

The authors declare no conflict of interest.

Funding

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Study approval

Institutional review board of Etlik Zübeyde Women's Health Education and Research Hospital; 26.08.2020-2020/126

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