Complete blood count derived haematological parameters do not correlate with disease activity in patients with radiographic axial spondyloarthritis

Tam kan sayımından türetilen hematolojik parametreler radyografik aksiyel spondiloartritlerde hastalık aktivitesi ile korele değildir

Didem Şahin Eroğlu[1], Murat Torgutalp[1], Serdar Sezer[1], Müçteba Enes Yayla[1], Maide Özel[2], Tahsin Murat Turgay[1], Aşkın Ateş[1], Gülay Kınıklı[1]

[1]Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey
[2]Ankara University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey

Abstract

Objective: Low disease activity is aimed to preserve functional status in radiographic axial spondyloarthritis (r-axSpA). However, disease activity indices use erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, which might not uniformly reflect active disease. Complete blood count (CBC) test is routinely performed in daily practice and components of CBC may reflect ongoing inflammation. In this single-centred retrospective study, we aimed to determine the associations of CBC parameters with disease activity indices in r-axSpA patients.

Methods: Patients and healthy controls, who presented to our rheumatology outpatient clinic from January 2018 to September 2020, were recruited to the study. Sixty-four patients diagnosed with r-axSpA were compared with sex- and age- matched 53 patients with Behçet's syndrome and 79 healthy controls. The demographic characteristics and laboratory parameters including CBC, ESR and CRP values of the participants were recorded. Disease activity indices such as Bath Ankylosing Spondylitis Disease Activity index (BASDAI) and Ankylosing Spondylitis Disease Activity score (ASDAS) were scrutinized. One-Way ANOVA and Spearman test were used to compare the groups and to calculate the correlation of parameters with disease activity indices, respectively. All statistics were done in SPSS version 21 with a p-value of <0.05 considered statistically significant.

Results: Demographic characteristics were similar among the groups. The mean platelet volume was significantly lower in r-axSpA patients than in diseased and healthy controls (9.8±0.9 vs 10.3±0.8 vs 10.4 0.9, respectively, p=0.001). CBC components did not correlate with BASDAI and ASDAS. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio were weakly correlated with CRP (r=0.399 and 0.316, respectively).

Conclusion: CBC components do not indicate disease activity in r-axSpA.

Keywords: Ankylosing spondylitis, radiographic axial spondyloarthritis, mean platelet volume, BASDAI, ASDAS

Öz

Amaç: Radyografik aksiyal spondiloartritte (r-axSpA) düşük hastalık aktivitesi sağlanarak fonksiyonel durumun korunması amaçlanmaktadır. Ancak halen kullanılmakta olan hastalık aktivite indeksleri eritrosit sedimentasyon hızı (ESH) ve C-reaktif protein (CRP) gibi aktif hastalığı net olarak yansıtmayan parametreleri kullanmaktadır. Tam kan sayımı (TKS) testi günlük pratikte rutin olarak kullanılmaktadır ve TKS'nin bileşenleri devam eden enflamasyonu yansıtabilir. Bu tek merkezli retrospektif çalışmamızda, r-axSpA hastalarında TKS parametrelerinin hastalık aktivite indeksleri ile ilişkisini belirlemeyi amaçladık.

Yöntem: Ocak 2018-Eylül 2020 tarihleri arasında romatoloji polikliniğimize başvuran hastalar ve sağlıklı kontroller çalışmaya alındı. Altmış dört r-axSpA tanısı olan hasta, cinsiyet ve yaş eşleştirilmiş 53 Behçet sendromlu hasta ve 79 sağlıklı kontrol ile karşılaştırıldı. Hastaların demografik özellikleri, TKS, ESH ve CRP gibi laboratuvar parametreleri kaydedildi. Bath Ankilozan Spondilit Hastalık Aktivite indeksi (BASDAI) ve Ankilozan Spondilit Hastalığı Aktivite skoru (ASDAS) gibi hastalık aktivite indeksleri kaydedildi. Grupları karşılaştırmak ve parametrelerin hastalık aktivite indeksleri ile korelasyonunu hesaplamak için sırasıyla tek yönlü ANOVA ve Spearman testi kullanıldı. Tüm istatistikler SPSS 21 versiyonunda yapıldı ve p değeri <0,05 anlamlı kabul edildi.

Bulgular: Demografik özellikler gruplar arasında benzerdi. Ortalama trombosit hacmi r-axSpA hastalarında, hastalıklı ve sağlıklı kontrollere göre anlamlı derecede daha düşüktü (sırasıyla 9,8±0,9, 10,3±0,8, 10,4±0,9, p=0,001). TKS bileşenleri BASDAI ve ASDAS ile korele değildi. Nötrofil-lenfosit oranı ve trombosit-lenfosit oranı, CRP ile zayıf bir şekilde korelasyon gösterdi (sırasıyla r=0,399 ve 0,316).

Sonuç: TKS bileşenleri r-axSpA'da hastalık aktivitesini göstermez.

Anahtar Kelimeler: Ankilozan spondilit, radyografik aksiyel spondiloartrit, ortalama trombosit hacmi, BASDAİ, ASDAS

Introduction

Radiographic axial spondyloarthritis (r-axSpA) or ankylosing spondylitis (AS) is an inflammatory disease characterized by the involvement of mainly the sacroiliac joints and the spine.[1] Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have been used for the assessment of disease activity in r-axSpA as well as Bath AS Disease Activity index (BASDAI), which includes patient-reported outcomes.[2] However, high ESR and CRP levels are detected in 40-50% of patients with r-axSpA, and they do not always reflect the actual disease activity.[3-5] Therefore, the combination of outcomes reported by patient and laboratory activity parameters, ESR and CRP, are used for the assessment of the Ankylosing Spondylitis Disease Activity score (ASDAS).[6] In recent years, there are increasing data about the usage of haematological markers such as the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), the mean platelet volume (MPV), red cell distribution width (RDW), and the lymphocyte-monocyte ratio (LMR) in rheumatic diseases. Complete blood count (CBC) test is routinely used in diagnosis and follow-ups of patients with r-axSpA and other rheumatic diseases. It is simple and has no additional cost for the evaluation work-up. NLR, PLR, MPV, RDW and LMR are the haematological parameters derived from CBC. It has been shown that these parameters could reflect disease activity in other rheumatic diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and rheumatoid arthritis (RA).[7-9] Nevertheless, there are conflicting results in the literature evaluating these haematological parameters and disease activity in patients with r-axSpA.[10-13]

There is still an unmet need to define simple biomarkers, and to test the accuracy of laboratory biomarkers related to CBC for the assessment of disease activity in patient with r-axSpA. The aim of this study was to evaluate the relationship between these parameters and disease activity in r-axSpA patients.

Materials and Methods

In this retrospective, single-centre, cross-sectional study, 64 patients with r-axSpA, who were classified according to modified New York criteria and who applied to our rheumatology outpatient clinic, were included.[14] Fifty-three patients with BS, who fulfilled international study group criteria, were accepted as the diseased control group.[15] Patients with active infection and/or malignancy and pregnant women at the recruitment time were not included into the study, as well as patients whose complete medical records were not available. As a healthy control group, 74 people were recruited into the study. Demographic characteristics of the groups (such as sex and age), haematological parameters that included neutrophil, lymphocyte, platelet counts, RDW, MPV in CBC, ESR and CRP levels were recorded by using electronic database of Ankara University Faculty of Medicine. Haematological parameters such as NLR, PLR, MPV and LMR were calculated by using the patients' CBC results. For the evaluation of disease activity and function in r-axSpA patients, BASDAI, ASDAS, and Bath AS Disease Functional index (BASFI) scores were obtained from patients' electronic medical records. Laboratory markers and disease activity indices were evaluated in the same visit with respect to cross-sectional design of the study.

This study was approved by the local research ethics committee of the Ankara University Faculty of Medicine (approval number: I9-586-20). The study was conducted according to the Declaration of Helsinki.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 21 was performed for statistical analyses. Data were shown as total numbers and percentages for categorical variables. Disease duration was given as the median and interquartile range (IQR). The variables were considered using analytical (Kolmogorov-Smirnov/Shapiro-Wilk's test) and visual (histograms, probability plots) methods to control the normal distribution. The chi-square or Fisher's Exact test was used to analyze proportions in diverse groups. Independent sample t-test (or Mann-Whitney U test as a non-parametric substitute) and ANOVA (or Kruskal Wallis test as a non-parametric substitute) were used to analyze the differences between extracted groups, followed by post-hoc tests with Bonferroni correction. The correlation coefficients and their significance were calculated by using the Spearman test. A p-value of <0.05 was considered statistically significant.

Results

There were not any differences with regard to demographic characteristics of three groups (Table 1). Among r-axSpA patients, 36 patients (56.3%) were male and diagnosed at an age of 34.3±12.5 years. The mean age at the study recruitment was 43.3±11.0 years in r-axSpA group. The median disease duration was 7.4 years (IQR 8.00). Among extra axial SPA features, the most common involvement was enthesitis (31.3%) followed by peripheral arthritis (29.7%), uveitis (18.8%), psoriasis (10.9%), inflammatory bowel disease (7.8%) and dactilitis (3.1%). HLA-B27 results were available in 29 patients, 17 of whom were positive. Acute phase reactans (APRs), either CRP or ESR, were high in 38

patients (59.4%), whereas 26 patients (40.6%) had normal APRs.

Among 53 patients with BS, genital ulcer was seen in 46 (86.8%) patients. Forty-three (81.1%) patients had either papulopustular eruption or erythema nodosum. Musculoskeletal involvement was seen in 33 (62.3%) patients. Major organ involvements such as ocular, vascular, neurological and gastrointestinal involvement were present in 33 (62.3%) patients. The mean age at BS diagnosis was 28.8±9.3 years. The median disease duration was 12.0 years (IQR 14.5).

When we compared haematological parameters in r-axSpA patients, patients with BS and healthy controls, platelet and neutrophil counts were higher in the patients with r-axSpA than in the healthy group. While there was no difference in NLR, PLR and RDW values between the r-axSpA and control groups, only the MPV values in the r-axSpA group were significantly lower compared to the healthy controls and the BS group (p=0.001) (Figure 1).

Considering the patients with BS, RDW was significantly higher in BS patients than in other two groups. Likewise, NLR was significantly higher than in the healthy subjects but NLR was similar to r-axSpA patients. Haemoglobin levels also differed in BS group from healthy subjects and patients with r-axSpA.

In r-axSpA group, overall BASDAI score and ASDAS-CRP were 3.95±2.52 and 2.64±1.17, respectively. BASDAI score of 34 patients (53.1%) was higher than 4, whereas
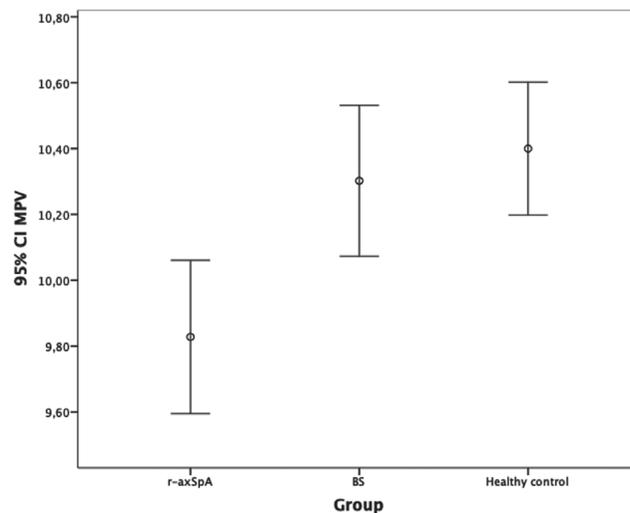

Figure 1. MPV values in patients with r-axSpA and BS, and healthy controls
BS: Behçet's syndrome, MPV: Mean platelet volume, r-axSpA: Radiographic axial spondyloarthritis (Post-hoc test results; for r-axSpA and BS, p=0.013; for r-axSpA and healthy control, p=0.001)

41 patients (64.0%) had high or very high disease activity according to their ASDAS-CRP. Within patients with r-axSpA, when NLR was compared between the patients with BASDAI ≥4 and with <4, there was not significant difference between the groups (median 1.82 vs 1.70, respectively, p=0.81). PLR, MPV and RDW were also similar between the groups (p-values are 0.97, 0.48 and 0.78 respectively). Furthermore, when evaluating according to ASDAS-CRP, NLR, PLR, MPV and RDW were not significantly different between the patients with an ASDAS <2.1 and with an ASDAS >= 2.1 (p-values are 0.27, 0.28, 0.94 and 0.57 respectively). No significant correlation was found between disease activity indices and haematological parameters in the whole group (Table 2) and when patients were divided according to high/normal APRs levels (data not shown). Only CRP level was weakly correlated with NLR and PLR (Table 2).

Among r-axSpA group, biological disease modifying antirheumatic drugs (bDMARDs) were being used in 30 patients (46.9%). The remaining 34 patients (53.1%) were being treated with either conventional DMARDs (cDMARDs) and/or non-steroidal anti-inflammatory drugs. None of the patients among r-axSpA group were using glucocorticoids. Haematological parameters and activity indices did not differ between different treatment groups (data not shown).

In patients with BS, most commonly used agent was colchicine (90.6%). Four patients (7.5%) took prednisolone ≤7.5 mg per day. Glucocorticoids had no effect on haematological parameters (data not shown).

Table 1. Clinical characteristics and laboratory parameters of the groups

	r-axSpA (n=64)	BS (n=53)	Healthy control (n=79)	p-value
Age, years	43.3±11.0	41.9±10.9	43.7±14.2	0.73
Sex, male, n (%)	36 (56.3)	33 (62.3)	42 (53.2)	0.58
Hemoglobin, g/dL	14.1±1.7	13.3±1.5	13.9±1.6	0.013
RDW (%)	13.4±1.4	14.2±1.4	13.3±1.3	0.002
Platelet count (x109/L)	312±86	281±75	271±62	0.003
MPV	9.8±0.9	10.3±0.8	10.4±0.9	0.001
Neutrophil count (x109/L)	5.0±2.1	4.9±1.8	4.1±1.2	0.004
Lymphocyte count (x109/L)	2.7±0.9	2.3±0.8	2.2±0.6	<0.001
NLR	2.05±1.03	2.53±1.64	1.93±0.54	0.007
PLR	127±50	141±66	130±39	0.329
ESR, mm/hour	15.1±14.3	14.8±13.2	10.2±7.8	0.021
High ESR, n (%)	13 (20.3)	11 (20.8)	6 (7.6)	0.048
CRP, mg/L	11.0±15.7	10.0±18.9	2.7±2.4	<0.001
High CRP, n (%)	35 (54.7)	20 (37.7)	10 (12.7)	<0.001

BS: Behçet's syndrome, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, r-axSpA: Radiographic axial spondyloarthritis, RDW: Red cell distribution width

Table 2. Correlation of hematological parameters with disease activity indices and acute phase reactants in radiographic axial spondyloarthritis patients

		RDW	MPV	NLR	PLR
BASDAI	r	0.137	0.100	0.074	0.029
	p	0.281	0.433	0.563	0.822
BASFI	r	0.069	0.092	-0.002	-0.067
	p	0.589	0.471	0.989	0.599
ASDAS	r	0.107	0.014	0.216	0.157
	p	0.399	0.914	0.087	0.216
ESR	r	0.147	0.120	0.085	0.217
	p	0.246	0.345	0.503	0.085
CRP	r	0.008	-0.226	0.399	0.316
	p	0.950	0.072	0.001	0.011

ASDAS: Ankylosing Spondylitis Disease Activity score, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, r-axSpA: Radiographic axial spondyloarthritis, RDW: Red cell distribution width

Discussion

ESR and CRP levels are widely used as disease activity parameters along with other indices in systemic autoimmune rheumatic diseases, but serum levels are affected by several other conditions, and normal levels do not consistently exclude active disease. These drawbacks of conventional APRs lead to the search of other parameters reflecting disease activity. CBC components such as neutrophils and platelets play a pivotal role in inflammation and secrete a wide range of cytokines which activate innate and adaptive immunity.[16-18] The interactions of these cell types are complex and play a pivotal role in disease pathogenesis. Ongoing chronic inflammation alters bone marrow homeostasis, and this alteration results in changes of blood cell parameters. It has been shown that peripheral blood-derived markers are different from healthy individuals and might indicate prognosis in some types of cancer.[19-23] Besides, decreased MPV level has been noted in active inflammatory bowel diseases.[24] Moreover, in a population-based study, a negative correlation between MPV and CRP was also described.[25] Likewise, blood cell parameters might be used for the assessment of inflammation, which is evident almost in every active autoimmune rheumatic disease. The present study assessed the relation between disease activity and CBC parameters in patients with r-axSpA.

In the case of RA, it has been shown by several articles that NLR and PLR are associated with disease activity score 28 (DAS 28).[26,27] Furthermore, in a recent paper published, their positive correlation with ultrasonographic parameters of disease activity such as power doppler was

also determined.[28] Likewise, NLR and PLR reflected disease activity in SLE, and the existence of lupus nephritis was also associated with higher NLR and/or PLR values.[29,30] These results were consolidated by a meta-analysis as well.[31] However, in our study, NLR and PLR were similar between patients with r-axSpA and healthy controls; they were only weekly correlated with CRP levels, which might reflect ongoing inflammatory state in r-axSpA. These results are in line with a recently performed meta-analysis which compared CBC parameters of r-axSpA patients and healthy controls.[10] These results might be the result of different pathophysiological mechanisms of the diseases.

The results of our study are consistent with some respects of previous studies performed in patients with r-axSpA. We showed that MPV levels in r-axSpA group were lower than in two control groups, but any other haematological parameters including MPV did not indicate active disease in r-axSpA. MPV reflects the platelet size and is considered as a relatively reliable marker of thrombopoiesis and platelet function.[32] Many rheumatological conditions, in which cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor alpha are secreted excessively, result in low MPV levels.[33,34] Low levels of MPV in r-axSpA patients were also demonstrated in a study conducted by Kisacik et al.[13], which showed that MPV was lower in active RA and r-axSpA patients compared to healthy controls; however, MPV levels increased after the treatment of RA and r-axSpA, reflecting a negative association between MPV and disease activity. Another study conducted in Turkey in r-axSpA patients revealed that RDW was positively correlated with BASDAI, ESR and CRP levels with a cut-off value 14.8% in contrast to MPV which was not related to BASDAI scores.[12] Mercan et al.[35] also showed that NLR was correlated with ESR and CRP levels but not with BASDAI, which is consistent with our results. In a recent study from Chinese population, there was no relation between ASDAS-CRP and haematological parameters.[11] In a systematic review and meta-analysis, which assessed the articles from Asia, Turkey and Middle East, elevated levels of RDW were found to be associated with r-axSpA, whereas MPV levels were not.[36] These inconsistent results might stem from the heterogeneity of the study populations.

BS is considered as an MHC-I-opathy, sharing similar pathogenetic mechanisms with spondyloarthropathies.[37] Given the fact that both diseases have some similarities with respect to pathophysiological pathways, it was more appropriate to use BS as diseased controls. Neutrophils play a major role in the etiopathogenesis of BS.[38,39] In a study published from Turkey, NLR was found to be an indicator of BS presence.[40] In addition, NLR was shown to be

associated with active disease, especially with mucocutaneous involvement.[41] RDW was found to be associated with BS as well.[42,43] In this report, we also showed that NLR and RDW were higher in patients with BS, consistent with the literature.

Study Limitations

The major limitation of our study is its retrospective and cross-sectional design. In addition, there were not any patients with non-radiographic axial spondyloarthritis, which represents an earlier phase of the disease and in which inflammation (in magnetic resonance imaging and/or CRP) plays more role than r-axSpA. As a result, the duration of the illness was longer, which precludes us from making an assumption about the relation of these parameters in earlier disease. Furthermore, due to cross-sectional design of the study, the analyses were also based on a single measurement of CBC, which may not reflect the relation over time. Therefore, we cannot predict the association between these haematological parameters and radiographic progression in patients with r-axSpA.

Conclusion

Our results indicate that haematological parameters such as NLR, PLR, MPV and RDW do not associate with commonly used disease activity indices of r-axSpA. Considering the conflicting results of the studies published about CBC-derived haematological parameters and the lack of the standardized measurement techniques, we believe that these parameters do not really help physicians to determine disease activity. As clinicians, we still need quick and accurate biomarkers that reflects the actual disease activity in patients with r-axSpA. More studies need to be conducted to ascertain prospective biomarkers for disease activity in r-axSpA.

Ethics

Ethics Committee Approval: This study was approved by the local research ethics committee of the Ankara University Faculty of Medicine (approval number: I9-586-20). The study was conducted according to the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: D.Ş.E., M.T., G.K., Design: D.Ş.E., M.T., M.E.Y., Data Collection or Processing: D.Ş.E., M.Ö., Analysis or Interpretation: M.T., T.M.T., A.A., Literature Search: D.Ş.E., S.S., M.E.Y., Writing: D.Ş.E., M.T., G.K.

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