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Mean platelet volume and neutrophil/lymphocyte ratio in adolescent idiopathic scoliosis: can they be predictive value in diagnosis?

M. ÇELİK[1], C. IŞIK[2], E. ARIKAN[3], M. KURTBOĞAN[4], M. BOZ[1]

[1]Department of Orthopedics and Traumatology, Malatya Training and Research Hospital , Malatya, Turkey; [2]Department of Orthopedics and Traumatology, Abant Izzet Baysal University, School of Medicine, Bolu, Turkey; [3]Department of Orthopedics and Traumatology, Çekirge Public Hospital, Bursa, Turkey; [4]Department of Orthopedics and Traumatology, Atatürk Public Hospital , Düzce ,Turkey.

Correspondence at: Metin ÇELİK, MD. Department of Orthopedics and Traumatology, Malatya Training and Research Hospital , 44090, Malatya, Turkey. E-mail: drmetincelik@hotmail.com

In our study, we evaluated whether mean platelet volume (MPV) and neutrophil lymphocyte ratio (NLR) are predictive values in the diagnosis of Adolescent Idiopathic Scoliosis in patients diagnosed with scoliosis in our clinic. Approximately 15000 patients who applied to our spine outpatient clinic with the suspicion of scoliosis between 2011 and 2018 were reviewed retrospectively. 292 patients were included in the study. The patients were divided into 3 groups. Group 1; control group group 2; group with the possibility of developing scoliosis under follow-upand group 3; the patient group diagnosed with scoliosis. Spinal curvature degrees of the patients were measured using the Cobb method. The MPV and NLR values of the patients were compared with the degree of curvature measured by the cobb method. NLR was 2.17 ± 2.10 K/ul in Group 1, 2.42 ± 1.76 K/ul in Group 2, and 2.72 ± 3.91 K/ul in Group 3. Although the NLR of the 3rd group was higher than the other 2 groups, it was not statistically significant. (p > 0.05). MPV was 7.90 ± 1.07 fL in Group 1, 7.95 ±1.39 fL in Group 2, 8.33 ± 1.37 fL in Group 3.MPV was higher in Group 3 and was found to be statistically significant (p=0.024). After adjusting for the effects of gender and age variables on the groups, the difference in MPV between groups became more significant (p=0.017) . While there was no statistically significant difference between the groups in terms of NLR, it was observed that MPV was statistically significantly higher in patients with AIS.Could this relationship be a promising inflammatory marker for AIS? We think that this question should be answered by studies involving larger patient and control groups.

Key words: adolescent idiopathic scoliosis, neutrophil/ lymphocyte ratio, mean platelet volume, cobb angle.

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a progressive spinal growth disease resulting in the occurrence of one or more coronal curvatures of the spine exhibiting a Cobb angle equal to or greater than 10with spinal rotation (Morrissy and Weinstein 1996; Lowe et al. 2000). The cause of 80% of scoliosis is unknown (idiopathic). It occurs unnoticed in children over time and progresses with skeletal development[1].

AIS is one of the challenging diseases of orthopedics, which we do not know yet how it formed today, but on which a lot of work has been done. Advance has been made in the pathomechanics and treatment of the deformity, but the theories of etiology alone are not sufficient to explain the disease[1,2]. The etiology of AIS is unclear. Researchers with different perspectives have tried to better define this etiology. Genetics, growth hormone secretion, connective tissue structure, muscle structure, vestibular dysfunction, melatonin secretion and platelet microstructure are the focu[3]. There is no accepted scientific theory for the diagnosis of AIS. Lowe et al. emphasized the activity of calmodulin, a systemic mediator in contractile tissues, in paraspinous muscles. In his study of Lowe, one of the topics of discussion; calmodulin is not generally used as a marker of platelet activation[4]. It has been discussed whether platelet calmodulin changes are associated with local and/or regional changes in the muscle, nervous system or immature vertebrae. Since platelet and muscle cells contain the same contractile proteins (actin-myosin), platelets can be used as models for muscle research[4,5].

MPV; The ratio of platelet volume to whole blood volume gives the plateletcrit value. It is obtained by dividing the 'plateletcrit' value by the total platelet count[6]. In various physiological and pathological conditions, megakaryocytopoiesis is rearranged according to the need for active platelet and causes time-dependent changes in platelet indices. However, these changes are not always linear, suggesting that they are affected by complex immune and inflammatory mechanisms[7]. It has been suggested in many studies

that MPV is important as an inflammation marker and reflects disease activity and anti-inflammatory treatment efficacy in chronic inflammatory diseases[8,9].

NLR; It is obtained by dividing the number of neutrophils by the number of lymphocytes. In recent studies, it is said that NLR is a marker of systemic inflammatory state[10,11].

Burwell et al. formulate an alternative platelet-skeletal hypothesis which involves: a small scoliosis curve; axial loads transmitted directly from the intervertebral discs to vertebral body growth plates (endplate physes) as axial inward bulges that create mechanical micro-insults. The latter cause dilatation of juxta-physeal vessels and, in deforming vertebrae, vascular damage with exposure of subendothelial collagen and other agonist proteins; subject to pre-disposition, platelet activation with calmodulin changes occurs within dilated vessels of deforming vertebral bodies; the activated platelets in juxta-physeal vessels release growth factors that, after extravasation, abet the hormone-driven growth of the already mechanically-compromised vertebral endplate physes to promote the relative anterior spinal overgrowth and curve progression of AIS[12]. Leboeuf et al. thought that various hormones, especially estrogens, play a role in the initiation and development of adolescent idiopathic scoliosis. Despite the fact that estrogens are not causative factors of AIS, they could impact the progression of spinal deformity by interacting with factors that modulate bone growth, biomechanics and structure[13]. It is well known that progression of scoliosis occurs during skeletal growth and that estrogens are large contributors to puberty and growth. Data from the literature and clinical orthopedic practice recognize skeletal immaturity as a crucial factor in the progression of spinal deformity. Skeletal growth is controlled by a complex interplay of sex, age and growth hormones[14,15]. Scoliosis is not known as an inflammatory disease. There are no reliable laboratory markers for the diagnosis of scoliosis. Based on this study, we think that axial loading and mechanical micro-movements will cause degeneration and inflammation. In addition, we aimed to determine both the occurrence of inflammation and the role of inflammatory markers in the early stage of AIS. Looking at the recent innovative studies in the literature, there are many studies on inflammatory markers MPV and NLR. We looked at the association of these inflammatory markers with AIS.

In our study, we aimed to evaluate whether MPV and NLR, which are inexpensive and easily accessible inflammatory markers, have a predictive value in the diagnosis of AIS .

MATERİALS AND METHODS

Ethics committee approval for the research to be carried out was obtained from the AIBÜTF Ethics Committee (AİBÜTF Ethics committee approval date: 20-12-2018, decision no: 2018/276) Approximately 15000 patients who applied to our spine outpatient clinic with the suspicion of scoliosis in Abant İzzet Baysal University Faculty of Medicine Orthopedics and Traumatology Clinic between 2011-2018 were retrospectively scanned. 292 patients who had both scoliosis radiographs and Complete Blood Count (CBC) were included in the study. Age, gender, neutrophil, lymphocyte and platelet counts, NLR and MPV levels were recorded. Considering the studies described above, 99 age- and sex-matched vertebral column scoliosis patients and 193 healthy controls were included in the study.

Retrospectively scanned patients were evaluated under 3 groups. Group 1; control group (cobb angle = 0 degrees), group 2; group with the possibility of developing scoliosis under follow-up (cobb angle 1- 9 degrees) and group 3; the patient group diagnosed with scoliosis (with apical vertebral rotation according to the Nash Moe classification and cobb angle>10). The radiographic incidence of AIS is low. Most idiopathic minor curves range from 5 to 20 degrees. The prevalence decreases as the degree of curvature increases. The progression of scoliosis curvature increases with large curvature and low skeletal maturity. During the period of rapid growth, the curves may increase by one or more degrees per month. It continues until skeletal maturation and then slows down considerably. The severity of the curvature along with the maturity of the skeleton aids in the assessment of the risk of progression. In skeletally immature patients, there is a risk of curve progression of approximately 20% for 20-degree curves, 60% for 30-degree curves and 90% for 50-degree curves[16-18].

The patient groups included in the study include patients who have not completed their skeletal maturity. Since the skeletal maturity was not completed and growth continued, the patients in the 2nd group were evaluated as the group with the possibility of developing scoliosis.The scoliosis (full spine plane, Anterior-Posterior(AP) Lateral) radiographs of the patients were taken; The proximal thoracic, thoracic, and lumbar vertebrae in the upper and lower vertebrae, apical, neutral and stable vertebrae were determined and the size of the curvatures was measured with the Cobb method.(Figure-1) In addition, CBC values of the patients were scanned from the system. The MPV

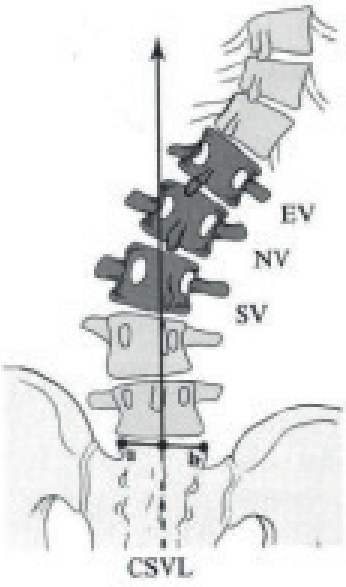

Figure 1 — The end vertebrae (EV) are those most tilted, and the apex (A) is the disk or vertebra deviated farthest from the center of the vertebral column. A neutral vertebra (NV) is one that is not rotated, and a stable vertebra (SV) is one that is bisected or nearly bisected by the CSVL which is exactly perpendicular to a tangent drawn across the iliac crests.

value was recorded according to the CBC result. NLR was calculated by dividing the neutrophil value of the patients by the lymphocyte value. It was compared with the degree of curvature determined by the Cobb method.

InclusionCriteria for the Study; Patients between the ages of 10 and 18 whose scoliosis radiographs and hemograms were studied were included in the study.

Exclusion Criteria for the Study: Patients with lumbar disc herniation, inflammatory diseases, spondylolisthesis and spondylosis excluded by plain X-ray or Magnetic Resonance İmaging (MRI), lower legs discrepancy, systemic-metabolic disease, rheumatological disease, active infection and previous spinal surgery were not included in the study.

All data were analyzed using the statistical software package SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). As descriptive statistics, mean and standard deviation for numerical variables, number and percentage values for categorical variables are given. Histograms and the Kolmogorov–Smirnov test were used to assess the variables' fit for a normal distribution. In group comparison for numerical variables, the Mann-Whitney U test was used for the difference between two means, while the chi-square test was used for categorical variables. ROC analysis and ROC area under the curve were used for the performance of the markers to distinguish groups. After removing the effects of gender and age variables on the groups, multiple linear regression analysis was used to examine the effects of the markers on the groups. The significance level was taken as ($p < 0.05$).

RESULTS

292 patients aged 10-18 years were included in the study. 149 (51.1%) were girls and 143 (48.9%) were boys. The mean age of the patients was 14.66 ± 4.01 (minimum 10, highest 18). Cobb Angle was found to be 0 degrees in 94 (32.2%) of 292 patients who underwent radiological evaluation for scoliosis, and they were included in the first group. Cobb Angle was found to be between 1 and 9 degrees in 99 (33.9%) of them, and they were included in the second group. In 99 (33.9%) cases, Cobb Angle of 10 degrees and above was detected and no additional pathological finding was detected in the locomotor and neurological system examinations, and all of them were evaluated as "Adolescent Idiopathic Scoliosis" and were included in the third group.

When we look at the gender distribution between the groups, there were 45 (47.8%) girls and 49 (52.2%) boys in Group 1. Group 2 consisted of 51 (51.5%) girls, 48 (48.5%) boys, and Group 3 included 53 (53.5%) girls and 46 (46.5%) boys. When we look at the mean age between the groups, it was 14.15 ± 3.50 in the 1st group, 14.06± 2.72 in the 2nd group, 14.73 ± 3.94 in the 3rd group. Although the mean age of the 3rd group was slightly higher, no significant difference was observed.

The two questions we asked were to determine whether there is a significant difference between AIS and patients who were not diagnosed with scoliosis. The first parameter we evaluated, NLR, was evaluated between 3 groups. It was observed that it was 2.17 ± 2.10 K/ul in the 1st group, 2.42 ± 1.76 K/ul in the 2nd group, 2.72 ± 3.91 K/ul in the 3rd group. Although the NLR value of the 3rd group was significantly higher, it was observed that there was no statistically significant difference between the groups($p>0.05$). The second parameter we evaluated, MPV value, was found to be 7.90 ± 1.07 fL in Group 1, 7.95 ±1.39 fL in Group 2, and 8.33 ± 1.37 fL in Group 3. It was observed that there was a statistically significant difference in MPV in the 3rd group. ($p=0.024$). (Table I)

Since there were more than 2 groups in the regression analysis, only one group was taken as a reference. In this study, the third group was taken as reference. Although the gender and age variables did not differ significantly according to the groups, the effect of

Table I. — Group comparison results according to measurement values

	1st Group	2nd Group	3rd Group	p
NEU	4.37 ± 1.98	4.40 ± 2.13	4.65 ± 2.11	0.543
LYM	2.41 ± 0.84	2.18 ± 0.92	2.31 ± 1.01	0.341
NLR	2.17 ± 2.10	2.42 ± 1.76	2.72 ± 3.91	0.364
MPV	**7.90 ± 1.07 fL**	**7.95 ±1.39 fL**	**8.33 ± 1.37 fL**	**0.024**

NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil lymphocyte ratio, MPV: Mean platelet volüme.

Table II — Group comparison results according to age and gender adjusted measurement values

		GROUP		
		B	**Standard error**	**p**
NEU(K/ul)	**Group 3**	0.241	0.273	0.378
	Group 2	0.018	0.362	0.961
LYM(K/ul)	**Group 3**	0.011	0.122	0.925
	Group 2	0.218	0.161	0.178
NLR (K/ul)	**Group 3**	0.392	0.398	0.326
	Group 2	0.190	0.528	0.719
MPV(fL)	**Group 3**	**0.402**	0.168	**0.017**
	Group 2	0.051	0.222	0.818

NEU: Neutrophil, LYM: Lymphocyte, NLR: Neutrophil lymphocyte ratio, MPV: Mean platelet volüme, B: Standardized Coefficients Beta

gender and age variables on the groups was examined after the analysis of variance was adjusted, whether there was a difference between the groups in terms of measurement values. According to this; The difference between the groups became more significant after the effects of gender and age variables on MPV values were refined. MPV value was close to the 1st and 2nd groups and was not statistically significant. But the MPV value was statistically different between the 2nd and 3rd groups, and the mean MPV value of the 3rd group was 0.402 units higher than the 2nd group, which represents the clinical difference. (p=0.017) (Table II)

DISCUSSION

In the study, we investigated whether there was a change in MPV and NLR levels, which are inflammatory markers, in patients with no curve below 10 degrees and AIS deformity above 10 degrees. Our results have reported that MPV was found to be statistically significant in patients diagnosed with AIS. When we looked at the literature, we observed that there were many studies on MPV and NLR, which are inflammatory markers recently[19-22]. To our knowledge, this is the first study using markers such as NLR and MPV to evaluate radiographic severity in AIS.

Aktürk S. et al. conducted a study on the evaluation of blood NLR and platelet distribution volume as inflammatory markers in patients with fibromyalgia (FM). They found that blood NLR and MPV were significantly higher in the patient FM group. The result of this study was to show NLR and MPV as promising inflammatory markers indicative of fibromyalgia. They thought that it could be useful in facilitating the diagnosis of FM patients[22]. In our study, while MPV was statistically significant in AIS patients, although NLR was high, no significant difference was observed. In our study, MPV increase in AIS was shown as an important inflammatory marker.

The study of Taşoğlu Ö et al.; aimed to determine whether MPV and PLR (platelet lymphocyte ratio) in the blood would be a new marker in hip osteoarthritis (OA). They stated that blood PLR and MPV are accepted as new markers in most of the systemic inflammatory diseases, but they emphasized that they have not been investigated yet in radiographic OA without synovitis. They performed a retrospective study for the evaluation of blood PLR and MPV in radiographic hip OA. They showed that there was a statistically significant difference between MPV, PLR / moderate hip OA group and severe hip OA group. As a result of this study, they suggested blood PLR and MPV as new inflammatory markers that predict the radiographic severity of hip OA in daily practice[19]. In our study, we evaluated NLR, the first parameter we evaluated, among 3 groups. Although the NLR of the 3rd group was significantly higher, there was no statistically significant difference (p>0.05). The second parameter we evaluated in our study was MPV.The MPV value of the 3rd group was found to be statistically significant(p=0.024). We also performed regression analysis between groups. After

the effects of gender and age variables on the 2nd and 3rd groups were adjusted, the statistical difference between the groups in MPV values was found to be more significant. (p=0.017).

Some studies have suggested that lymphocytes and neutrophils may play a role in the pathogenesis of spondyloarthritis (SpA) and NLR value was examined. Gokmen et al. and Mercan et al. While it was seen that it was not significant in his study, Esra et al. found that it was significantly higher in the study conducted by[23-25]. In our study, although both of the two parameters we looked at were higher than the other groups, only the MPV value was significant. Possible causes in studies with high NLR may be due to differences in comorbidities and active infection between study populations. In addition, the fact that the NLR was found to be high in our study suggests that a study in larger sample groups may make the NLR meaningful.

Very serious research has been done about the etiology of scoliosis until today; but the reason has not been clearly explained yet. It is thought to be multifactorial rather than a single factor[1,4]. One of the factors not addressed is that inflammatory markers have not been evaluated in scoliosis.It is well known that during inflammation, neutrophil and platelet counts increase while lymphocytes decrease.NLR and MPV are easy and inexpensive to measure.It can be used as a marker of subclinical inflammation.These markers are; It has been studied in various diseases such as otolaryngology, neurotology, diabetes mellitus, coronary artery disease, ulcerative colitis and cancer[26-32]. Scoliosis is not known as an inflammatory disease. There are no laboratory markers determined in the diagnosis of scoliosis to date. Considering the studies, we thought to investigate the role of inflammation in AIS.

In the literature review, we come across many studies on the level of platelet calmodulin and endocrine mechanisms (such as melatonin, leptin). In the study of Lowe et al., especially the effect of platelet calmodulin levels on the etiology of AIS was emphasized. To explain the relationship between platelet calmodulin levels, scoliosis curve and AIS, Dr. Lowe suggested that platelet calmodulin modulates paraspinous muscle activity and calmodulin acts as a systemic mediator of tissues with contractions. There has been some speculation as to whether changes in platelet calmodulin cause changes locally or regionally in a part of the spine in the muscles, nervous system, or immature vertebrae. And the result of this thought was the indisputable idea that more research is needed on the immature deforming skeleton related to the etiology and prognosis of platelets[4].

Burwell et al referred to altered paraspinal muscle activity defined by Lowe et al., which explained the relationship between AIS Cobb angle and platelet calmodulin level. As a result, they formulated the following hypothesis. 1- In those with small scoliosis curvature, 2- Axial loading is transferred to the endplate physis via the vertebral bodies with inward protrusions created by mechanical micro-movements, 3- Later, it causes dilatation of juxta-physeal vessels in deformed vertebrae, 4-It shows that changes in calmodulin together with platelet activation in dilated veins in deformed vertebral bodies cause susceptibility to scoliosis , 5- They stated that the activated platelets in the juxta-physeal vessels secrete growth factor and the growth factors that are extravasated make the physial growth in the endplate more sensitive, provide relatively overgrowth of the anterior spinal column and encourage the curve progression of AIS[12].

The major limitation of this study is that a single blood sample was used and did not allow the stability of blood levels to be evaluated over time.

In conclusion, MPV was found to be statistically significant in patients diagnosed with AIS although NLR value was high in AIS, it was not found to be statistically significant in our study. Although inexpensive and readily available, it was found to be non-specific and non-sensitive. We concluded that the inflammatory markers identified in this study may be useful in facilitating the diagnosis of AIS patients. This is the first study to show that MPV is significantly elevated in AIS. Could this relationship be a promising inflammatory marker for AIS? We think that this question should be answered by studies involving larger patient and control groups.

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