Scientific Research Publishing

Open Journal of Rheumatology and Autoimmune Diseases, 2023, 13, 41-49
https://www.scirp.org/journal/ojra
ISSN Online: 2164-005X
ISSN Print: 2163-9914

Neutrophil Count, Platelet Indices, CRP and Their Association with Disease Activity of Juvenile Idiopathic Arthritis (JIA): A Study from Bangladesh

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How to cite this paper: Sonia, S.P., Ferdous, E., Islam, M.I. and Rahman, S.A. (2023) Neutrophil Count, Platelet Indices, CRP and Their Association with Disease Activity of Juvenile Idiopathic Arthritis (JIA): A Study from Bangladesh. *Open Journal of Rheumatology and Autoimmune Diseases*, **13**, 41-49.
https://doi.org/10.4236/ojra.2023.131004

Received: January 12, 2023
Accepted: February 25, 2023
Published: February 28, 2023

Abstract

Background: Chronic inflammation of the joints in JIA patients is associated with raised levels of serum inflammatory biomarkers, which vary according to disease activity. Neutrophil count, platelet count, mean platelet volume (MPV), platelet distribution width (PDW), ESR and CRP are the essential markers to evaluate the disease activity status of JIA patients. **Objectives:** To assess neutrophil count, platelet count, MPV, PDW, CRP and Juvenile Arthritis Disease Activity Score (JADAS) in JIA patients and determine their association at the initial visit and six months after treatment. **Methods**: This prospective observational study was conducted from March 2019 to December 2020 in the department of paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Fifty newly diagnosed JIA cases fulfilling the ILAR classification criteria were included in the study. Disease activity was assessed by JADAS 27. JADAS 27 and inflammatory biomarkers were measured at the initial visit and six months of treatment and these were compared. **Results:** Mean neutrophil count, platelet count, and CRP significantly decreased at follow-up after six months of treatment. MPV and PDW were increased after six months compared to the initial visit, and the change was significant. Mean JADAS 27 also decreased significantly at follow-up. Neutrophil count, Platelet indices and CRP had a significant association with JADAS 27. **Conclusion:** In this study, neutrophil count, platelet indices, and CRP after six months of treatment were improved. A significant association of JADAS 27 was found with platelet indices, neutrophil count and CRP.

Keywords

Arthritis, Chronic Inflammation, Inflammatory Biomarkers

1. Introduction

Juvenile idiopathic arthritis (JIA) is a common rheumatic illness characterized by chronic inflammation of one or more joints in children and adolescents, resulting in short and long-term morbidity and disability [1].

JIA is a complex inflammatory disease with a multi-factorial pathogenesis [2]. Both immunogenetic susceptibility and external triggers play a role in the pathogenesis of the disease. T lymphocyte has a central role in releasing pro-inflammatory cytokines like TNF-*α*, IL-6 and IL-1 which induces inflammation in JIA. Inflammation results in an elevated white blood cell (WBC) count, a common haematological abnormality in JIA patients. Haar *et al.* in a study in the Netherlands found neutrophilic leukocytosis in systemic JIA patients which decreased dramatically at follow-up after treatment [3].

Platelet is an important blood cell, also considered as inflammatory cells as they release chemokines and cytokines. One of the effects of cytokines (thrombopoietin and IL-6) produced in response to inflammation results in megakaryocyte stimulation and thus increases the number of platelets (thrombocytosis), changes the size (mean platelet volume) and platelet distribution width (PDW) [4]. Vakili *et al.* in an Iranian study showed that platelet count is one of the most remarkable inflammatory markers of JIA and Gunes *et al.* in a Turkish study suggested that MPV might be a useful marker for disease activity in JIA patients [5] [6].

Besides these haematological biomarkers, changes in two common acute phase reactants—Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are also associated with the disease activity in JIA patients [7].

The Juvenile Arthritis Disease Activity Score (JADAS) is the most widely accepted scoring system for JIA patients to evaluate disease activity. There are several types of JADAS depending upon the joint count e.g. JADAS 10, JADAS 27 and JADAS 71. In this study, JADAS 27 was used which includes 0 - 27 joints [8].

It is essential to monitor the disease activity periodically in JIA patients because persistently active disease plays a significant role in causing joint damage and physical disability. This study aimed to assess the neutrophil count, platelet count, Mean platelet volume (MPV), Platelet distribution width (PDW), CRP and JADAS 27 in JIA patients and to find out the association between the inflammatory biomarkers with disease activity at the initial visit and at six months of follow up after treatment.

2. Methodology

This prospective observational study was carried out in the paediatric rheumatology clinic and paediatric rheumatology division of the department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2019 to December 2020. Fifty newly diagnosed cases of different subtypes of JIA patients fulfilling International League of Association of Rheumatology (ILAR) criteria were included in this study. Children who received steroid or DMARDs

(Disease Modifying Anti-Rheumatic Drugs) before the enrollment of the study and had any chronic illness including gastrointestinal disease, chronic renal failure, chronic liver disease and haematological disorders associated with JIA were not included in this study. A semi-structured questionnaire was formulated and pre-testing was done to validate the questionnaire. This questionnaire was filled up by the investigator including history, clinical examination, JADAS score and relevant investigations. Disease activity status was assessed by JADAS 27 at initial visit (N_1) and at follow-up after 6 months of treatment (N_2).

JADAS 27 was calculated by the sum of four components [8]:

1) Physician's global assessment of disease activity by visual analogue scale (VAS)

2) Parents/patients global assessment of well-being by VAS

3) Joint counts with active disease and

4) ESR.

Disease activity status was categorized as no disease activity, low disease activity, moderate disease activity and high disease activity according to the score [9]. After taking informed written consent blood samples were collected for complete blood count and CRP. This study was conducted with prior approval of the Institutional Review Board (IRB) of BSMMU, Dhaka, Bangladesh (BSMMU/2019/1431, Date-12.02.2019).

Data were checked, verified and analyzed by SPSS (statistical program for social science) software 22. Paired t-test was done to see the changes of inflammatory biomarkers among N_1 and N_2 groups. Pearson's coefficient was used to see the association between two quantitative variables. P-value less than 0.05 was considered as significant.

3. Results

Mean age of children was 9.3 ± 3.56 years and 58% of our study cases were male. Majority (52%) of the cases presented within 6 months of disease onset and in 28% cases disease duration at diagnosis was more than 1 year (**Table 1**). Enthesitis related arthritis was the commonest type (32%) followed by systemic JIA (30%) and RF negative polyarticular JIA (**Table 2**).

Mean neutrophil count, platelet count and CRP were higher in group N_1 and decreased significantly in group N_2. Mean MPV and PDW were lower in group N_1 and increased in N_2. Changes of PDW were significant but significant change of MPV was found only among SJIA patients. Mean JADAS 27 improved significantly at follow up (**Table 3**).

Most of the patient (98%) had high disease activity at enrollment (N_1), but 40% patients had inactive disease status at follow up (N_2), followed by low, high and moderate disease activity in 28%, 24% and 8% patients respectively (**Table 4**).

There was positive correlation between the changes of neutrophil count, platelet count and CRP with the change of JADAS 27 in both the groups and

Table 1. Demographic characteristics of study cases (n = 50).

Age of the patients (in years)	Number (%)
<5 years	6 (12%)
5 - 10 years	23 (46%)
>10 years	21 (42%)
Mean (years) ± SD	9.3 ± 3.56
Sex	
Male	29 (58%)
Female	21 (42%)
Duration of illness (in months)	
6 weeks to 6 months	26 (52%)
>6 months to 12 months	10 (20%)
More than 12 months	14 (28%)
Mean (months) ± SD	12.71 ± 14.97

Table 2. Different types of JIA among the study cases (n = 50).

JIA types	n (%)
Oligo arthritis	5 (10)
Polyarthritis (RF positive)	2 (4)
Polyarthritis (RF negative)	12 (24)
Systemic JIA (sJIA)	15 (30)
ERA	16 (32)

Data presented in number (n) and frequencies.

Table 3. Changes of Neutrophil count, platelet indices, CRP and JADAS 27 at initial visit and at follow up visit.

Parameters	Visits	Oligo arthritis (n = 5)	Poly arthritis (RF +ve) (n = 2)	Poly arthritis (RF −ve) (n = 12)	SJIA (n = 15)	ERA (n = 16)	TOTAL Patients (N = 50)
Neutrophil Count (per cubic mm)	N_1	4900 ± 1446.10	5490 ± 1272.79	6850.75 ± 2715.20	11580 ± 6960.07	7025.12 ± 2544.47	8093.82 ± 4835.64
	N_2	7086 ± 4244.82	8395 ± 1138.44	6423.25 ± 2473.75	7541 ± 4059.21	5462.93 ± 2292.20	6596.48 ± 3218.71
	p-value	**0.309**	**0.386**	**0.683**	**0.036**	**0.014**	**0.033**
Platelet count (per cubic mm)	N_1	274000 ± 45055	400000 ± 28284	462500 ± 125923	593333 ± 200487	454187 ± 146535	477740 ± 174957
	N_2	296200 ± 56010	400000 ± 70710	423333 ± 87835	439333 ± 212752	391000 ± 88211	404140 ± 138275
	p-value	**0.547**	**1.00**	**0.258**	**0.035**	**0.013**	**0.003**

Continued

Mean Platelet volume (MPV) fL	N_1	10.92 ± 0.82	9.65 ± 0.21	9.46 ± 0.81	8.97 ± 0.79	9.67 ± 1.1	9.53 ± 1.03
	N_2	10.48 ± 1.67	10.15 ± 0.35	9.72 ± 1.10	9.94 ± 0.94	9.93 ± 1.60	9.94 ± 1.26
	p-value	**0.577**	**0.430**	**0.532**	**0.011**	**0.612**	**0.073**
Platelet distribution width (PDW)fL	N_1	12.96 ± 1.99	10.70 ± 0.42	10.22 ± 1.32	9.27 ± 0.77	12.46 ± 7.16	10.95 ± 4.33
	N_2	15.20 ± 8.01	11.05 ± 1.62	18.29 ± 12.90	11.24 ± 2.18	16.49 ± 11.23	15 ± 9.54
	p-value	**0.572**	**0.751**	**0.049**	**0.004**	**0.278**	**0.009**
CRP (mg/L)	N_1	1.06 ± 0.75	47.13 ± 40.54	50.09 ± 58.13	109.16 ± 91.82	42 ± 71.78	60.20' ± 77.52
	N_2	0.67 ± 0.39	31.85 ± 9.39	18.08 ± 27.63	25.64 ± 46.57	8.92 ± 13.35	16.22 ± 30.45
	p-value	**0.114**	**0.740**	**0.024**	**0.001**	**0.083**	**<0.0001**
JADAS 27	N_1	19.80 ± 3.11	28.55 ± 1.48	30.14 ± 5.02	32.17 ± 5.68	23.78 ± 9.33	27.61 ± 7.83
	N_2	0.82 ± 1.30	20.25 ± 6.85	6.86 ± 5.98	4.96 ± 7.01	2.71 ± 4.56	4.89 ± 6.58
	p-value	**<0.0001**	**0.393**	**<0.0001**	**<0.0001**	**0.001**	**<0.0001**

Data are presented as mean ± SD. p value reached from paired t-test.

Table 4. Disease activity status of the cases according to JADAS 27 Score at initial visit and at follow up (n = 50).

Parameters	Visits	Inactive disease n (%)	Low disease activity n (%)	Moderate disease activity n (%)	High disease activity n (%)
Total Patients (N = 50)	N_1	0 (0%)	0 (0%)	1 (2%)	49 (98%)
	N_2	20 (40%)	14 (28%)	4 (8%)	12 (24%)

Data presented in number (n) and frequencies (%).

p value was significant except platelet count in N_2 group. Both MPV and PDW had negative correlation with JADAS 27. But only the association of MPV in N_1 group was significant. (Table 5)

Table 5. Association of JADAS 27 with Neutrophil count, Platelet indices (Platelet count, MPV, PDW) and CRP at Initial Visit and Follow up (N_1 and N_2).

Parameters	Visits	JADAS 27	
		r value	p value
Neutrophil Count (per cubic mm)	N_1	0.426	0.002
	N_2	0.372	0.008
Platelet count (per cubic mm)	N_1	0.611	0.0001
	N_2	0.067	0.643
Mean Platelet volume (MPV) (fL)	N_1	−0.538	0.0001
	N_2	−0.087	0.547
Platelet distribution width (PDW) (fL)	N_1	−0.195	0.174
	N_2	−0.184	0.202
CRP (mg/L)	N_1	0.361	0.010
	N_2	0.508	0.0001

r value and p value are reached by Pearson's correlation test.

4. Discussion

Persistent disease activity in JIA patients may cause severe morbidity including articular damage and joints' deformity [10]. Therefore, monitoring the disease activity of the JIA patients is very important. Mean age of JIA patients in our study was 9.3 years which was similar to another Bangladeshi study done by Rumana *et al.* where the mean age was 9.36 years [11]. A Turkish study done by Sen *et al.* also found similar result which found mean age of their cases was 10.92 years [12]. Females are generally more affected than males in JIA, but our study showed male predominance (M: F-1.3:1) which is similar to other Bangladeshi studies done in the same centre [13] [14]. This could be due to our socio-cultural background, where male children are given more attention and brought to the hospitals more frequently than female children. Another reason for male predominance could be because ERA was the commonest type of JIA in this series.

Among the sub-types of JIA patients, ERA was the predominant subtype found in 37% and 36% of Taiwanese and Indian children respectively in their studies [15] [16]. The present study also found similar findings. The increased frequency of ERA might be due to ethnicity, geographical variation and male preference in these regions.

In the present study, the majority (52%) of the JIA patients presented with a duration of 6 weeks to 6 months of illness and mean duration of illness was 12.71 months. In a previous Bangladeshi study done by Rahman *et al.*, the majority (48.6%) of JIA patients' disease duration at presentation was more than 12 months [13]. The duration of illness at presentation was lower in this study, which might be due to increased awareness of the physicians and early referral to the tertiary center.

In this study, higher mean neutrophil count and platelet count was found at the initial visit (N_1) which subsequently decreased at follow up (N_2). Highest number of neutrophil was present in systemic JIA, possibly due to the release of inflammatory cytokines [17]. Similar findings also shown by Haar *et al.* where neutrophilic leukocytosis was found in JIA patients, which decreased at follow up [3]. Similar to the present study, Vakili *et al.* and Gunes *et al.* also found raised mean platelet count in the active disease state of JIA patients [5] [6].

Platelet Distribution Width (PDW) is a measurement of the variability in platelet size distribution in the blood, whereas MPV is the average volume of the platelets. Vakili *et al.* showed that MPV and PDW have an inverse relationship with the disease activity of JIA patients which were in accordance with the present study [5]. In this study, mean MPV and PDW were lower at the active disease state (N_1) and increased at follow up (N_2). Only the change of PDW was statistically significant.

Mean ESR and CRP in this study were raised in all JIA patients at the initial visit and subsequently decreased significantly at follow-up after 06 months. These results explain the strong association of CRP and ESR with JIA disease activity. These results are consistent with the study of Sen *et al.* and Wu et al, where the active state of JIA patients had higher ESR and CRP [12] [18].

Mean JADAS 27 in this study was higher at the initial visit and decreased significantly at follow-up after treatment. This finding was similar to Vidovic *et al.*, where the mean value of JADAS was decreased at follow up from that of initial visit [19]. This study showed that most of the patients (98%) had severe disease activity at the initial visit due to severe manifestations with increased number of joint involvements. At follow-up, after 06 months of treatment 40% of patients were in inactive disease status.

The present study observed a significant association between neutrophil count, platelet count, ESR and CRP with JADAS 27, both at initial visit (N_1) and at follow-up (N_2). Feng *et al.* and Wulandari *et al.* also found significant association between JADAS, ESR and CRP which were similar to the present study [20] [21]. But there was no published data available regarding the association between JADAS with neutrophil count and platelet indices. So, no comparison was possible with our study findings.

5. Conclusion

Neutrophil count, platelet count and CRP had a significant association with JADAS 27 in JIA patients. MPV and PDW had a negative correlation with JADAS. From this study, it may be concluded that neutrophil count, platelet indices and CRP were useful biomarkers to assess the disease activity status of JIA patients.

Acknowledgements

We express our heartfelt thanks and gratitude to all the pediatricians and resi-

dents of department of pediatrics, Bangabadhu Sheikh Mujib Medical University (bsmmu), all the children with JIA and their parents, all the doctors, technicians and staffs of Laboratory services department of Bangabandhu Sheikh Mujib Medical University.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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