PARAMETERS OF TOTAL BLOOD COUNT; MIGHT THEY BE INDICATORS OF INFLAMMATION IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS?

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ABSTRACT

Introduction*: Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic inflammatory disorders. Inflammation is the probable underlying cause of disability. Platelet indices and complete blood compounds such as neutrophils and leukocytes are used to assess inflammation. This study investigated the relation between inflammation and the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV) and platelet distribution width (PDW) in RA and AS.*

Materials and methods*: 425 subjects aged 17-89 (mean 44.64±14.07), 225 (52.9%) female and 200 (47.1%) male, were included in this retrospective study. One hundred five subjects had RA, 216 had AS, and 104 were healthy. RA was diagnosed based on 2010 ACR/EULAR Classification Criteria and AS according to Modified New York Criteria. RA disease activity was determined using DAS28 scores and AS disease activity using BASDAI.*

Results*: Hemoglobin values in patients with RA were statistically significantly lower compared to the control group (p=0.001), while ESR, CRP, NLR and PLR values were higher (p=0.001, p=0.001, p=0.001, and p=0.040). No difference was determined in MPV or PDW (p>0.05). Hemoglobin, ESR, CRP and NLR values in AS patients were significantly higher than in the control group (p=0.001, p=0.001, p=0.006, and p=0.001), while PDW values were lower (p=0.027; p<0.05). No difference was determined in PLR or MPV values (p>0.05). No correlation was determined between disease activity indices and NLR, PLR, MPV, PDW.*

Conclusion*: Being cost-effective and easily calculated, NLR and PLR in RA and NLR in AS can be used together with ESR and CRP or as inflammation markers when these are unavailable.*

Keywords*: Ankylosing spondylitis, inflammation, rheumatoid arthritis, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, mean platelet volume.*

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Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are the first conditions that come to mind in the context of inflammatory rheumatic disease. Although the two conditions differ in terms of etiology, the age group and sex they affect, the regions of the locomotor system they involve and the extra-articular organs on which they impact, the common and most important factor in coping with them is bringing inflammation under control. Inflammation is the principal factor requiring monitoring in terms of the disability the two diseases cause, comorbid conditions and the associated increased risk of mortality. Easily available, inexpensive and reliable markers are needed to assess inflammation. The most commonly used markers in daily practice are C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). The main handicap of these markers is their low specificity. In addition to inflammatory rheumatic diseases, these markers also increase in conditions involving infection, malignity, trauma (surgery, burn, fracture) or necrosis (myocardial infarction, acute pancreatitis). Sedimentation also exhibits a physiological increase with age. It is

also higher in females than in males, in individuals with hypercholesterolemia and at high altitude[1,2].

Numerous recent studies, particularly involving cardiovascular diseases and cancer research, have used platelet indices and complete blood compounds such as neutrophils and lymphocytes to evaluate inflammation. It has been suggested that these compounds, heralded as novel inflammatory markers, and the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) easily calculated from these can be used when ESR and CRP are unavailable or in doubtful cases due to superimposed conditions[3-11].

The purpose of this study was to investigate the association between inflammation in RA and AS with the NLR and PLR obtained from neutrophil, lymphocyte and platelet numbers and the platelet markers mean platelet volume (MPV) and platelet distribution width (PDW).

Materials and methods

This retrospectively designed study was performed in June-December, 2016. Forty hundred twenty-five patients aged between 17 and 89 (mean 44.64±14.07) years, 225 (52.9%) female and 200 (47.1%) male, were included in the study. One hundred five cases were RA, 216 were AS and 104 were healthy individuals. Individuals with acute or chronic infection, other systemic inflammatory diseases apart from RA and AS, hematological diseases other than anemia, a history of malignancy, symptomatic cardiovascular diseases, metabolic diseases, in receipt of steroid in the previous 3 months, or with chronic kidney-liver disease, pregnant subjects and women in the postpartum period (6 months) were excluded from the study. Patient and control group data were obtained from the patient record system. Diagnosis of RA was made according to 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria, and diagnosis of AS was made using Modified New York Criteria[12,13].

The activity of RA was determined with DAS28 score and AS was determined with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[14,15]. DAS28 cutoffs were used for classification of RA activity: ≤2.6 remission and >2.6 active disease. BASDAI cutoffs were used for classification of AS activity: ≤4 remission and >4 active disease active disease.

Complete blood count parameters were determined from EDTA anticoagulated blood samples by means of an automatic counter. The Westergren method was used to calculate ESR, and CRP was measured using the turbidimetric method.

Ethical committee approval was received before the study began.

Statistical Analysis

Statistical analysis of the study data was performed on IBM SPSS Statistics 22 (IBM SPSS, Turkey) software. Normal distribution of parameters was evaluated using the Shapiro Wilks test. Student's t test was used to compare normally distributed parameters between two groups in the analysis of numerical data in addition to descriptive statistical methods (mean, standard deviation, frequency), while the Mann Whitney U test to compare non-normally distributed parameters between two groups. The chi square test and Continuity (Yates) Correction were used to compare quantitative data. Relations between parameters were assessed using Pearson's correlation analysis. Significance was set at $p<0.05$.

Results: No statistically significant difference was observed between the RA and control groups in terms of mean age or gender distribution ($p>0.05$). Mean ages of the cases in the AS group were significantly lower ($p=0.001$; $p<0.05$) and the preponderance of male gender was higher (69.4% vs 29.8%) than in the control group ($p=0.001$; $p<0.05$). In the RA group, 18.1% of patients were not using drugs, while 1.9% were using non-steroidal anti-inflammatory drugs (NSAIDs), 72.4% disease-modifying antirheumatic drugs (DMARDs) and 7.6% tumor necrosis factor antagonist (anti-TNF). In the AS group, 16.2% were not using any medication, while 42.6% were using NSAIDs, 21.8% DMARDs and 19.4% anti-TNF. In the RA group, 44.8% of patients were rheumatoid factor (RF) positive and 50.5% were anti-CCP positive. In addition, 24.1% of RF-negative cases were anti-CCP positive. In the AS group, 66.7% of patients were HLAB27-positive.

Demographic characteristics and laboratory findings of the patient and control groups are shown in Table 1.

Hemoglobin values of the cases in the RA group were statistically significantly lower than in the control group ($p=0.001$; $p<0.05$), while ESR, CRP, NLR and PLR values were significantly higher ($p=0.001$; $p<0.05$, $p=0.001$; $p<0.05$,

p=0.001; p<0.05, and p=0.040; p<0.05). No statistically significant variation was determined in term of MPV and PDW values (p>0.05).

	Group				
	Rheumatoid arthritis	Ankylosing spondylitis	Control	[a]p	[b]p
	Mean±SD	Mean±SD	Mean±SD		
Sex, no. (%)					
Female	86 (81.9%)	66 (30.6%)	73 (70.2%)	[1]0.068	[2]0.001*
Male	19 (18.1%)	150 (69.4%)	31 (29.8%)		
Age	52.67±10.61	38.53±11.31	49.25±16.38	[3]0.076	[3]0.001*
Hemoglobin level	12.57±1.15	13.81±1.5	13.37±1.21	[3]0.001*	[3]0.001*
ESR	31.14±17.97	20.88±15.91	16.34±8.58	[3]0.001*	[3]0.006*
CRP (median)	0.8±0.95 (0.5)	0.99±1.54 (0.4)	0.2±0.13 (0.1)	[4]0.001*	[4]0.001*
Neutrophil count	3.9±1.24	4.3±1.22	3.48±0.97	[3]0.008*	[3]0.001*
Lymphocyte count	2.14±0.74	2.32±0.59	2.29±0.62	[3]0.121	[3]0.725
NLR	1.99±0.93	1.96±0.78	1.62±0.66	[3]0.001*	[3]0.001*
Platelet count	256.77±60.06	258.78±57.51	251.27±56.18	[3]0.495	[3]0.271
PLR	130.61±47.22	118.21±38.2	117.42±44.81	[3]0.040*	[3]0.870
MPV	8.17±1.27	7.94±1.23	7.93±1.11	[3]0.157	[3]0.946
PDW	17.53±0.95	17.38±0.95	17.64±1.03	[3]0.416	[3]0.027*

Table 1: Demographic and Laboratory Characteristics of Rheumatoid Arthritis, Ankylosing Spondylitis Patients and Control Subjects.

*[a]p: RA and control group p value; [b]p: AS and control group p value; [1]Continuity (Yates) correction; [2]Chi square test; [3]Student's t test; [4]Mann Whitney U test *p<0.05*

When the remission and active RA groups were compared, hemoglobin values were higher in the remission group (p=0.018; p<0.05) and ESR (p=0.001; p< 0.05), CRP (p=0.005; p<0.05) and PDW (p=0.048; p<0.05) values were lower. No difference was determined between NLR, PLR, or MPV values (p>0.05). When the remission RA and control group were compared, CRP (p=0.016; p<0.05) and NLR (p=0.011; p<0.05) values were higher compared to the control group, while no difference was observed in the other values (p>0.05). When the active RA and control group were compared, hemoglobin values were lower, and ESR (p=0.001; p<0.05), CRP (p=0.001; p<0.05), NLR (p=0.005; p<0.05) and PLR (p=0.030; p<0.05) values were higher in the active RA group, while no difference was observed in the other parameters (p>0.05) (Table 2).

	Group					
	Remission RA	Active RA	Control	[a]p	[b]p	[c]p
	Mean±SD	Mean±SD	Mean±SD			
Hemoglobin level	12.96±1.25	12.39±1.07	13.37±1.21	[1]0.018*	[1]0.089	[1]0.001*
ESR	19.64±12.02	36.42±17.84	16.34±8.58	[1]0.001*	[1]0.085	[1]0.001*
CRP (median)	0.52±0.68 (0.3)	0.93±1.03 (0.6)	0.2±0.13 (0.1)	[2]0.005*	[2]0.016*	[2]0.001*
NLR	1.99±0.87	2±0.96	1.62±0.66	[1]0.982	[1]0.011*	[1]0.005*
PLR	124.8±44.02	133.27±48.68	117.42±44.81	[1]0.396	[1]0.409	[1]0.030*
MPV	8.28±0.98	8.12±1.39	7.93±1.11	[1]0.536	[1]0.109	[1]0.336
PDW	17.8±1.07	17.4±0.87	17.64±1.03	[1]0.048*	[1]0.447	[1]0.115

Table 2: Analysis of the study parameters between the remission and active RA and control groups.

*[a]p: Remission RA and active RA group p value; [b]p: Remission RA and control group p value; [c]p: Active RA and control group p value; [1]Student's t test; [2]Mann Whitney U test *p<0.05*

Hemoglobin, ESR, CRP and NLR values in the AS group were significantly higher compared to the control group (p=0.001; p<0.05, p=0.006; p<0.05, p=0.001; p<0.05, and p=0.001; p<0.05, respectively). There was no difference between the two groups in terms of PLR and MPV values (p>0.05). PDW values were lower than in the control group (p:0.027; p<0.05).

CRP (p=0.003; p<0.05) and ESR (p=0.001; p<0.05) were lower and MPV values (p=0.023; p<0.05) were higher in the remission AS group compared to the active AS group, while no difference was determined between other values (p>0.05). When the remission AS group was compared with the control group, hemoglobin (p=0.001; p<0.05), CRP (p=0.001; p<0.05), and NLR (p=0.002; p<0.05) values were higher, while no difference was determined in other values (p>0.05). When the active AS group was compared with the control group, ESR (p=0.001; p<0.05), CRP (p=0.001; p<0.05), and NLR (p=0.001; p<0.05) values were higher, while no difference was observed in other values (p>0.05) (Table 3).

	Group					
	RemissionAS	Active AS	Control	[a]p	[b]p	[c]p
	Mean±SD	Mean±SD	Mean±SD			
Hemoglobin level	13.95±1.48	13.59±1.53	13.37±1.21	[1]0.084	[1]0.001*	[1]0.280
ESR	17.3±13.29	26.08±17.93	16.34±8.58	[1]0.001*	[1]0.504	[1]0.001*
CRP (median)	0.6±0.69 (0.3)	1.54±2.15 (0.5)	0.2±0.13 (0.1)	[2]0.003*	[1]0.001*	[1]0.001*
NLR	1.94±0.84	1.99±0.69	1.62±0.66	[1]0.663	[1]0.002*	[1]0.001*
PLR	117.6±37.27	119.11±39.7	117.42±44.81	[1]0.775	[1]0.974	[1]0.784
MPV	8.09±1.41	7.73±0.87	7.93±1.11	[1]0.023*	[1]0.351	[1]0.168
PDW	17.39±0.99	17.37±0.9	17.64±1.03	[1]0.910	[1]0.059	[1]0.059

Table 3: Analysis of study parameters between the remission AS, active AS and control groups.

*[a]p: Remission AS and Active AS group p value; [b]p: Remission AS and Control group p value; [c]p: Active AS and Control group p value; [1]Student's t test; [2]Mann Whitney U test; *p<0.05*

Statistically significant positive correlations were observed between ESR and CRP and NLR and PLR values in the active RA group and between ESR and NLR and PLR values in the active AS group. No correlation was determined between DAS 28 and BASDAI and NLR, PLR, MPV, PLR.

Discussion

On the basis of our findings, hemoglobin values were low and ESR, CRP, NLR and PLR were

high in RA patients, while hemoglobin, ESR, CRP and NLR values were high and PDW values were low in AS patients. There was no difference between the groups in terms of MPV values.

Low hemoglobin values may be expected in chronic diseases, as in RA patients. We think that hemoglobin being higher in the patients with AS compared to the control group may be due to the majority of patients with AS being young males and to the mean duration of disease being shorter than in the RA group.

Conditions such as normochromic anemia, thrombocytosis, neutrophilia, and lymphopenia are seen at complete blood count in the majority of inflammatory conditions. Neutrophils, macrophages and platelets are important cells in the inflammatory response. They produce and release various cytokines that affect the inflammation mechanism[16,17]. Complete blood parameters have recently been heralded as novel inflammatory markers in several recent studies[11,17,18]. Mercan et al. compared 136 RA and 140 AS patients with healthy controls and, similarly to the present study, observed elevated ESR, CRP and NLR values in both disease groups. NLR was correlated with ESR and CRP in both AS and RA. NLR was found to be correlated with DAS28 but notwith BASDAI[17]. Tekeoğlu et al. determined a positive correlation between DAS 28 and NLR and a negative correlation between DAS28 and MPV, while observing no difference in PDW values between the groups[18]. Another study reported significant elevation of NLR and PLR in patients with RA and correlation with DAS 28[19].

Similarly to our results, one study comparing patients with AS with healthy controls observed significant elevation in ESR, CRP and NLR levels, but no difference in terms of PLR and MPV. In contrast to our findings BASDAI was correlated with NLR, PLR and MPV[20]. We also determined negative correlation between ESR and CRP, and NLR and PLR values in the RA group, and negative correlation between ESR and NLR and PLR values in the active AS group. However, there was no correlation between complete blood parameters and disease activity indices.

Studies concerning MPV have reported very different results. In our study, we determined no significant difference between the patient and control groups, while Sahin et al. reported that MPV was inversely correlated with ESR and CRP and suggested that MPV could therefore be used as a negative acute phase reactant in rheumatic diseases[21]. Kisacik et al. compared 30 patients with active AS and 30 patients with active RA with healthy controls. They reported a significant decrease in MPV during active disease and a negative correlation with BASDAI[22]. Işik et al. reported that both MPV and PDW could be used as negative acute phase reactants in RA[23]. In support of these studies and the possibility of MPV being used as a negative acute phase reactant, MPV values of 21 patients with RA were investigated on weeks 1, 2 and 12 of anti-TNF therapy, and a significant time-dependent increase was observed in MPV[24].

However, other studies have reported results incompatible with those of the above studies. One study comparing 100 patients with RA and 100 healthy controls reported significant MPV elevation in patients with RA, but no correlation with DAS 28[25]. In agreement with that study, Talukdar et al. determined a higher MPV value in RA patients with high disease activity compared to those with low disease activity[26]. A similar study compared 133 patients with AS and 133 healthy controls. MPV values were significantly higher in patients with AS, but were not correlated with BASDAI[27].

These parameters have been investigated not only in inflammatory rheumatic diseases, but also in cardiovascular diseases and cancer, and in such different disease groups as end stage kidney disease[28], obstructive pulmonary disease[29], pulmonary embolism[30], ischemic stroke[31], and major depression[32]. The general opinion is that these parameters can be used as inflammation markers, and that elevation can even be used as a predictor of poor prognosis in some conditions[29,31].

Major limitation of this study isits retrospective nature and the fact that while some patients were under treatment, others were not. Despite exclusion of the patient group receiving steroids, other disease-modifying agents may affect the complete blood count. In addition, the difference in terms of age and sex between the AS group and the control group may also be regarded as a limitation. However, RA and AS in their nature differ in terms of age and gender in which they are mainly seen. We therefore think that the control group could not be expected to be compatible with both patient groups.

The fact that NLR and PLR can be easily calculated from complete blood count and are cost-

effective further increases their value. NLR and PLR can be used as inflammation markers in RA, and NLR in AS, together with ESR and CRP, or when these are unavailable. Although numerous studies have reported that they are also well correlated with disease activity, we found no correlation. We elicited no significant findings regarding MPV and PDW. However, there are both mutually supportive and contradictory findings in the literature concerning the value of platelet parameters.

In conclusion, we think that total blood parameters are not sufficient by themselves to evaluate disease activation, but that NLR and PLR can be used with the support of other acute phase reactants in the evaluation of inflammation.

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