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Hematological parameters in pediatric atopic dermatitis: correlation with disease severity and duration

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Background: Atopic dermatitis (AD) is a prevalent, chronic, inflammatory skin disorder that primarily affects children, with just a few cases persisting into adulthood. Many theories exist to ascertain the relationship between atopic dermatitis and systemic inflammation. Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and Mean platelet volume (MPV) are biomarkers of systemic inflammation, which in turn are related to atopic dermatitis. The present study aimed to assess the association between atopic dermatitis and NLR, PLR, and MPV values by calculating NLR, PLR, and MPV ratio and correlating their levels with the disease duration and severity of AD in pediatric atopic dermatitis.

Methods: This cross-sectional study included 165 pediatric atopic dermatitis patients who met the clinical confirmation criteria of the U.K. working party. The patients with co-existing conditions such as molluscum contagiosum, impetigo, hand-foot-and-mouth disease, and eczema herpeticum were excluded. The mean ± SD values of NLR, PLR, and MPV were compared after the severity groups were classified using SCOR Atopic Dermatitis (SCORAD). The association of SCORAD and disease duration with NLR, PLR, and MPV levels was evaluated.

Results: Significant differences were noted between severity groups based on NLR, PLR, and MPV values. PLR and NLR had a positive correlation with the SCORAD score, whereas MPV was negatively correlated. In addition, NLR had a positive correlation with disease duration. PLR exhibited a higher diagnostic accuracy in predicting high SCORAD with a 100% sensitivity and specificity cut-off value of > 172.

Conclusion: NLR, PLR, and MPV were cost-effective, feasible, and widely available tests to detect systemic inflammation in AD with high sensitivity and specificity.

Keywords: dermatitis, atopic, platelet lymphocyte ratio, neutrophil lymphocyte ratio, mean platelet volume

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INTRODUCTION

Atopic dermatitis (AD) is a prevalent, chronic, inflammatory skin disorder that primarily affects children, with few AD cases advancing into adulthood [1]. It is characterized by severe itching, dryness, and eczematous areas with crusting that appear in an

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age-dependent pattern, involving the scalp, face, and extensor extremities in infants group and intertriginous areas more frequently in older age groups [2,3]. Most affected individuals have a family or personal history of "atopic diathesis." The term "atopic diathesis" simply refers to the presence of a disorder, such as allergic rhinitis, bronchial asthma, or atopic dermatitis [4].

There are no gold standard diagnostic criteria or diagnostic laboratory markers [5]. The original Hanifin and Rajka criteria were modified in 1994 to establish the United Kingdom Working Party criteria (UKC), which were intended to be simpler and more appropriate for population-based research [6,7]. They serve as the only diagnostic criteria that have undergone extensive population-based and hospital validation trials [6,8-10].

The severity of atopic dermatitis must be assessed to evaluate the disease process and measure therapy or elimination. As a result, it must be as impartial as possible. This is critical for clinical work and research. The SCORAD Index assesses the area of involvement of the disorder, the intensity of six components, and subjective symptoms [11].

Inflammation is a biological process that the body uses to protect itself, and epithelial and endothelial cells in the tissues work in conjunction with blood-circulating cells such as neutrophils, monocytes, lymphocytes, and platelets [12]. Several studies suggested an association between AD and systemic inflammation [13-16]. The levels of serum interleukin (IL) 10, 17, and 23 were related to activation-regulated chemokine, serum thymus, and the severity of atopic dermatitis [17,18]. However, regulated testing for these agents is not possible. The platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and mean platelet volume (MPV) are all associated with disease activity in a variety of inflammatory disorders, including chronic urticaria, systemic lupus erythematosus (SLE), psoriatic arthritis, and psoriasis vulgaris [19-23].

A limited number of studies in AD found correlations between NLR, PLR, and MPV values with disease duration and severity. This could imply the presence of both systemic and local inflammation [24-27].

The present study aimed to assess the association between atopic dermatitis and NLR, PLR, and MPV values by comparing them with disease duration and severity.

METHODS

This study was approved by an institutional ethical committee at BLDE (Deemed to be University) and carried out in accordance with the Declaration of Helsinki.

Study population

This study was a hospital-based prospective cross-sectional study. In total, 165 pediatric atopic dermatitis patients, confirmed clinically using U.K. Working party criteria, attended a tertiary care hospital in North Karnataka between January 2021 to June 2022, and were included in the study. Written informed consent was obtained from the participants before recruiting to the study. Patients with co-existing conditions such as eczema herpeticum, molluscum contagiosum, impetigo, and hand, foot, and mouth disease were excluded.

Methodology

A complete initial clinical examination was performed, and clinical symptoms and signs were documented in the proforma. The time between the patient's first disease complaint and inclusion in the study and testing was referred to as disease duration. The severity was calculated using SCORAD [sum of extent (A)/5 + 7 x intensity (B)/2+C (subjective symptoms)] – A: The affected area was calculated using the rule of nine, B: The intensity of the lesions was assessed as none (0), mild (1), moderate (2), severe (3), C: Subjective symptoms such as itching, and insomnia were scored up to 20. The patient was classified as mild (less than 25 scores), moderate (25-50 score), and severe (more than 50 scores) using the SCORAD index.

Laboratory investigation

A 3 mL blood sample was collected in an EDTA tube and sent for a complete blood count. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing by absolute lymphocytes, and the Platelet-lymphocyte ratio (PLR) was derived by dividing the total number of platelets by absolute lymphocytes. The mean platelet volume (MPV) was determined from the laboratory blood report.

Statistical analysis

Following data collection, statistical analysis was

performed using JMP® Pro 16 software, version 16, from the SAS Institute, Cary, NC, 1989-2021. The results were presented as graphs, counts, percentages, and Mean (Median) ± SD. Pearson or Spearman's Correlations were utilized to determine the relationship between quantitative variables. The Chi-square test was applied to examine the relationship between categorical variables. P-values of less than 0.05 were regarded as significant. All statistical tests were two-tailed.

RESULTS

The study population consisted of 89 males (53.9%) and 76 females (46.15%), with a sex ratio of 1.17:1 (Table 1). The mean age ± SD of the AD patients was 6.21 ± 5.125 years. The majority of the patients were between 2-12 years old, accounting for 109 (66.1%) patients, followed by less than 2 years of age with 32 (19.4%) patients, and least more than 12 years of age with 24 (14.5%) patients (Table 1). Based on the SCORAD index, patients were classified as mild, moderate, and severe. Among them, 78 (47.3%) were classified as mild, 52 (31.5%) as moderate, and 35 (21.2%) as severe (Table 1). There were significant differences between these groups in the mean/standard deviation of NLR, PLR, and MPV values (Table 2). NLR and PLR values increased with severity, while MPV values decreased with severity (Figure 1). NLR and PLR were positively correlated with the SCORAD score. However, MPV was negatively correlated (Table 3 and Figure 2). NLR had a positive correlation with disease duration; however, PLR and MPV did not have any correlation with duration (Table 3 and Figure 3).

The Receiver Operating Characteristics (ROC) curve for diagnostic accuracy of severity index (SCORAD more than 50) showed that PLR had a higher AUROC (1.000 and $P < 0.001$) than NLR and MPV, with 100% sensitivity and specificity (Table 4 and Figure 4).

Table 1. Age and sex distribution along with the severity of the disease in the study population

Basic characteristics	No. of. Patients	Percentage
Sex Distribution		
Male	89	53.9%
Female	76	46.1%
Age Distribution		
Less than 2 years	32	19.4%
2-12 years	109	66.1%
More than 12 years	24	14.5%
Severity Group		
Mild	78	47.3%
Moderate	52	31.5%
Severe	35	21.2%

Table 2. Demonstrates the differences between NLR, PLR, and MPV values among severity groups classified according to SCORAD

	N	Mean	Standard deviation	*P*-value
NLR				
Mild	78	0.641154	0.2595700	
Moderate	52	2.202115	0.3732703	0.000
Severe	35	3.106000	0.4276626	
PLR				
Mild	78	63.318333	12.7334057	
Moderate	52	122.739808	19.3360721	0.000
Severe	35	217.676286	23.6393483	
MPV				
Mild	78	8.776923	0.9232809	
Moderate	52	8.436538	0.9188716	0.000
Severe	35	7.600000	0.5599370	

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume. P < 0.05 was considered statistically significant.

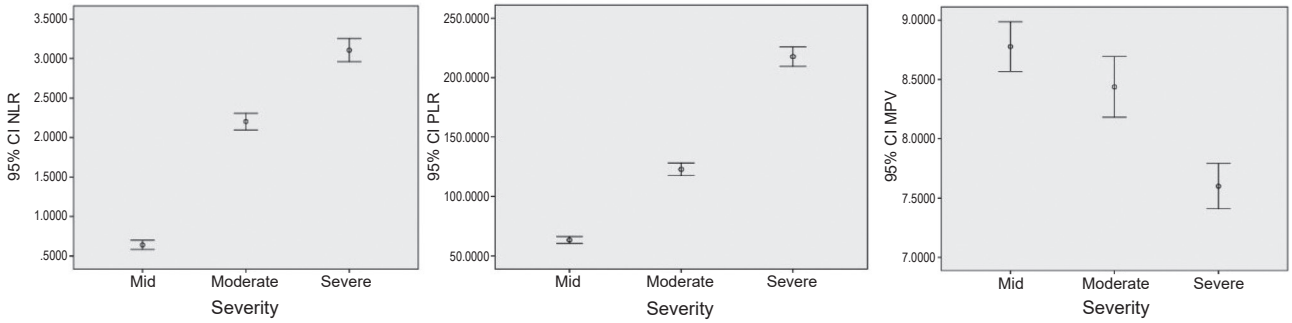

Figure 1. Relationship of NLR, PLR, and MPV values with disease severity (A)-NLR values increased with the severity of the disease, (B)-PLR values increased with the severity of the disease, (C)-MPV values decreased with the severity of the disease. NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume; $P < 0.05$ was considered statistically significant.

Table 3. Correlation of NLR, PLR, and MPV values with disease severity and duration

Parameters	Severity		Duration	
	P	r	*P*	r
NLR	< 0.001	0.868	0.033	0.166
PLR	< 0.001	0.836	0.212	0.098
MPV	< 0.001	-0.405	0.586	-0.043

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume; *P* < 0.05 was statistically significant, r: coefficient.

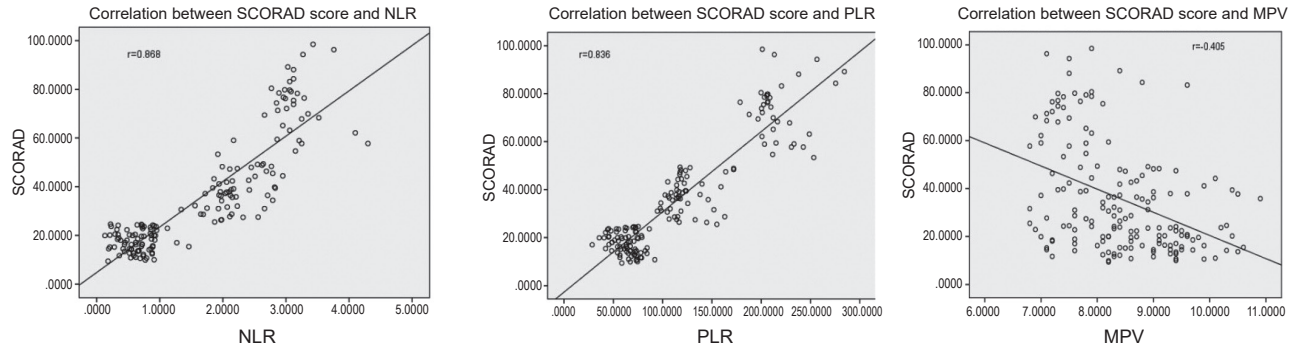

Figure 2. Scatter plot showing the Correlation of NLR, PLR, and MPV values with SCORAD score (A)-NLR has a positive correlation with SCORAD, (B)-PLR has a positive correlation with SCORAD, (C)-MPV has a negative correlation with SCORAD. NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume; SCORAD: SCORing atopic dermatitis.

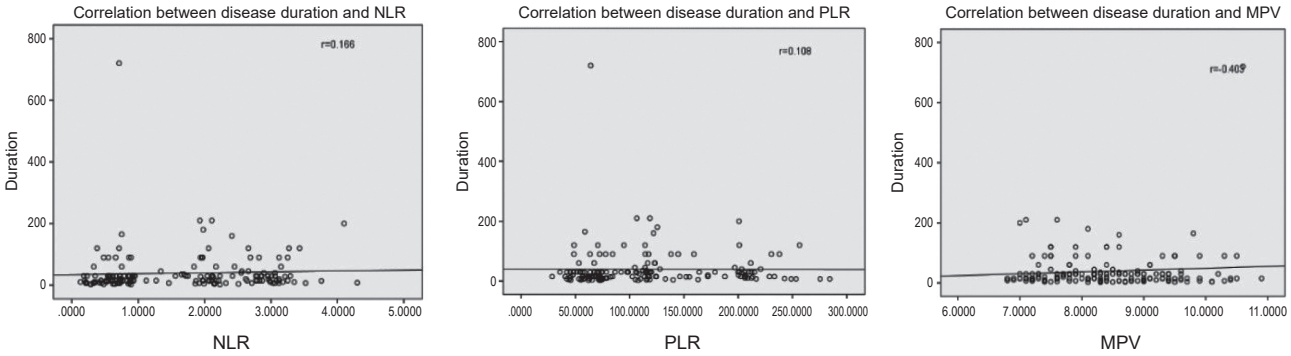

Figure 3. Scatter plot showing the Correlation of NLR, PLR, and MPV values with disease duration (A)-NLR has a positive association with disease duration, (B)-PLR has no association with disease duration, (C)-MPV has no association with disease duration. NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume.

Table 4. Diagnostic accuracy of NLR, PLR, and MPV values with SCORAD (More than 50)

Parameters	AUROC	Sensitivity	Specificity	Cut off value	95% Confidence interval
NLR	0.982	88.57	99.23	> 2.83	> 2.71 to > 2.95
PLR	1.000	100.00	100.00	> 172	> 164 to > 172
MPV	0.827	85.71	76.92	≤ 7.9	≤ 7.72 to ≤ 8.2

AUROC: Area under the receiver operating characteristics; SCORAD: Scoring atopic dermatitis; NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume.

DISCUSSION

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disorder that primarily affects children, with very few cases progressing into adulthood [1]. Recently, the pathogenesis of atopic dermatitis was related to the development of systemic and local inflammation [25]. In the present study, the levels of NLR, PLR, and MPV values were correlated with disease duration and severity and the accuracy of these inflammatory biomarkers in determining the severity.

Women had a higher prevalence of AD [28]. Recent studies indicated a male predominance at a younger age. The sex ratio in the present study was 1.17:1,

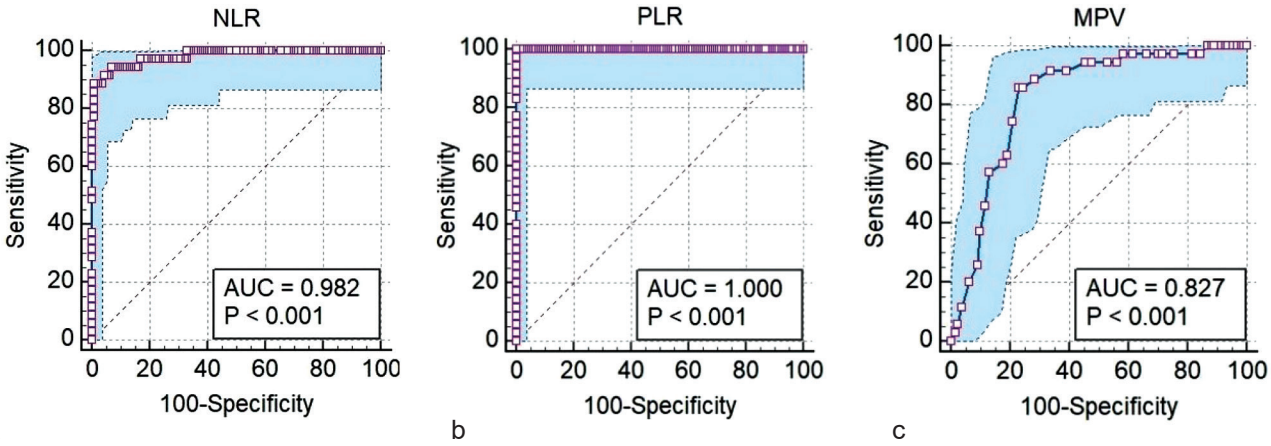

Figure 4. The receiver operating characteristic curve showing sensitivity and specificity of NLR, PLR and MPV values in terms of SCORAD more than 50 (A)- ROC curve of NLR is 0.982 with 88.57% sensitivity and 99.23% specificity, (B)- ROC curve of PLR is 1.000 with 100% sensitivity and specificity, (C)- ROC curve of MPV is 0.827 with 85.71% sensitivity and 76.92 specificity. NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MPV: Mean platelet volume; ROC: Reciever operating characteristics curve.

with a male predominance, which was in line with the findings of Jiang Y *et al.* [24] The findings of the present study indicated that the majority of the patients (66.1%) were between the ages of 2 and 12 years old, with less than 2 years old accounting for 19.4%, indicating that the majority of the patients had atopic dermatitis during their childhood stage.

The neutrophil-to-lymphocyte ratio is a systemic inflammatory marker. Increased NLR values were associated in the literature with disease presence and outcome in a wide range of nonallergic conditions. Asthmatics had a higher NLR than healthy controls [29,30]. Dogru M *et al.* hypothesized that NLR values were elevated with the severity of illness and were higher in allergic rhinitis individuals than in the control group [31]. Additionally, the occurrence of asthma or allergic rhinitis was associated with the severity of atopic dermatitis as determined by the SCORAD index [32].

Two previous studies, conducted by Batmaz *et al.* and Jiang *et al.,* found a positive correlation between NLR and disease duration and severity [24,25], which was in line with our findings. There were significant differences in mean values of NLR between severity groups. This suggested that systemic inflammation associated with AD might be related to the duration and severity of the cutaneous manifestation, as indicated by the NLR value being directly proportional to increasing duration and severity, which was also revealed with a significant statistical correlation in the present study.

Numerous studies were conducted to evaluate the role of platelets in inflammation. Platelets become activated during inflammation, and the rate of platelet synthesis increases. Platelets produce chemotaxis signals and increase the production of adhesion molecules by interacting with endothelial. They augment inflammation by increasing the release of pro-inflammatory mediators [33,34]. The platelet-to-lymphocyte ratio was found to be positively correlated with the SCORAD index but not with disease duration in our study. Jiang *et al.* reported comparable findings in their study. However, Batmaz *et al.* concluded that PLR had a positive correlation with duration. Besides, the present study indicated a statistically significant difference in PLR values between severity groups. An increase in severity leads to an increase in PLR. The platelet-to-lymphocyte ratio demonstrated 100% specificity and sensitivity in predicting severe illness, with an optimal cut-off value of > 172.

The role of MPV in inflammation indicated that cytokines reduce platelet size during inflammation, allowing smaller platelets to be discharged into the bloodstream and making decreased MPV a sign of inflammation [35]. Other studies found that more giant platelets released into the bloodstream due to increased platelet turnover caused by platelet activation serve as an indicator of inflammation [25]. The mean platelet volume had an inverse correlation with the SCORAD index but showed no association with disease duration in the present study. The mean platelet volume values differed between severity

groups, decreasing significantly as severity increased. Gunes *et al.* concluded that MPV values were lower in AD patients than the healthy controls, and there was no correlation with disease severity [27]. Gayret *et al.* found that MPV was positively correlated with disease severity and was significantly higher in the AD group than in controls [26], which contradicted the findings of the present study.

In pediatric atopic dermatitis, we aimed to correlate the levels of NLR, PLR, and MPV with the severity and duration of the disease, and we concluded that as the duration and intensity of cutaneous manifestation increased, there was a possibility of systemic inflammation accumulating in the body, paving the way for the atopic march, including bronchial asthma and allergic rhinitis. This study observed statistical differences in NLR, PLR, and MPV values between severity groups. Secondly, NLR and PLR increased with SCORAD, whereas MPV decreased, reflecting inflammation and severity of the disease. Third, NLR increased with disease duration, denoting chronic inflammation. Higher NLR value might suggest the inclusion of systemic immunosuppressants as the treatment modality in addition to topical emollients, corticosteroids, and calcineurin inhibitors. Fourth, a comparison between inflammatory markers such as NLR, PLR, and MPV showed that PLR had a better sensitivity and specificity in predicting severe disease. However, it should be noted that PLR alone, without considering other factors, might not be able to reliably predict the severity of the disease in AD-affected patients. Hence, inflammatory markers such as NLR, PLR, and MPV could be used to assess the systemic inflammation associated with atopic dermatitis.

However, this study had a few limitations, including the absence of a control group, the small number of patients in the severe group, and the absence of intrinsic and extrinsic groups.

CONCLUSION

The neutrophil-to-lymphocyte ratio, PLR, and MPV were affordable, easily accessible alternative tests to detect systemic inflammation in AD with high sensitivity and specificity in clinical settings with limited resources. Additionally, it provided insight into the inclusion of therapeutic approaches such as systemic immunosuppressants alongside conventional management techniques such as topical therapy.

Authors Contributions

All authors have been involved in the development of study design, manuscript preparation and approval.

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Conflicts of Interest: None declared.

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