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ORIGINAL ARTICLE

Role of Hematological Parameters in the Diagnosis of Juvenile Idiopathic Arthritis in Children with Arthritis

Papel de los parámetros hematológicos en el diagnóstico de Artritis Idiopatica Juvenil en niños con artritis

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What do we know about the subject matter of this study?

The differential diagnosis of childhood arthritis is extensive. Therefore, the diagnostic period may be long. However, early diagnosis and treatment of Juvenile Idiopathic Arthritis, which is the most common cause of chronic arthritis, is important for the prognosis of the disease.

What does this study contribute to what is already known?

Although there is a change in the neutrophil-lymphocyte ratio and platelet distribution width among the hematological parameters in the presence of inflammation, its contribution to the differential diagnosis is limited.

Abstract

Early diagnosis and treatment of arthritis are essential for the prognosis of the disease. Especially during the active phase of juvenile idiopathic arthritis (JIA), a prompt diagnosis is necessary to manage the disease properly. New inflammation markers such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), mean platelet volume (MPV), and platelet distribution width (PDW) have been investigated in various inflammatory disorders. This study aimed at the diagnostic value of NLR, MLR, MPV, and PDW in differentiating JIA in children with arthritis. **Patients and Method:** Case-control study with 324 children with arthritis (case group) and 324 healthy children (control group). Additionally, children with arthritis were grouped into JIA and non-JIA. Medical records of children aged 0-18 were retrospectively reviewed. Hematological parameters at the time of diagnosis were recorded. NLR, MLR, MPV, and PDW were analyzed in the study groups. **Results:** In the case group, 52.8% were boys, and 47.2% were girls; the mean age was 7.7 ± 4.0 years. The NLR in the case group was significantly higher than the control one ($p = 0.001$). The mean MPV was lower in the case group than the control group ($p = 0.001$). There were no differences in NLR and MPV between JIA and non-JIA groups ($p = 0.062$, $p = 0.689$). The JIA group's mean PDW was lower than the non-JIA group ($p = 0.001$). **Conclusion:** The increase in NLR may indicate inflammation but has no superiority in distinguishing JIA from other arthritis causes. Platelet distribution width was lower in JIA patients, but its clinical utility is limited.

Keywords:
Arthritis;
Child;
Leukocyte Number;
Mean Platelet Volume;
Juvenile Idiopathic Arthritis

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Introduction

Childhood arthritis includes a heterogeneous group of disorders, thus requiring a broad spectrum of differential diagnoses ranging from infectious diseases to multisystem inflammatory disorders[1]. Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. Diagnosis is challenging due to arthritis lasting more than six weeks among the diagnostic criteria[2]. However, a prompt diagnosis will be essential in the active phase of JIA to manage the disease and prevent its comorbidities. There is no gold standard test for the diagnosis of JIA. Although laboratory tests and radiological imaging help in the differential diagnosis, the diagnosis of JIA is based on clinical findings[1]. The most commonly used nonspecific inflammatory markers are Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, their benefits are limited and nonspecific, so new adjunct diagnostic tests are under investigation. Recent studies reported differences in some markers obtained in the complete blood count (CBC) in infectious and inflammatory diseases compared to healthy controls. This research suggested that neutrophil to lymphocyte ratio (NLR) and monocyte to lymphocyte ratio (MLR) can be used as inflammatory markers such as leukocytosis and thrombocytosis[3,4]. One of the effects of proinflammatory cytokines produced in response to systemic inflammation in the liver is megakaryocytes' stimulation. This condition causes the production of more giant and more reactive platelets[5]. Therefore, platelet indices such as mean platelet volume (MPV) and platelet distribution width (PDW), which are known to be altered by platelet synthesis, also vary depending on the inflammatory process[6]. Mean platelet volume and platelet distribution width was investigated to demonstrate disease activity in various inflammatory conditions such as chronic hepatitis B infection, familial Mediterranean fever, rheumatoid arthritis (RA), psoriasis, and ankylosing spondylitis[7-9]. However, the literature contains conflicting results and is mostly based on studies in adults. We aimed to evaluate the changes in inflammatory markers in CBC and the diagnostic value of NLR, MLR, MPV, and PDW in diagnosing JIA in children presenting with arthritis.

Patients and Method

Study design

This is a case-control study. Children younger than 18 years of age who were admitted to our hospital due to arthritis between 2012 and 2019 were included in the study. The diagnoses and laboratory results of the patients were reviewed from the medical records retrospectively.

Patient selection

The control group consisted of healthy children admitted to our hospital for pre-operative research for elective surgery or routine control, similar in age and gender to the case group. Children with any sign of infection or systemic illness were excluded from the control group. Also, patients with arthritis were grouped as JIA and non-JIA.

Variables analyzed

Hematological parameters were recorded at the time of diagnosis. Complete blood counts were measured on the Beckman Coulter UniCel® DxH 800 cellular analysis system. All samples were analyzed within the first 30 minutes after being collected due to the quality standards of our hospital. The WBC, absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute lymphocyte count (ALC), NLR, MLR were statistically analyzed in the case and control groups.

Ethics

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee (2017/184).

Statistical analyses

Analysis were performed using the SPSS version 24.0 program (IBM Corporation, Armonk, NY, USA). Demographic and clinical data were analyzed descriptively and reported as proportions of total patients. Numbers (n) and percentages (%) were used for categorical data. The mean ± standard deviation was used when the continuous data were compatible with the normal distribution. Numerical data with normal distribution were compared with 'Student's t-test. Comparisons for categorical variables were made using the Chi-Square test. The performance of diagnostic tests was evaluated by ROC analysis. $p < 0.05$ level was considered statistically significant.

Results

The study included 324 children with arthritis and 324 healthy children. In the case group, 52.8% were boys, and 47.2% were girls; the mean age was 7.7 ± 4.0 years. The control 'group's mean age was 7.1 ± 3.4 years; the mean age of the groups was matched ($p = 0.074$). The distribution of boys and girls in the case and control groups were similar ($p = 0.720$). The most common diagnosis in the case group was *Henoch-Schönlein Purpura* (HSP) (table 1).

The case group's mean WBC, ANC AMC, and NLR were significantly higher than the control group ($p = 0.001$; each) (table 2). Whereas mean ALC and

MLR of the case and control groups were similar (p = 0.806, p = 0.480, respectively) (table 2). As for platelet count and indices, the mean platelet counts in the case group were higher than in the control group, and the difference was statistically significant (p = 0.001). Moreover, the mean MPV was lower in the case group than the control group (p = 0.001). There was no significant difference in mean PDW between groups (p = 0.928) (table 2).

Of the 324 patients in the case group, 44 (13.6%) patients were diagnosed with JIA. In the groups with JIA and non-JIA arthritis, girls' and boys' distribution were similar (p = 0.090). The JIA group's mean age was higher than the non-JIA group (9.0 ± 4.3 years vs. 7.5 ± 3.9 years; p = 0.019). However, mean WBC, ANC, ALC, AMC were not statistically different between these two groups (p = 0.142; p = 0.074; p = 0.159, p = 0.808, respectively). Also, mean NLR, MLR were similar (p = 0.062; p = 0.250, respectively). There was no difference in mean platelet counts and MPV (p = 0.492 and p = 0.698, respectively) (table 3). The JIA group's mean PDW was lower than the non-JIA group (p = 0.001). When the ROC curve evaluated the PDW value, sensitivity was 61.4% and specificity 60.4% (AUC = 0.646) for PDW < 15.5 for JIA (figure 1).

Table 1. Diagnosis of patients with arthritis

	n = 324	%
HSP	95	29.3
Transient synovitis	64	19.8
JIA	44	13.6
ARF	31	9.6
Unknown	27	8.4
FMF	22	6.8
Malignancy	14	4.3
Brucellosis	11	3.4
Kawasaki	2	0.6
SLE	1	0.3
Salmonella	1	0.3

HSP: Henoch-Schönlein purpura. JIA: Juvenile idiopathic arthritis. ARF: Acute rheumatic fever. FMF: Familial mediterranean fever. SLE: Systemic lupus erythematosus.

Discussion

The evaluation of arthritis in childhood is challenging because of a broad spectrum of etiology and prognosis, ranging from very mild self-limiting to highly destructive. Therefore, inexpensive and useful markers that can assist the clinician in the differential diagnosis of patients presenting with arthritis have been investigated. According to our results, although WBC, ANC, AMC, and NLR values are significantly higher among pediatric patients with arthritis, they have no value in differentiating JIA from other arthritis causes.

NLR was previously reported to increase in pediatric patients with septic arthritis, arthritis of brucellosis, and healthy controls[10-12]. Balın et al. said that NLR and MLR values were higher in those with osteoarticular involvement of brucellosis. In contrast, Kazanasmaz et al. reported that the NLR between the brucella positive and negative groups were similar[13,14].

Table 2. Inflammatory markers in the complete blood count in the case and control groups

	Case (n = 324) Mean ± SD	Control (n = 324) Mean ± SD	p
WBC (/mm³)	11.501 ± 4.785	7.826 ± 2.049	0.001
ANC (/mm³)	7.471 ± 4.366	3.871 ± 1.547	0.001
ALC (/mm³)	3.136 ± 1.684	3.164 ± 1.115	0.806
AMC (/mm³)	708 ± 390	578 ± 515	0.001
NLR	3.2 ± 2.9	1.4 ± 0.8	0.001
MLR	0.3 ± 0.2	0.2 ± 0.7	0.480
Platelet Counts (/mm³)	411.490 ± 348.088	329.791 ± 139.190	0.001
MPV (fL)	8.4 ± 1.1	9.0 ± 0.9	0.001
PDW (%)	15.7 ± 0.6	15.7 ± 1.8	0.928

SD: Standard Deviation. WBC: White Blood Cell. ANC: Absolute Neutrophil Count. ALC: Absolute Lymphocyte Count. AMC: Absolute Monocyte Count. NLR: Neutrophil/Lymphocyte Ratio. MLR: Monocyte/Lymphocyte Ratio. MPV: Mean Platelet Volume. PDW: Platelet Distribution Width.

Table 3. Inflammatory markers in the complete blood count in JIA and non-JIA arthritis

	JIA Mean ± SD (n = 44)	Non-JIA Mean ± SD (n = 280)	p
WBC (/mm³)	12.487 ± 5.709	11.346 ± 4.615	0.142
ANC (/mm³)	8.840 ± 5.531	7.255 ± 4.123	0.074
ALC (/mm³)	2.803 ± 1.333	3.188 ± 1.728	0.159
AMC (/mm³)	695 ± 393	710 ± 391	0.808
NLR	4.3 ± 4.1	3.1 ± 2.7	0.062
MLR	0.3 ± 0.3	0.3 ± 0.2	0.250
Platelet Counts (/mm³)	445.045 ± 137.748	406.217 ± 370.329	0.492
MPV (fL)	8.3 ± 1.2	8.4 ± 1.1	0.698
PDW (%)	15.5 ± 0.4	15.8 ± 0.6	0.001

JIA: Juvenile idiopathic arthritis. SD: Standard Deviation. WBC: White Blood Cell. ANC: Absolute Neutrophil Count. ALC: Absolute Lymphocyte Count. AMC: Absolute Monocyte Count. NLR: Neutrophil/Lymphocyte Ratio. MLR: Monocyte/Lymphocyte Ratio. MPV: Mean Platelet Volume. PDW: Platelet Distribution Width.

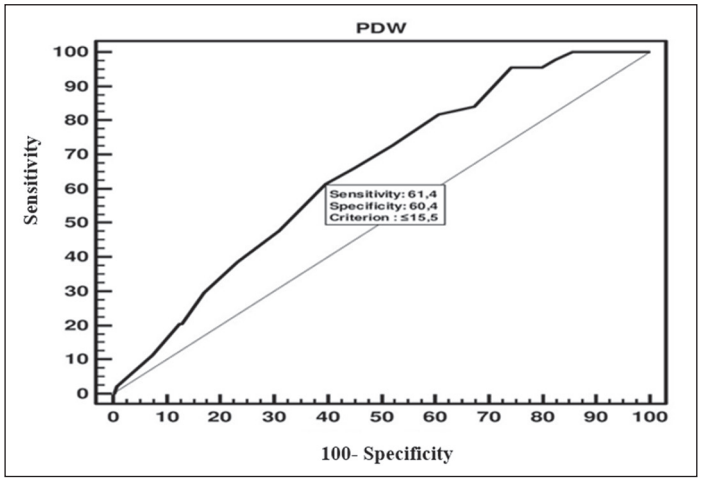

Figure 1. ROC curve for Platelet Distribution Width (PDW) in Juvenile Idiophatic Arthritis (JIA) and non-JIA group (AUC:0.646).

Although 'JIA's etiology and pathogenesis are largely unknown, it is accepted as an autoimmune disease associated with alterations in humoral and cell-mediated immunity resulting in concomitant proinflammatory cytokines[15]. Thus, we hypothesized that markers that reflect inflammation are likely to distinguish JIA from other arthritis causes. But, the results of this study showed that the most commonly used inflammatory markers obtained in CBCs, including NLR and MLR of JIA and non-JIA groups, were similar; thus, NLR and MLR are not useful markers in distinguishing JIA and non-JIA reasons. In the literature, Gunes et al. reported that NLR was significantly higher in patients with active or inactive JIA than control subjects[16]. However, NLR was not a predictive marker of disease activity in JIA patients[16]. In the meta-analysis in which Hao et al. and Erre et al. evaluated the research of hematological indices in RA patients, NLR was statistically significantly higher in RA patients than in control[17,18]. According to these results, regardless of the underlying etiology, an increase in NLR may indicate the presence of subclinical or significant inflammation.

Beyond its traditional role in hemostasis and thrombosis, platelets are essential coordinators of inflammation as they have numerous inflammatory mediators to modify leukocyte and endothelial responses to different inflammatory stimuli. In literature, MPV was higher in cardiovascular diseases, cerebral stroke, respiratory infections, chronic renal failure, intestine diseases, and rheumatoid diseases[19]. In contrast, decreased MPV was noted in ulcerative colitis, systemic lupus erythematosus in adults, and different neoplastic disorders[19]. In our research, the mean platelet count in the case group was higher than the control group; moreover, the MPV in the case group was significantly lower than the control group. The literature has conflicting results on this issue. Some studies have reported that MPV was lower in acute rheumatic fever, brucellosis, and HSP than healthy volunteers[20,21]. However, in another study that included children with HSP, there was no difference in platelet indices between the case and control groups[22]. This current study's findings revealed that mean platelet counts and MPV were similar in patients with and without JIA arthritis. Consequently, MPV changes do not appear to help evaluate inflammatory diseases.

Platelet distribution width, which reflects the anisocytosis of platelets, is usually parallel to MPV; thus, PDW increases as the mean platelet volume increases. In one study involving JIA patients, PDW was significantly higher in patients with active JIA disease than in

the healthy control group[16]. Despite this, Vakili et al. reported that evaluation of PDW changes did not help follow-up and disease assessment in JIA[23]. Platelet distribution width was similar between case and control groups in our study, while the JIA group's mean PDW was significantly lower than the non-JIA group. The sensitivity of the PDW value for < 15.5 was 61.4%, and the specificity was 60.4% in JIA detection. However, its usefulness is limited in differentiating disease due to AUC = 0.646.

Our study has some limitations. It is retrospective, and no evaluation was made according to JIA subgroups because of the limited number of patients diagnosed with JIA arthritis in the case group.

Conclusion

According to our results, NLR has no additional contribution to WBC and platelet counts, which are directly presented in CBC results to evaluate children presenting with arthritis. Moreover, they are not useful to diagnose JIA in childhood arthritis. Only PDW is lower in JIA patients than other causes of arthritis, but its clinical utility is limited due to the nonpredictive value of AUC.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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