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The Relationship of Neutrophil Lymphocyte Ratio With Prognosis And Disease Activity In Patients With Rheumatoid Arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease associated with systemic inflammation. Laboratory parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and various disease evaluation indexes (such as DAS 28; HAQ score, SF-36) are used as indicators of the severity of inflammatory activity. Neutrophil-to-lymphocyte ratio (NLR); It has attracted attention in recent years as a non-specific inflammatory marker. In our study, it was aimed to investigate the possible role of peripheral blood NLR, which is easy and inexpensive to measure, in demonstrating disease activity and prognosis in patients with RA.

Materials and Methods: Forty-three patients who were diagnosed with RA according to the criteria of the American Rheumatology Association and who had not received prior specific treatment for RA were included in the study. Laboratory parameters such as ESR, CRP, and disease assessment indices (DAS 28; HAQ score) were compared with the NLR at the time of diagnosis and at the time of enrollment after treatment.

Results: There were no significant correlation found between the mean NLR and DAS 28, HAQ which provide information about the prognosis of the disease. When the relationship between NLR, ESR and CRP was examined in order to evaluate the relatonship between the disease activity and inflamation during the diagnosis instead of a composite index such as DAS 28, moderately weak relationship between NLR and CRP level was found (p=0.033, r=0,343) while the tendency between NLR and the average ESR was found to be also moderately weak (p=0.056, r=0.301).

Conclusions: Moderate to weak correlation between mean NLR and mean CRP levels (p=0.033, r=0.343); between the mean ESR level, a moderate-weak correlation was found (p=0.056, r=0.301). The association with baseline CRP and the trend towards association with ESR suggest that NLR may be associated with inflammation. It was thought that the loss of this relationship during the study, that is, after the treatment, may be due to the fact that other factors such as medication affect this rate.

Keywords: Rheumatoid arthritis, Neutrophil-to-lymphocyte ratio, Prognosis

Romatoid Artrit Hastalarında Nötrofil Lenfosit Oranının Prognoz Ve Hastalık Aktivitesi İle İlişkisi

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ÖZ

Amaç: Romatoid artrit (RA), sistemik inflamasyonla ilişkili otoimmün bir hastalıktır. İnflamatuar aktivite şiddetinin göstergesi olarak Eritrosit sedimantasyon hızı (ESH), C-reaktif protein (CRP) gibi laboratuar parametreler, çeşitli hastalık değerlendirme indeksleri (DAS 28; HAQ, SF-36 gibi) kullanılmaktadır. Nötrofil-lenfosit oranı (NLO); spesifik olmayan inflamatuar bir belirteç olarak son yıllarda dikkat çekmektedir. Çalışmamızda RA'li hastalarda ölçümü oldukça kolay ve ucuz olan periferik kan NLO'nın hastalık aktivitesi ve prognozu göstermedeki olası rolünü araştırmak amaçlanmıştır.

Materyal ve metod: Çalışmaya Amerikan Romatoloji Derneği kriterlerine göre RA tanısı alan, daha önce RA için spesifik tedavi almamış 43 hasta alındı. ESH, CRP gibi laboratuar parametreleri ve hastalık değerlendirme indeksleri (DAS 28; HAQ) ile tanı anındaki ve tedavi sonrasında çalışmaya alındığı tarihteki NLO ile karşılaştırılmıştır.

Bulgular: Tanı sırasındaki ortalama NLO ile RA'in seyrinde bakılan ve hastalık prognozu hakkında bilgi veren parametreler (DAS 28, HAQ) arasında anlamlı bir ilişki saptanmamıştır. Tanı anında hastalık aktivitesi için DAS 28 gibi kompozit bir indeks kullanılamadığından, NLO'nun inflamasyon ile ilişkisini değerlendirmek üzere tanı sırasındaki ESH ve CRP ile ilişkisine bakıldı. Ortalama NLO ile ortalama CRP düzeyleri arasında orta-zayıf derecede ilişki (p=0.033, r=0,343); ortalama ESH düzeyi arasında ise orta-zayıf derecede ilişkiye eğilim (p=0.056, r=0.301) tespit edilmiştir. Başlangıçtaki CRP ile ilişki ve ESH ile ilişkiye eğilim, NLO'nın inflamasyonla ilişkili olabileceğini düşündürmektedir. Çalışma sırasında yani tedavi sonrasında bu ilişkinin kaybolması ilaç gibi diğer faktörlerin bu oranı etkilemesi nedeniyle olabileceği düşünülmüştür.

Sonuç: Sonuç olarak tanı ve çalışma sırasındaki ortalama NLO ile hastalık prognozu hakkında bilgi veren parametreler (DAS 28, HAQ ve deformite varlığı) arasında bir ilişki saptanmamıştır. Ortalama NLO ile ortalama CRP düzeyleri arasında ise orta-zayıf derecede ilişki (p=0.033, r=0,343) saptanmıştır. NLO'nın RA'li hastalarda hastalık aktivitesi ve prognozla ilişkisinin olup olmadığının ortaya konulması için ileri araştırmalara ihtiyaç vardır.

Anahtar sözcükler: Romatoid Artrit, Nötrofil Lenfosit Oranı, Prognoz

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease which is associated with systemic inflammation, mainly affects the synovial joints, causes joint deformity and loss of function, and seriously affects quality of life [1]. Although the pathogenesis is still unknown, it is thought that RA occurs with immune mechanisms triggered by the effect of environmental factors in individuals with genetic predisposition [2]. Synovitis is the main pathological change associated with RA [3]. Clinical, laboratory parameters, radiological findings and various disease evaluation indices (such as DAS 28; HAQ, SF-36) are used to determine disease activity, response to treatment and prognosis in RA. Laboratory parameters such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) are helpful as an indicator of the severity of inflammatory activity [4,5]. However, despite the technological developments in recent years, a simple indicator that can practically evaluate the activity and prognosis in RA has not been found.

It has been reported that neutrophils, lymphocytes and platelets play a role in the control of inflammation and are also associated with changes secondary to inflammation [6]. Neutrophil to lymphocyte ratio (NLR) has drawn attention as a new non-specific inflammatory marker in recent years. Previous studies have shown that NLR has a prognostic value in cardiovascular diseases, malignant tumours and sepsis [7-12]. In some studies conducted to investigate its values in RA, it was concluded that NLR may be useful and its role is limited in others [13-18].

In this study, it is aimed to investigate the possible role of peripheral blood NLR in demonstrating disease activity and prognosis in patients with RA.

Material and Method

Patient selection

Forty-three rheumatoid arthritis patients diagnosed in the rheumatology polyclinic and followed for at least 6 months were included in the study. All patients met the criteria of the American College of Rheumatology. At the time of diagnosis, patients were not taking any rheumatic drugs other than analgesics and/or non-steroidal anti-inflammatory drugs. Those who did not have an infectious disease, major surgery, serious trauma during diagnosis and evaluation and within the last 1 month, and those who did not have a history of malignancy and serious cardiovascular disease were included in the study. No special method was used in patient selection: Patients who applied to the rheumatology polyclinic between February and May 2013, met the inclusion and exclusion criteria, and signed an informed consent form after necessary explanations were included in the study.

Permission was obtained from the ethics committee of İzmir Atatürk Training and Research Hospital (number/date: 22/ 07.02.2013).

Evaluation of Patients

Patients were physically examined, and they were questioned in terms of history and additional diseases. When the patients were included in the study, they were evaluated in terms of deformity development (concave appearance of the back of the hand as a result of muscle atrophy, subluxation in the metacarpophalangeal joints, ulnar deviation, swan neck deformity, boutonniere deformity, deformities defined as Z deformity in the thumb, etc.).

The hemogram values (neutrophil, lymphocyte and thrombocyte counts), ESR and CRP values at the time the patients were was first diagnosed, when the treatment was not started, and at the time they were included in the study were learned from the patient files. NLR values of the patients both at the time of diagnosis and when they were included in the study were calculated by dividing the neutrophil percentage by the lymphocyte percentage.

DAS 28 was used to evaluate disease activity at the time of the study. HAQ was used to evaluate the patients' performance in daily activities. However, DAS 28 and HAQ values of the patients at the time of diagnosis were not included in the evaluation process because they could not be accessed from the files.

Statistical analysis

Numerical data are given as mean ± standard deviation. The distribution of the data was evaluated with Kolmogorov-Smirnov test and Student's T test was used for dependent or independent variables for those with normal distribution, and Wilcoxon test or Mann Whitney U test for those who did not show normal distribution. P value, <0.05, was considered significant. Statistical operations were performed by using the SPSS 16 program.

Findings

Thirtyone (72%) were female and 12 (28%) were male of 43 RA patients. Mean age was 54±11 years (30-73). The mean disease duration was 41±29 months (6-162) (table 1). While 20 (47%) of the patients had additional disease, 23 (53%) did not have any additional disease. Existing comorbidities did not affect NLR.

Table 1. Demographic characteristics of patients

Gender (female/male)	31 (72%) / 12 (28%)
Age (years)	54±11
Illness duration (months)	41±29
Comorbidity (yes/no)	20 (47%) / 23 (53%)

Values are given as mean ± standard deviation

Mean leukocyte count at diagnosis was 8930/mm3±2655/mm3 (5340-15600); mean neutrophil count was 5770±2113/mm3 (2560-11400); mean lymphocyte count was 2417±700/mm3 (1310-4500). When they were included in the study, the mean leukocytes were 8967±2486 (5680-15800); mean neutrophil count was 5744±2029 (3210-11540); mean lymphocyte count was 2406 ±778 (920-4130). There was no significant difference between these values at diagnosis and during the study (p values 0.926, 0.945 and 0.918, respectively). However, while the mean platelet count was 328000±88000 (181000-549000) at the time of diagnosis, it was 299000±82000 (160000-518000) during the study, and this difference was significant (p=0.011) (table 2). While the mean NLR was 2.44 ±1.03 (0.99-6.8) at the time of diagnosis, it was 2.59±1.47 (1.31-9.2) when they were included in the study, and there was no significant difference between them (p=0.571) (table 2).

Table 2. Laboratory findings of the patients during diagnosis and study.

Parameter	During diagnosis	During study	P
WBC (/mm^3)	8930±2655	8967±2486	0,926
Neutrophil count (/mm^3)	5770±2113	5744±2029	0,945
Lymphocyte count (/mm^3)	2406±778	2406±778	0,918
PLT (/mm^3)	328000±88000	299000±82000	**0,011**
NLR	2,44±1,03	2,59±1,47	0,571
ESR (mm/saat)	37±23	24±15	**<0,001**
CRP (mg/dl)	3,77±5,56	1,95±1,09	**<0,001**

At the time of diagnosis, the mean ESR was 37±23 mm/h (6-95), and the mean CRP level was 3.77±5.56 mg/dL (0.12-22.9). When they were included in the study, the mean ESR was 24±15 mm/hour (2-57), and the mean CRP level was 1.99±1.09 mg/dL (0.17-5.32). Both ESR and CRP levels at diagnosis and study were significantly decreased (p<0.001 for both) (table 2).

The mean NLR at diagnosis was compared with the mean ESR and CRP at diagnosis. There was a moderate-weak correlation between mean NLR and mean CRP level (p=0.033, r=0.343). There was a moderate-weak correlation between mean NLR and mean ESR level (p=0.056, r=0.301). There was no correlation between mean NLR during the study and mean ESR and CRP (p 0.661 and 0.154, respectively).

During the study, the mean DAS 28 of the patients was 3.64±0.85 and mean HAQ score was 0.90+0.80. No correlation was found between the NLR at diagnosis and mean DAS 28 and HAQ score calculated when they were included in the study (p 0.32 and 0.79, respectively). There was no correlation between mean NLR when they were included in the study and DAS 28 and HAQ scores (p value 0.205 and 0.698, respectively). While 7 (16%) patients had deformity, 36 (84%) did not have any. All those with the deformity were women. Autoantibody (RF and/or anti-CCP) was positive in 6 patients. The mean DAS was 28 3.5 ± 0.81 in patients without deformity when they were included in the study; it was found as 4.29 ± 0.72 in patients with deformity. There was a significant difference between the mean DAS 28 values of those with and without deformity (p:0.025).

The mean HAQ score was 0.76 ± 0.75 in patients without deformity when they were included in the study; it was found as 1.64 ± 0.68 in patients with deformity. A significant difference was found between the mean HAQ score of those with and without deformity (p:0.006). The mean NLR measured in patients without deformity when they were included in the study was 2.55 ± 1.53; it was found as 2.77 ± 1.25 in patients with deformity. There was no significant difference between the NLR of those with and without deformity (p:0.727). The mean NLR at diagnosis was 2.34 ±0.81 in patients who had no deformity during the study; it was determined as 2.98 ± 1.76 in patients with deformity. There was no significant difference between the NLR at the time of diagnosis of those with and without deformity (p:0.133) (table 4).

Table 3. Clinical characteristics of patients during the study.

DAS 28	3.64±0.85
HAQ score	0.90+0.80
Presence of deformity (yes/no)	7 (16%) / 36 (84%)

Table 4. Disease activity indicators and NLR according to the presence of deformity.

	No Deformity (n=36)	Yes Deformity (n=7)	P
DAS 28	3,5±0,81	4,29±0,77	**0,025**
HAQ score	0,76±0,75	1,64±0,68	0,006
NLR- diagnosis	2,34±0,81	2,98±1,76	0,113
NLR- study	2,55±1,53	2,77±1,25	0,727

Table 5. NLR, platelet count and HAQ score by disease activity.

	DAS 28 ≥ 3,2 (n=29)	<3.2 (n=14)	P
NLR- diagnosis	2.53+1.14	2.26+0.72	0.425
NLR- study	2.78+1.71	2.19+0.70	0.228
PLT (/mm^3)	314000+90000	268000+53000	0.87
HAQ score	1.08+0.84	0.53+0.58	**0.018**

The patients were divided into 2 groups according to the DAS 28 value; the first was low disease activity (DAS 28<3.2) group and the second was moderate and high disease activity (DAS 28 ≥3.2) group. Accordingly, when they were included in the study, 29 (67%) patients had moderate and high disease activity, and 14 (33%) patients had low disease activity. The mean NLR at diagnosis was 2.53 ± 1.14 in patients with moderate and high disease activity, and 2.26 ± 0.72 in those with low disease activity (p:0.425). The mean NLR during the study was 2.78 ± 1.71 in patients with moderate and high disease activity, and 2.19 ± 0.70 in those with low disease activity (p:0.228). When they were included in the study, the mean platelet count of patients with moderate and high disease activity was 314000 ± 90000, and 268000 ± 53000 in patients with low disease activity (p:0.87). When they were included in the study, the mean HAQ values of patients with moderate and high disease activity were found as 1.08 ± 0.84, and 0.53 ± 0.58 for those with low disease activity, and the difference between them was significant (p:0.018) (table 5).

Discussion

In our study, there was no relationship between NLR and disease activity and prognosis in patients with RA. The course of RA has a wide spectrum; on the one hand, there are patients who have only a few active periods throughout their life, and on the other hand, there are patients who develop disease-related disability despite all treatment options and they constitute approximately 20% of the patients. In RA, both active findings (arthritis; swelling and pain) and chronic changes (such as deformity) cause limitation of movement and disability. This can make it difficult to perform normal daily activities and seriously affect the patient's life quality. It is important to determine or at least predict patient's disease course in advance for determining whether the patient needs early aggressive treatment or not. Today, it is impossible to know this precisely. However, prognostic factors can give an idea about this issue [19].

Studies have shown that NLR has a prognostic value in various diseases in which inflammation plays an important role, such as cardiovascular diseases, malignant tumours, and sepsis [7-12]. In some of the studies conducted to investigate values of NLR in RA, it was concluded that it may be beneficial and its role is limited in others [13-18]. In this study, it was investigated whether NLR can provide information about the course of the disease and its relationship with disease activity in RA patients in which inflammation plays a leading role. In our study, deformity due to RA, disease activity despite treatment (DAS 28) and the effect of the disease on daily life (HAQ) were investigated to evaluate the course of the disease. Other results such as mortality were not evaluated.

In our study, disease activity at the time of diagnosis could not be evaluated with a composite index due to the lack of data in the patient file. Disease activity during the study was evaluated with DAS 28 (average 3.64±0.85). HAQ (average 0.90+0.8) is associated with disease activity, but certainly does not mean the same. In our study, patients only had HAQ scores during the study due to the lack of data.

There was no significant difference was observed between mean leukocyte, neutrophil and lymphocyte counts among hemogram parameters during diagnosis and study. However, a significant difference was found

between the mean platelet counts. This can be explained by the fact that the platelet count is an indicator of inflammation.

No significant difference was found between the mean NLR at diagnosis and during the study. In a meta-analysis of 16 studies, NLR was found as high in RA patients, but a weak correlation was found with disease activity [20]. RA is a disease in which many factors play a role. Factors such as gender, presence of autoantibodies and drugs taken affect the course of the disease. For these reasons, only NLR assessment may not be a guide in RA. However, it is necessary to study with a larger patient group to reach a clear conclusion.

The patients were divided into two groups according to the presence of deformity; 16% of the patients developed deformity during the follow-up period. There was a significant difference in both DAS 28 and HAQ scores between the groups with and without deformity (p values 0.025; 0.006, respectively). It is expected that daily life will be affected more negatively in patients who develop deformity. In addition, the fact that the disease is still more active in patients with deformity suggests that RA does not lose its speed despite the treatment.

Since a composite index such as DAS 28 was not used initially, the relationship of NLR with ESR and CRP at the time of diagnosis was examined to at least evaluate its relationship with inflammation instead of disease activity; there was a moderate-weak correlation between mean NLR and average CRP level (p=0.033, r=0.343). There was a moderate to weak correlation between the NLR at the time of diagnosis and the mean ESR level (p=0.056, r=0.301). There was no relationship between mean NLR and ESR and CRP during the study. The trend towards the relation with first CRP and ESR suggest that NLR may be associated with inflammation. The loss of this relationship during the study, after the treatment, may be due to other factors such as medication affecting this rate.

To evaluate whether the average NLR at diagnosis can provide an insight into the course of the disease, the relationship between average DAS 28, average HAQ score and presence of deformity during the study was investigated, but no relationship was found. This result suggests that NLR does not provide information about the prognosis of the disease, at least according to these parameters. This result suggests that NLR does not provide information about the prognosis of the disease, at least according to these parameters.

It was investigated whether the mean NLR during the study varied according to both the presence of deformity and the degree of disease activity (low activity/medium and high activity). But there was no difference. Again, this suggests that NLR does not provide sufficient information about the course of the disease.

When the literature reviewed, it was concluded that NLR in RA may be useful in some studies, and its role is limited in others [13-18]. In a meta-analysis of 16 studies, NLR was found as higher in patients with RA compared to healthy controls, but its relationship with disease activity was weak [20].

One of the limitations of our study is the absence of one of the composite disease activity indicators at the time of first diagnosis, which will perhaps show the relationship of NLR with disease activity. Because there are many factors that affect NLR, such as the drugs taken and age. The small number of patients in our study limited the evaluation of disease activity and prognostic significance.

Conclusion

Consequently, there was no correlation between the mean NLR at diagnosis and the parameters (DAS 28, HAQ, and presence of deformity) measured in the course of RA and providing information about the prognosis of the disease. When the laboratory parameters demonstrating inflammation such as ESR and CRP at the time of diagnosis are compared with the mean NLR; moderate to weak correlation was found between mean CRP levels and NLR (p=0.033, r=0.343); a moderate-weak correlation was found between the mean ESR level (p=0.056, r=0.301). No correlation was found between mean NLR during the study and mean ESR and CRP. The trend towards the relation with first CRP and ESR suggest that NLR may be associated with inflammation. Further studies are required to determine whether NLR is associated with the disease activity and prognosis in patients with RA.

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