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The Hemogram Parameters in Juvenile Idiopathic Arthritis: Relation to Disease Activity and Ultrasound Findings

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Abstract:

Background: Juvenile idiopathic arthritis (JIA) is an autoimmune chronic disease of childhood with existent challenges to monitoring the disease activity. The hemogram parameters are utilized as inflammatory markers in several diseases. Purpose: This study aimed to evaluate neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), mean platelet volume (MPV), platelet distribution width (PDW) and red cell distribution width (RDW) in JIA patients with correlating them to disease activity along with ultrasonographic parameters. **Subjects and methods:** This case-control study incorporated 50 JIA children and 50 healthy control children. Laboratory investigations included the CBC derived parameters (RDW, PDW, MPV, NLR, LMR and PLR), ESR and CRP. Assessment of JIA disease activity was performed. JIA functional status was assessed by Juvenile Arthritis Multidimensional Assessment Report (JAMAR). Musculoskeletal ultrasound (MSUS) was done to JIA children using 10-joint score according to OMERACT definitions. **Results:** In JIA patients, PDW, MPV and LMR were lower than controls ($P<0.05$), conversely NLR and PLR were higher than controls ($P<0.001$). Significant positive correlations were found regarding NLR and PLR with the disease activity, JAMAR domains, ESR and CRP but LMR, PDW and MPV revealed significant negative correlations ($P<0.05$). NLR and PLR showed positive correlations with MSUS grey scale and Power Doppler, although MPV was negatively correlated ($P<0.05$). NLR could differentiate active JIA patients from inactive patients (AUC=0.903). **Conclusion:** This study verified that the hemogram parameters are beneficial parameters for evaluating the JIA disease activity. MPV, NLR and PLR help to predict MSUS activity.

Keywords: Juvenile idiopathic arthritis; Disease activity; Neutrophil-lymphocyte ratio; Platelet-lymphocyte ratio; Musculoskeletal ultrasound.

Introduction

Being a widespread rheumatic disease during childhood, juvenile idiopathic arthritis (JIA) is an autoimmune chronic disorder with genetic susceptibility affecting the joints as well as internal organs [(1)]. JIA incorporates various arthritic disorders of unknown aetiology, lasting more than six weeks and with onset less than 16 years old. The International League of Associations for Rheumatology (ILAR) identifies seven JIA categories including oligoarticular type (persistent and extended), polyarticular negative rheumatoid factor (RF), polyarticular positive RF, juvenile psoriatic arthritis, systemic onset JIA (sJIA), enthesitis-related arthritis (ERA), and undifferentiated arthritis [(2)]. With the ongoing advances in JIA treatment, the disease activity evaluation turns into an ultimate part in managing this disease and the studies are converged on identifying the efficient measures for appraising the JIA disease status [(3)]. C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) are usually used for identifying the disease activity in JIA. Nonetheless, recent research has declared that CRP and ESR could not precisely demonstrate the disease status [(4)]. This highlights the necessity for sensitive and simple markers for evaluating the JIA disease activity [(5)]. Systemic inflammation also stimulates the cellular reactions, producing changes within the haematopoietic cells. Several research has been dedicated on the changes of peripheral blood cells in JIA reflecting their importance as markers to reveal systemic inflammation [(4,6)].

Derived from the routine complete blood count (CBC), there are different hemogram parameters including red cell distribution width (RDW) that is considered a standard index denoting the disparity of red blood cells in size[(6)], platelet distribution width (PDW) that measures the variability in size distribution of the platelets[(7)], mean platelet volume (MPV) that is defined as the average platelet volume[(8)], neutrophil-lymphocyte ratio (NLR) that is estimated via dividing the absolute neutrophils by the lymphocytes[(8)], lymphocyte-monocyte ratio (LMR) that is obtained via dividing the lymphocytes by the monocytes[(6)] and platelet-lymphocyte ratio (PLR) that is determined through dividing the platelets by the lymphocytes[(6)]. They are determined from CBC without additional cost. They have been newly considered as inflammatory biomarkers in numerous conditions (such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Behçet's disease, ankylosing spondylitis (AS), thyroiditis, etc) [(6,9)]. There are few studies evaluating the importance of the hemogram parameters in detection of systemic inflammation along with the JIA disease flare. Although these parameters are easily performed and of low cost, they are commonly rarely used by the physicians [(8)]. Musculoskeletal ultrasound (MSUS) is considered a well-acceptable, simple and dynamic imaging tool that is widely used in pediatrics. It is more sensitive to detect early beside subclinical synovitis, tenosynovitis and structural damage in JIA patients compared to the clinical examination [(10)]. Therefore, our study aimed to assess the different hemogram parameters in JIA patients for evaluating their role in detecting disease activity along with correlating them with the different disease activity parameters and ultrasound findings.

Subjects and methods:

Study design and participants: This case-control study incorporated fifty JIA children with different subtypes diagnosed based on the ILAR JIA classification criteria **[(11)]** attending to Rheumatology and Rehabilitation Department at Benha University Hospitals, Egypt from May 2022 to April 2024 and fifty age and sex matched apparently healthy children as controls. The Ethical Committee of Faculty of Medicine, Benha University, Egypt approved this study (code: MD 5-5-2022) and an informed consent was obtained from parents of individual

children participants included in this study. Data obtained from JIA patients included medical history, clinical examination, assessment of the functional status by juvenile arthritis multidimensional assessment report (JAMAR) questionnaire[12] and assessment of disease activity with juvenile arthritis disease activity score (JADAS–10) for oligoarticular and polyarticular subtypes[13], juvenile Spondyloarthritis disease activity index (JSPADA) for ERA[14] and systemic juvenile arthritis disease activity score (sJADAS) for sJIA[15]. Excluded cases were those having history of previous infection, surgery or blood transfusion within three months prior to the evaluation, known hematological disorders or other autoimmune diseases.

Laboratory investigations: Blood samples were collected for CBC using Sysmex-XP300®, CRP that was done via latex agglutination slide test, ESR that was done via the Westergren method, anti-nuclear antibody (ANA) by immunofluorescence and RF that was done via latex agglutination slide test. The assessed hemogram parameters, that are derived from CBC, included RDW, MPV, PDW, NLR, PLR and LMR.

Musculoskeletal ultrasound (MSUS) examination: Ten joints were evaluated in JIA patients including bilateral knees, ankles, wrists, elbows and the 2nd metacarpophalangeal joints using the 10-joint score according to Collado et al., 2013[16] with Logiq P9 ultrasound machine (General Electric, Wisconsin, USA®) on the same day of clinical examination. It is performed by two rheumatologists with experience of more than five years and were blinded to clinical examination. Evaluation of these joints with greyscale (GS) and Power Doppler (PD) was done relying on the Outcome Measures for Arthritis Clinical Trials (OMERACT) definitions of synovitis using semiquantitative scoring system. The total scores were obtained by summation of GS synovitis along with PD signals separately from the assessed joints [16].

Statistical analysis: It was implemented using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA®) and the Jamovi Project 2022 (Version 2.3®). The normally distributed data were tested with mean, standard deviation (SD) and range, whereas non-parametric data were tested with median, interquartile range (IQR, between 1st and 3rd quartiles) and range. Student t test was utilized for two groups comparison between normally distributed data, and Mann-Whitney test was utilized for non-parametric data. Correlations of the hemogram parameters with disease activity parameters and ultrasound were tested by Pearson's correlation for parametric data as well as the Spearman correlation coefficient (rho) for non-parametric data. For prediction of the active JIA patients, receiver operating characteristic (ROC) curve plot was conducted. Area under the curve (AUC), cutoff values, sensitivity and specificity were calculated. If P value is <0.05, it is declared as significant.

Results:

Fifty JIA cases were encompassed in the study, 28 of them (56%) were girls and 22 (44%) were boys. Mean age ± SD was 9.36±3.79 years. Patients were age and sex matched to the controls with non-significant difference. Mean BMI±SD of patients was 18.91±3.58 kg/m^2, and it was significantly lower among JIA patients. The demographic, clinical, disease activity scores, laboratory and MSUS data for JIA cases were presented in **table 1**.

As regards the medications used, 31 patients (62%) were using corticosteroids. 46 patients (92%) were on conventional disease modifying anti-rheumatic drugs (DMARDs) and the commonly used one was methotrexate (82%). Other given DMARDs were leflunomide (8%) and sulfasalazine (2%). 29 patients (58%) were on biologic DMARDs, the most frequently used was etanercept (22%). Other used biologics were tocilizumab (18%), adalimumab (16%) and rituximab (2%).

Table 1: Characteristics of JIA patients and controls

	Variable		JIA patients (n=50)	Controls (n=50)	P value
Demographic	Age (Years)	mean±SD (range)	9.36±3.79 (2-16)	9.68±3.62 (2 - 16)	0.67
	Gender	(Girls: Boys)	(28:22)	(27:23)	0.84
	BMI (kg/m^2)	mean±SD (range)	18.91±3.58 (10.97 – 30.7)	20.09±3.58 (16.64 – 24.5)	**0.04**
	Disease duration (years)	Median (IQR) (range)	2 (3.75) (0.5 – 12)	----	----
Clinical	JIA subtypes:	N. (%)		-----	----
	Polyarticular		13 (26%)		
	Oligoarticular		16 (32%)		
	– Persistent oligoarticular		12 (24%)		
	– Extended oligoarticular		4 (8%)		
	sJIA		18 (36%)		
	ERA		3 (6%)		
	Active joint count	Median (IQR) Range	3 (3) (0 – 18)	----	----
	Eye (uveitis)	N. (%)	8 (16%)	----	----
	Skin rash	N. (%)	8 (16%)	----	----
	Fever	N. (%)	13 (26%)	----	----
	Lymphadenopathy	N. (%)	6 (12%)	----	----
	Hepatomegaly and/or splenomegaly	N. (%)	6 (12%)	----	----
	Serositis (pleuritis, pericarditis or peritonitis)	N. (%)	3 (6%)	----	----
JAMAR	Assessment of PF	Mean±SD (range)	7±5.7 (0 – 25)	----	----
	HRQOL	Mean±SD (range)	8.16±5.06 (0 – 19)	----	----
	Patient overall wellbeing score	Mean±SD (range)	4.69±2.45 (0 – 9)	----	----
	Intensity of pain (VAS)	Mean±SD (range)	3.98±2.71 (0 – 10)	----	----
	Parent level of disease activity	Mean±SD (range)	4.87±2.79 (0 – 10)	----	----
Laboratory investigations	ESR (mm/1st hr)	Median (IQR) (range)	32.5 (32.25) (5 – 100)	5.5 (4) (3 – 15)	**<0.001**
	CRP (mg/L)	Median (IQR) (range)	6 (21) (0 – 64)	0 (2.75) (0 – 6)	**<0.001**
	Hemoglobin (g/dL)	Median (IQR)	11.98 (1.96)	12.8 (1.63)	**< 0.001**
	RBCs (×10^6/µL)	Median (IQR)	4.61 (0.67)	4.9 (0.47)	**0.018**
	WBCs (×10^3/µL)	Median (IQR)	8.5 (3.855)	7.31 (3.12)	**0.013**
	Platelets (×10^3/µL)	Median (IQR)	372 (175.25)	292.5 (93.5)	**<0.001**
	RDW (fL)	Median (IQR)	40.5 (7.13)	41.95 (6.63)	0.16
	PDW (fL)	Median (IQR)	11.15 (3.52)	14.15 (3.08)	**<0.001**
	MPV (fL)	Median (IQR)	10 (1.73)	10.9 (1.43)	**<0.001**
	Neutrophils (×10^3/µL)	Median (IQR)	5.29 (3.13)	4.01 (2.54)	**<0.001**
	Lymphocytes (×10^3/µL)	Median (IQR)	2.29 (2.51)	2.51 (1.07)	0.137
	Monocytes (×10^3/µL)	Median (IQR)	0.64 (0.51)	0.60 (0.33)	0.071
	NLR	Median (IQR)	2.40 (1.32)	1.60 (0.82)	**<0.001**
	LMR	Median (IQR)	3.44 (2.24)	4.44 (2.20)	**0.004**
	PLR	Median (IQR)	165.93 (76.69)	116.09 (47.26)	**< 0.001**
	RF positivity	N. (%)	7 (14%)	----	----
	ANA positivity	N. (%)	13 (26%)	----	----
Disease activity scores	JADAS-10 (oligoarticular)	Mean±SD (range)	11.91±7.52 (1 -25.5)	----	----
	JADAS-10 (polyarticular)	Mean±SD (range)	23.04±11.36 (1 -37)	----	----
	sJADAS (sJIA)	Mean±SD (range)	19.6±10.2 (1 – 36)	----	----
	JSPADA (ERA)	Mean±SD (range)	4.5±0.5 (4 -5)	----	----
MSUS	Total score of GS	Median (IQR) Range	8.5 (8.5) (0 – 24)	----	----
	Total score of PD	Median (IQR) Range	2 (4.5) (0 – 13)	----	----

JIA: juvenile idiopathic arthritis; BMI: body mass index; sJIA: systemic onset JIA; ERA: enthesitis related arthritis; JAMAR: Juvenile Arthritis Multidimensional Assessment Report; PF: physical function; HRQOL: health related quality of life; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RBCs: white blood cells; WBCs: white blood cells; RDW: red cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio; RF: rheumatoid factor; ANA: Anti-nuclear antibody; JADAS: juvenile arthritis disease activity score; sJADAS: systemic juvenile arthritis disease activity score; JSPADA: juvenile spondylarthritis disease activity index; MSUS: musculoskeletal ultrasound; GS: grey scale; PD: Power Doppler; NSAIDs: nonsteroidal anti-inflammatory drugs; SD: standard deviation; N: number; IQR: interquartile range; Bold values are significant at $p<0.05$.

The median (IQR) of ESR and CRP in JIA group revealed highly statistically significant difference between both groups (P<0.001). RDW revealed a non-significant difference between JIA patients and the controls (P=0.16). PDW, MPV and LMR were lower in JIA cases than the controls with significant difference (P<0.001, P<0.001 and P=0.004, respectively). But PLR and NLR were inversely elevated in JIA patients (P<0.001).

Correlations of hemogram parameters in JIA group with clinical, laboratory, disease activity scores and MSUS data were represented in **table 2**.

GS and PD of MSUS were correlated with the activity parameters of JIA **(table 3).** Significant positive correlations of both GS and PD were found with the JAMAR domains, JADAS–10 for oligoarticular and polyarticular JIA, ESR and CRP among the studied JIA patients (P<0.05). Additionally, significant positive correlation was found between GS and sJADAS–10 among sJIA patients (P =0.005). GS synovitis and PD signal in active JIA patients were illustrated in **Figure 1**.

The ROC curve plot was performed to predict disease activity by the hemogram parameters in JIA patients discriminating inactive and low active cases from moderate and severe active cases. The area under the curve (AUC) of RDW was 0.539 with the best cutoff point of 39.2, sensitivity 64.3% and specificity 62.5%. The AUC of PDW was 0.385 with the best cutoff point of 16.3, sensitivity 9.52% and specificity 100%. The AUC of MPV was 0.390 with the best cutoff point of 8.4, sensitivity 88.1% and specificity 25%. The AUC of NLR was 0.903 with the best cutoff point of 2.01, sensitivity 83.3% and specificity 100%. The AUC of LMR was 0.265 with best cutoff point of 1.72, sensitivity 95.2% and specificity 12.5%. The AUC of PLR was 0.676 with the best cutoff point of 130.66, sensitivity 76.2% and specificity 62.5%. NLR was considered as a good predictor for discriminating against the active JIA patients from the inactive as it had the highest AUC. While PLR could be a fair predictor for discriminating against the active JIA patients from the inactive **(figure 2)**.

Table 2: Correlations of the hemogram parameters with clinical, laboratory, disease activity scores and ultrasound

Variable	RDW		PDW		MPV		NLR		LMR		PLR	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
ESR	0.171	0.236	-0.444	**0.001**	-0.509	**<0.001**	0.775	**<0.001**	-0.416	**0.003**	0.547	**<0.001**
CRP	0.151	0.295	-0.396	**0.004**	-0.500	**<0.001**	0.704	**<0.001**	-0.366	**0.009**	0.439	**0.001**
JADAS–10 (oligo.)	-0.250	0.409	-0.499	0.083	-0.422	0.151	0.575	**0.040**	-0.396	0.180	0.385	0.194
JADAS–10 (poly.)	0.426	0.100	-0.109	0.687	-0.614	**0.011**	0.722	**0.002**	-0.027	0.920	0.755	**<0.001**
sJADAS	-0.038	0.881	-0.734	**<0.001**	-0.526	**0.025**	0.683	**0.002**	-0.441	0.067	0.199	0.427
JSPADA	-0.849	0.354	-0.374	0.756	0.915	0.265	-0.540	0.637	1.000	**0.009**	-0.500	1.000
PF	0.111	0.441	-0.185	0.197	-0.336	**0.017**	0.301	**0.034**	-0.001	0.996	0.339	**0.016**
HRQOL	0.164	0.254	-0.212	0.139	-0.215	0.135	0.315	**0.026**	-0.158	0.273	0.330	**0.019**
Wellbeing	0.033	0.818	-0.294	**0.038**	-0.463	**<0.001**	0.575	**<0.001**	-0.282	**0.048**	0.446	**0.001**
Pain VAS	0.187	0.193	-0.226	0.114	-0.454	**<0.001**	0.480	**<0.001**	-0.236	0.099	0.356	**0.011**
Parent level of disease activity	0.117	0.416	-0.277	0.051	-0.457	**<0.001**	0.546	**<0.001**	-0.233	0.103	0.395	**0.005**
GS	0.176	0.221	-0.152	0.292	-0.280	**0.049**	0.489	**<0.001**	-0.200	0.164	0.430	**0.002**
PD	0.066	0.647	-0.167	0.247	-0.290	**0.041**	0.283	**0.047**	-0.113	0.435	0.293	**0.039**

RDW: red cell distribution width; PDW: platelet distribution width; MPV: mean platelet volume; NLR: neutrophil-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; JADAS: juvenile arthritis disease activity score; sJADAS: systemic juvenile arthritis disease activity score; JSPADA: juvenile spondylarthritis disease activity index; PF: physical function; HRQOL: health related quality of life; VAS: visual analogue scale; GS: grey scale, PD: Power Doppler; r: Spearman's correlation coefficient; Bold values are significant at p<0.05.

Table 3: Correlations between ultrasound scores and different parameters among JIA patients

Variables	GS		PD	
	r*	P-value	r*	P-value
JAMAR				
PF	0.728	**<0.001**	0.620	**<0.001**
HRQOL	0.541	**<0.001**	0.485	**<0.001**
Wellbeing	0.700	**<0.001**	0.591	**<0.001**
Pain (VAS)	0.693	**<0.001**	0.603	**<0.001**
Parent level of disease activity	0.978	**<0.001**	0.571	**<0.001**
Disease activity score				
JADAS–10 (Oligoarticular)	0.899	**<0.001**	0.752	**<0.001**
JADAS–10 (Polyarticular)	0.844	**<0.001**	0.815	**<0.001**
sJADAS	0.634	**0.005**	0.302	0.223
JSpADA	-0.741	0.469	-0.866	0.333
ESR	0.529	**<0.001**	0.482	**<0.001**
CRP	0.438	**0.001**	0.430	**<0.001**

GS: grey scale; PD: Power Doppler; JAMAR: Juvenile Arthritis Multidimensional Assessment Report; PF: physical function; HRQOL: health related quality of life; VAS: visual analogue scale; JADAS: juvenile arthritis disease activity score; sJADAS: systemic juvenile arthritis disease activity score; JSPADA: juvenile spondylarthritis disease activity index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ***** Spearman's correlation coefficient; significant <0.05.

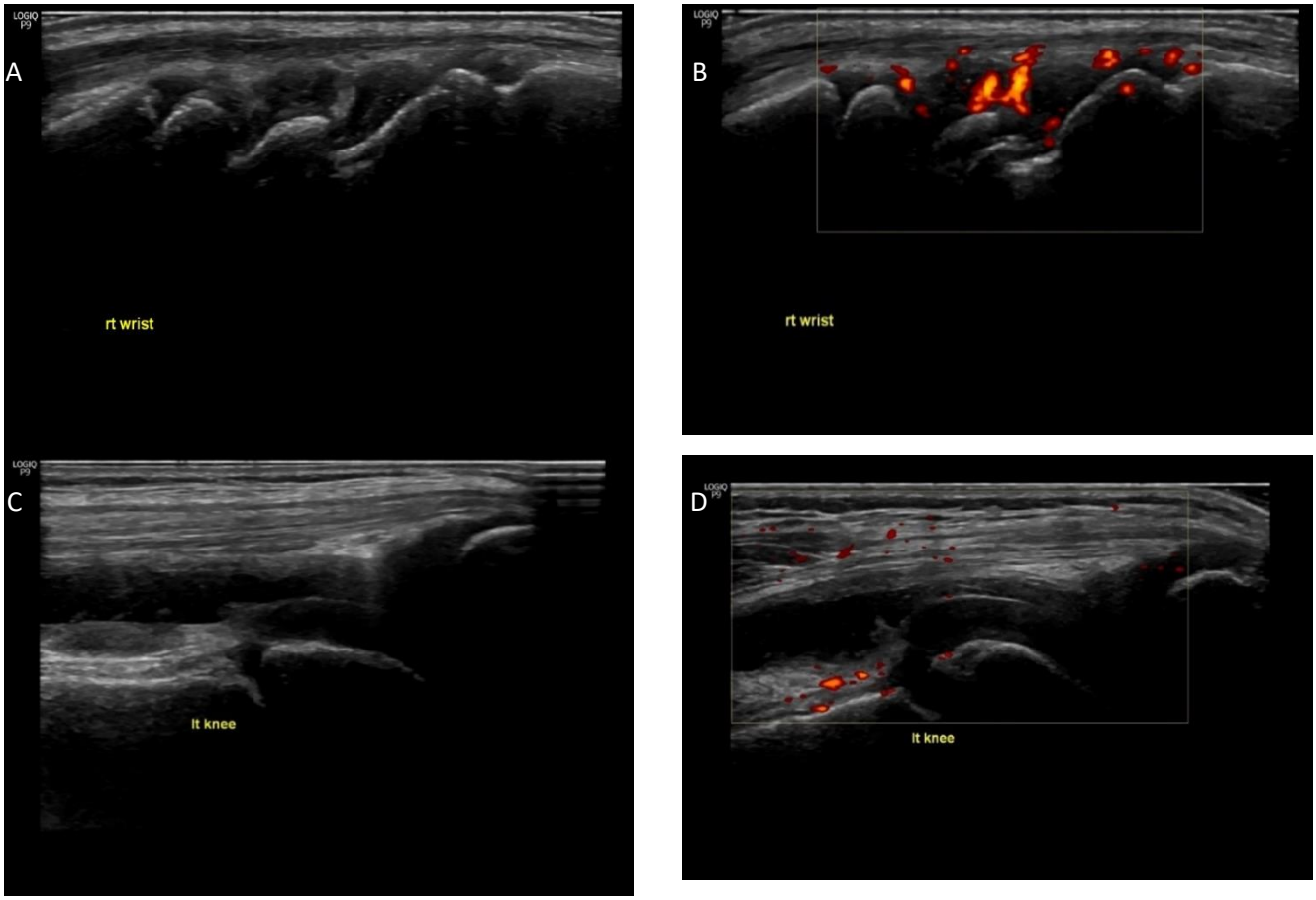

Figure 1: musculoskeletal ultrasound of wrist and knee joints of JIA patients
(A) grey scale and (B) Power Doppler of wrist synovitis in polyarticular JIA child. (C) grey scale and (D) Power Doppler of knee synovitis in oligoarticular JIA child.

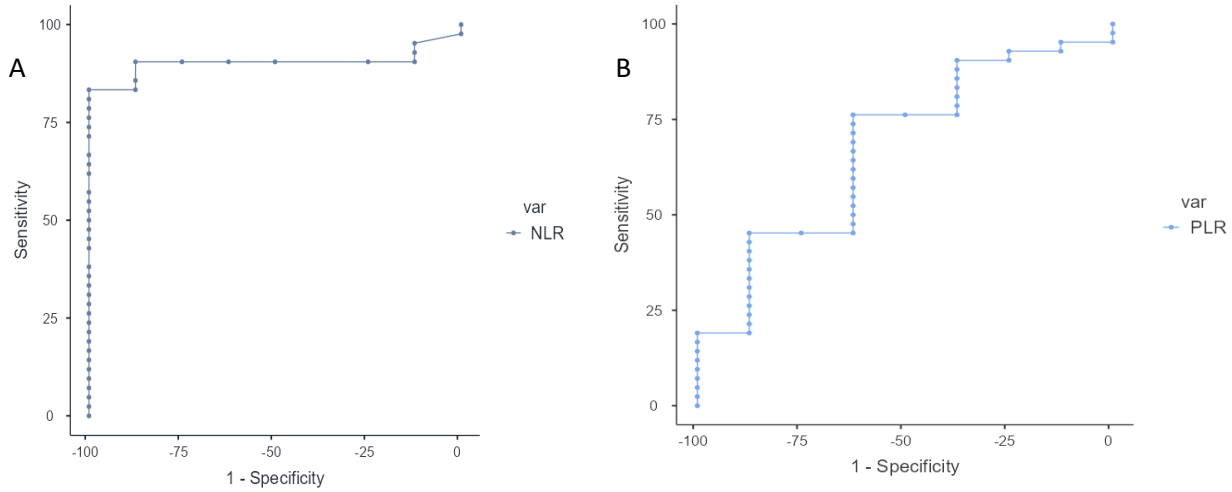

Figure 2: ROC curve of NLR and PLR for predicting disease activity in JIA patients (A) NLR and (B) PLR for predicting disease activity in JIA patients.

Discussion:

JIA is the most frequent arthritic disorder in childhood. It may cause decreasing quality of life and long-lasting joint impairment [17]. With the myriad medications available for JIA treatment, the recent scope for treat-to-target strategy encompassed repeated evaluation of the disease activity, adjustment of medications to attain the aim of quiescent illness, and combined decision making from both physician and patient for enhancing the disease outcomes [18]. So, there is utmost need for sensitive markers for evaluating the disease status because the frequently used acute phase reactants do not reveal precisely the disease activity in most JIA patients [19]. Variations in the count, shape and size of blood cells occur as a result from the inflammatory changes in the autoimmune diseases. Hence, occult inflammation and activity could be implied through the CBC-derived parameters [20]. In this study, the different hemogram parameters in JIA cases were evaluated and correlated to the parameters of disease activity and ultrasound findings. Interestingly, we are the first to evaluate the JIA disease activity by different disease activity scores according to the JIA subtype and to correlate the hemogram parameters with MSUS.

As regards JIA subtypes in this study, sJIA subtype was the most common followed by oligoarthritis and polyarthritis then ERA. This is contrary to other studies in which oligoarticular JIA was the most frequent category followed by polyarticular then sJIA[8,21-23]. BMI was significantly lower among JIA patients than controls agreeing with previous studies [24,25]. Reduced BMI may be due to cytokines over secretion, high chronic systemic inflammation, malnutrition, malabsorption, loss of lean mass due to physical inactivity and increased energy expenditure especially in sJIA [25].

NLR is recently considered an inflammatory marker because with systemic inflammation, neutrophils increase and lymphocytes decrease [8]. This study revealed higher NLR in JIA cases than the controls with significant positive correlations with the disease activity parameters and MSUS. NLR had the highest AUC (0.903) for prediction of JIA disease activity. So, NLR could be utilized as good tool for discriminating the active JIA patients from the inactive.

In agreement with this study, some authors found that NLR was elevated in JIA patients relative to others [4,8,26,27]. A study performed in 2024 reported a significant positive correlation regarding NLR with the JIA activity parameters and NLR

presented acceptable discrimination ability for the disease activity (AUC=0.761) [4]. Another study demonstrated significant positive correlation of NLR with CRP and NLR presented fair discrimination ability for the disease activity (AUC=0.668)[26]. Contrary to these results, other authors didn't report a variation concerning NLR between the active JIA, inactive JIA patients and controls or significant correlation of NLR with JADAS-27 in JIA cases [28].

PLR is an inflammatory marker in autoimmune diseases, as there are increased platelets and decreased lymphocytes with chronic inflammation [29]. Higher PLR was found in the studied JIA cases than the controls with significant positive correlations with JADAS–10 for oligoarticular JIA, the JAMAR domains, ESR, CRP and MSUS. PLR had AUC =0.676 for prediction of JIA disease activity. So, it could be a fair predictor to discriminate the active JIA patients from the inactive. Few studies were present evaluating PLR in JIA patients. Contrary to these results, another study found no difference in PLR between the active JIA cases, inactive JIA cases and the controls without significant correlation of PLR with JADAS-27[28]. This might be because they performed the study on non-systemic JIA patients and most of the patients in our study were of sJIA subtype and thrombocytosis is a common feature in sJIA. In comparison with the adult studies, the authors reported significantly higher PLR in RA, SLE and AS cases than the controls and PLR was positively correlated with the activity parameters in SLE patients [6].

LMR is considered as a marker of inflammation in the same way as leukocytosis and thrombocytosis. As inflammation usually causes increased monocytes and decreased lymphocytes, LMR is decreased in the autoimmune disorders [6]. In this study, LMR was lower in JIA cases than the controls with significant negative correlations with JSPADA for ERA, wellbeing domain of JAMAR questionnaire, ESR and CRP, and no significant correlation with ultrasound findings. However, other authors did not report significant variance of LMR between JIA cases and the controls or value in distinguishing the JIA cases from additional causes of arthritis [27]. In comparison with adult studies, previous study found significantly lower LMR in RA, AS and SLE cases than controls with no significant correlations with the disease activity parameters [6].

MPV is defined as the average platelet volume reflecting the platelet activation and function. It reflects global thrombocyte content and enzymatic activity [8]. In this study, MPV was lower in JIA cases than the controls. There were significant negative correlations with JADAS–10 for oligoarticular JIA, sJADAS–10 score for sJIA, the JAMAR domains, ESR, CRP and MSUS. Likewise, authors of previous studies demonstrated that MPV was lower in the active JIA cases than controls and negatively correlated with JADAS [7,27]. While other authors identified that the JIA patients exhibited significantly higher MPV relative to the controls, and there were positive correlations of MPV with ESR and CRP [8,30].

PDW is related to the platelet activation, and the cytokines (like thrombopoietin and interleukin 6) released as a result of inflammation causes change in PDW [31]. This present study showed lower PDW in JIA cases than the controls and significant negative correlations concerning PDW with sJADAS–10 score for sJIA, wellbeing domain of JAMAR questionnaire, ESR and CRP. While there was no significant correlation with ultrasound findings. This agreed previous studies that found significantly lower PDW in JIA group than non-JIA group. However, its usefulness is limited in differentiating JIA patients [7,27,31]. On the contrary, other authors didn't find

significant difference in PDW between the JIA group and the controls or between the active patients and the inactive [8].

Lately, RDW is considered helpful diagnostic and prognostic predictor for several non-hematological disorders including cardiovascular disorders, hepatic diseases and cancer. Some studies have shown that RDW is increased in various rheumatic illnesses as RA, SLE and Sjögren's syndrome; however, some have demonstrated conflicting conclusion [29]. In this study, RDW revealed a non-significant variance between JIA patients and the controls or among different JIA subtypes without significant correlations with the disease activity scores, JAMAR questionnaire, laboratory parameters or ultrasound findings. Consistent with these results, authors found a non-significant variance regarding RDW between JIA patients and reactive arthritis patients [26]. Compared with adult studies, other authors found significantly higher RDW in RA and SLE cases than the controls with strong correlations with the activity parameters [6].

MSUS is an important and valuable modality to evaluate disease activity in JIA cases[10]. In this present study, significant positive correlations of both GS and PD were found with JAMAR domains, disease activity scores and inflammatory markers among the JIA patients. This in agreement with other studies that found significant correlations of the MSUS score with parent global assessment of child well-being, the disease activity indices, childhood health assessment questionnaire, the pain assessment, ESR and CRP [32-34].

This study has many strength points. We evaluated the hemogram parameters that are simple, routinely obtained from CBC and easily calculated. Additionally, MSUS is latterly utilized in pediatric patients in assessment of the JIA disease activity as well as we were the first authors to correlate MSUS findings with the hemogram parameters. This study has some limitations. Our patients were enrolled from one center with a small sample size. Follow up of the active patients was problematic to evaluate the changes of the hemogram parameters after controlling the disease activity. Another limitation is the availability of a few studies discussing the hemogram parameters and MSUS in JIA to compare them with ours. There are also few validated ultrasound scores to be utilized to assess the JIA disease activity.

Conclusion:

NLR, PLR, LMR, PDW and MPV are valuable screening tools for clinical JIA disease activity. MPV, NLR and PLR are good predictors of ultrasound disease activity. Further research is warranted to validate these findings and explore their potential clinical applications in larger cohorts and longitudinal settings.

List of abbreviations:

JIA: Juvenile idiopathic arthritis
RDW: red cell distribution width
PDW: platelet distribution width
MPV: mean platelet volume
NLR: neutrophil-lymphocyte ratio
LMR: lymphocyte-monocyte ratio
PLR: platelet-lymphocyte ratio
ESR: erythrocyte sedimentation rate
CRP: C-reactive protein
ILAR: International League of Associations for Rheumatology
RF: rheumatoid factor
sJIA: systemic onset JIA
ERA: enthesitis-related arthritis
CBC: complete blood count
SLE: systemic lupus erythematosus
RA: rheumatoid arthritis
AS: ankylosing spondylitis
MSUS: musculoskeletal ultrasound
JAMAR: juvenile arthritis multidimensional assessment report
JADAS: juvenile arthritis disease activity score
JSPADA: juvenile spondyloarthritis disease activity index
sJADAS: systemic juvenile arthritis disease activity score
ANA: anti-nuclear antibody
GS: greyscale
PD: Power Doppler

OMERACT: Outcome Measures for Arthritis Clinical Trials
SD: standard deviation
IQR: interquartile range
ROC: Receiver operating characteristics
AUC: Area under the curve
DMARDs: disease modifying anti-rheumatic drugs
BMI: body mass index

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