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ORIGINAL RESEARCH

The Association of Inflammatory Indexes Derived from Peripheral Blood Cell Count and Clinical Signs with Response to Treatment with Dupilumab in Pediatric Patients with Moderate-to-Severe Atopic Dermatitis

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Background: Dupilumab is a safe and effective treatment for moderate to severe atopic dermatitis (AD), but real-world data in pediatric patients in China are limited. Currently, there is no exploration of changes in blood cell counts derived indexes in pediatric patients, especially under 6 years old.

Purpose: To investigate the changes in blood cell counts derived indexes before and after dupilumab treatment in Chinese children with AD, the relationship with clinical scores, and the potential role of these indexes on treatment efficacy.

Patients and Methods: We conducted a retrospective study of 109 children with moderate to severe AD treated with dupilumab. Derived inflammatory indexes, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), eosinophil-to-lymphocyte ratio (ELR), eosinophil-to-neutrophil Ratio (ENR), monocyte-to-lymphocyte ratio (MLR), inflammation response index (SIRI), systemic inflammation index (SII), and aggregate inflammation systemic index (AISI) were calculated. The correlation between clinical scores and inflammatory indexes at different treatment time points were analyzed. Logistic regression and ROC curve was employed to explore factors associated with treatment efficacy.

Results: Baseline ELR and ENR were positively correlated with the baseline Eczema Area and Severity Index (EASI) and the Scoring Atopic Dermatitis (SCORAD). Additionally, baseline ENR levels showed a positive correlation with the baseline Peak Pruritus Numeric Rating Scale (PP-NRS). At 4 and 16 weeks of treatment, the percentage reduction in ELR was significantly associated with the percentage reduction in EASI and PP-NRS. Logistic regression results indicated that high baseline ELR could predict a poor response to dupilumab treatment.

Conclusion: ELR was significantly correlated with disease severity score during the treatment with dupilumab. Baseline ELR could act as a predictor of the efficacy of dupilumab in the treatment of children with atopic dermatitis under 6 years of age.

Keywords: atopic dermatitis, dupilumab, eosinophil-to-lymphocyte ratio, blood cell count

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by intense pruritus, significantly impacting patients' quality of life and mental health.[1] In China, the prevalence of AD among children aged 1 to 7 years is 12.94%.[2] Dupilumab is a monoclonal antibody that targets the interleukin-4 receptor alpha (IL-4Rα), inhibiting the signaling of interleukin-4 (IL-4) and interleukin-13 (IL-13).[3] It has been approved in China for use in children over 6 months of age with moderate to severe AD. Clinical studies indicate that dupilumab is effective and well-tolerated in Chinese patients with atopic dermatitis aged under 6 years.[4]

In recent years, several indicators derived from peripheral blood cell tests, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and eosinophil-to-lymphocyte ratio (ELR), have been recognized as biomarkers reflecting systemic inflammation. These ratios are readily obtainable and have been reported to hold significant clinical relevance across various diseases, including cancer, cardiovascular conditions, and immune and autoimmune disorders. In patients with psoriasis, NLR has been found to correlate with the Psoriasis Area and Severity Index (PASI) score, indicating that NLR may serve as a reliable biomarker for assessing the efficacy of biologic agents targeting IL-17.[5,6] PLR may be associated with the response of psoriasis patients to TNF-α inhibitor therapy.[7] In AD, studies have reported that eosinophil counts correlate with the severity of itching in patients.[8] Additionally, ELR, NLR, and PLR are positively correlated with the Scoring Atopic Dermatitis (SCORAD) index, reflecting the inflammatory response and disease severity in AD patients.[9,10] Two retrospective studies conducted in 2023 and 2024 revealed that total eosinophil counts and ELR serve as biomarkers for assessing the efficacy of upadacitinib treatment in AD.[11,12] NLR and systemic inflammation response index (SIRI) showed a significant decrease earlier than lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC) after Tralokinumab treatment for moderate-to-severe AD.[13] Furthermore, the combination of SIRI, systemic inflammation index (SII), and aggregate inflammation systemic index (AISI) significantly correlates with early treatment responses at four weeks in adult AD patients receiving dupilumab.[14] However, there have been no studies reporting the changes and significance of these parameters in children with AD treated with dupilumab.

In this study, we aim to explore the dynamic changes of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), eosinophil-to-lymphocyte ratio (ELR), eosinophil-to-neutrophil Ratio (ENR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SIRI), systemic inflammation index (SII), and aggregate inflammatory score index(AISI) during dupilumab treatment in children with AD in clinical practice. We will assess the relationship between these parameters and clinical scores changes, and their potential as indicators for predicting the improvement of clinical symptoms in pediatric patients with moderate to severe AD treated with dupilumab.

Material and Methods

Study Design

This was a retrospective study in which data were collected from the medical records of children aged 10 months to 17 years with AD who received dupilumab treatment at the outpatient dermatology department of Chongqing Medical University Affiliated Children's Hospital from August 2021 to March 2024. The study was approved by the Ethics Review Committee of Chongqing Medical University Affiliated Children's Hospital (Ethical approval number: Report No: [2021] Clinic-R [113] and [2022] Clinic-R [013]) and registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx) under registration number ChiCTR2100053167 and ChiCTR2200063385. We reviewed the data of 109 patients who were clinically diagnosed with AD based on the Hanifin and Rajka criteria.[15] All patients received dupilumab treatment, administered subcutaneously once every four weeks. A total of 99 patients completed the 16-week follow-up. Assessments were conducted at baseline (0 week), 4 weeks, and 16 weeks post-treatment, using the Eczema Area and Severity Index (EASI), Scoring Atopic Dermatitis (SCORAD), and Peak Pruritus Numeric Rating Scale (PP-NRS) to evaluate disease severity, along with the Infant Dermatitis Quality of Life Index (IDQOL) and Children's Dermatology Life Quality Index (CDLQI) for questionnaire surveys.

Data Collection

At baseline, patients' demographic data were collected, including age, sex, BMI, duration of illness, and IgE levels. Blood cell count parameters, including neutrophils, lymphocytes, monocytes, eosinophils, and platelets, were recorded at 0, 4, and 16 weeks of treatment. Subsequently, the following derived inflammatory indexes were calculated: Neutrophil-to-Lymphocyte Ratio (NLR) [Neutrophils / Lymphocytes], Platelet-to-Lymphocyte Ratio (PLR) [Platelets / Lymphocytes], Eosinophil-to-Lymphocyte Ratio (ELR) [Eosinophils/ Lymphocytes], Eosinophil-to-Neutrophil Ratio (ENR) [Eosinophils/ Neutrophils], Monocyte-to-Lymphocyte Ratio (MLR) [Monocytes / Lymphocytes], Systemic Inflammation Response Index (SIRI) [(Neutrophils × Monocytes) / Lymphocytes], Systemic Inflammation Index (SII) [(Neutrophils × Platelets) / Lymphocytes], and Aggregate Inflammatory Systemic Index (AISI) [(Neutrophils × Monocytes × Platelets) / Lymphocytes].

Statistics

Normal quantitative data were described using mean ± standard deviation, while skewed quantitative data were presented as median and interquartile range. Qualitative data were described using absolute values and percentages. Statistical analyses were performed using independent samples *t*-test for normally distributed data and Mann–Whitney *U*-test for non-normally distributed data. Pearson and Spearman correlation analyses were employed to evaluate the correlation between laboratory indicators and other clinical parameters. Logistic regression analysis was utilized to identify risk factors affecting the efficacy of atopic dermatitis treatment. Based on previous evidence, we selected potential parameters that may influence the response to dupilumab, including gender, age, disease duration, IgE levels, and BMI.[4,16] Receiver Operating Characteristic (ROC) curves were plotted to determine the optimal cutoff value for the Eosinophil-to-Lymphocyte Ratio (ELR). Statistical analyses and graphing were conducted using SPSS 26.0 and GraphPad Prism 9.0, with a significance level set at $P < 0.05$.

Results

Demographic Data and Clinical Characteristics of the Study Population

Table 1 summarizes the demographic data and baseline clinical characteristics of all patients. A total of 109 patients were included in this study. Among them, 81.7% (89/109) were under 6 years of age, while 18.3% (20/109) were aged 6 to 17 years. The mean ages of the two groups were 40.0 (25.0, 53.5) months and 116.4 ± 28.6 months, respectively. Nearly all inflammatory indices (NLR, PLR, ELR, MLR, SIRI, SII, AISI) in the group of children aged 6 years and older were higher than those in the group of children under 6 years.

The Relationship Between Baseline Inflammatory Indexes and Baseline Clinical Scores

The baseline values of ELR and ENR were positively correlated with the baseline EASI and baseline SCORAD. Additionally, the baseline value of ENR showed a positive correlation with the baseline PP-NRS (Table 2).

Changes in Inflammatory Indexes After 4 and 16 weeks of Dupilumab Treatment

Rapid and significant improvements were observed in different age groups of children during dupilumab treatment. The EASI, SCORAD, PP-NRS, and IDQoL/CDLQI scores significantly decreased by Week 4 and further decreased by Week 16 (Figure 1). In patients under 6 years of age, the mean scores for EASI, PP-NRS, and IDQoL/CDLQI decreased by 87.2%, 80.0%, and 75.0%, respectively, from Week 0 to Week 16. In the 6–17 years age group, the corresponding reductions at Week 16 were 72.6%, 80.0%, and 71.5%. This suggests that the efficacy in the younger age group (<6 years) was superior to that in the older age group (6–17 years).

Compared to Week 0, the level of ENR was significantly reduced by Week 16 (Figure 2D). MLR decreased at Week 4 but returned to baseline levels by Week 16 (Figure 2E). Although a transient increase in ELR was observed in the 6–17 years age group at Week 4, it showed a decrease compared to baseline at Week 16 (Figure S1). Conversely, no transient increase in ELR was noted in the <6 years age group, which exhibited a continuous decrease over time. The remaining indexes did not show significant changes (Figure 2).

Table 1 Demographic and Baseline Characteristics of Children with Atopic Dermatitis (n = 109)

	Total(n=109)	<6y(n=89)	≥6y(n=20)	p
Sex, n(%)				0.897
Male	64(58.7%)	52(58.4%)	12(60.0%)	
Female	45(41.3%)	37(41.6%)	8(40.0%)	
Age(months)	40.5(26.0,56.3)	40.0(25.0,53.5)	116.4±28.6	**<0.001**
BMI(kg/m^2)	15.7(14.7,17.4)	15.7(14.7,17.3)	15.7(14.8,19.3)	0.314
Disease duration (months)	37.0(21.0,51.3)	35.0(20.8,49.3)	93.2±40.9	**<0.001**
Clinical indexes				
EASI	23.0(17.9,27.5)	21.9(17.4,26.9)	21.2±8.1	0.320
SCORAD	63.1±10.6	62.2±10.2	66.5±15.8	0.376
PP-NRS	8(7,9)	8(7,9)	7±2	**0.004**
IDQoL/CDLQI	12(8,17)	12(8,17)	13±6	0.897
Laboratory parameters				
NLR	0.83(0.56,1.15)	0.72(0.55,1.14)	1.29(1.11,1.79)	**<0.001**
PLR	86.6(68.0,108.9)	84.3(66.9,107.2)	123.4±38.8	**0.001**
ELR	0.15(0.10,0.25)	0.14(0.08,0.21)	0.22(0.12,0.35)	**0.033**
ENR	0.19(0.10,0.33)	0.18(0.09,0.33)	0.18±0.10	0.436
MLR	0.10(0.07,0.12)	0.09(0.06,0.11)	0.14(0.12,0.19)	**<0.001**
SIRI	0.28(0.18,0.46)	0.27(0.17,0.44)	0.51(0.33,0.66)	**0.001**
SII	267(175,424)	250(175,412)	408(298,578)	**0.007**
AISI	93.4(55.6,144.8)	88.3(55.0,146.6)	139.6(98.9,213.7)	**0.017**

Notes: Values in boldface are significant ($p < 0.05$).

Abbreviations: BMI, body mass index; EASI, eczema area and severity index; SCORAD, Scoring Atopic Dermatitis; PP-NRS, peak pruritus numerical rating scale; IDQoL, Infants' Dermatitis Quality of Life Index; CDLQI, Children's Dermatology Life Quality Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; ENR, eosinophil-to-neutrophil ratio; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic inflammation index; AISI, aggregate inflammation systemic index.

Table 2 The Correlation Between Baseline Values of Inflammatory Indexes and Baseline Values of Clinical Scores in Children with Atopic Dermatitis (n = 109)

Variables	EASI		SCORAD		PP-NRS		IDQoL/CDLQI	
	Rho	p	Rho	p	Rho	p	Rho	p
NLR	−0.068	0.480	−0.049	0.640	−0.147	0.127	−0.031	0.748
PLR	−0.120	0.212	−0.119	0.254	−0.019	0.842	0.045	0.641
ELR	0.316	**0.001**	0.394	**<0.001**	0.098	0.310	0.117	0.226
ENR	0.363	**<0.001**	0.417	**<0.001**	0.211	**0.027**	0.185	0.054
MLR	0.030	0.758	0.115	0.271	−0.067	0.491	−0.021	0.827
SIRI	0.059	0.539	0.073	0.485	−0.051	0.600	0.027	0.779
SII	−0.022	0.824	−0.065	0.532	−0.044	0.647	0.036	0.711
AISI	0.080	0.407	0.045	0.665	0.032	0.739	0.087	0.369

Notes: Values in boldface are significant ($p < 0.05$).

Abbreviations: EASI, eczema area and severity index; SCORAD, Scoring Atopic Dermatitis; PP-NRS, peak pruritus numerical rating scale; IDQoL, Infants' Dermatitis Quality of Life Index; CDLQI, Children's Dermatology Life Quality Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; ENR, eosinophil-to-neutrophil ratio; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic inflammation index; AISI, aggregate inflammation systemic index.

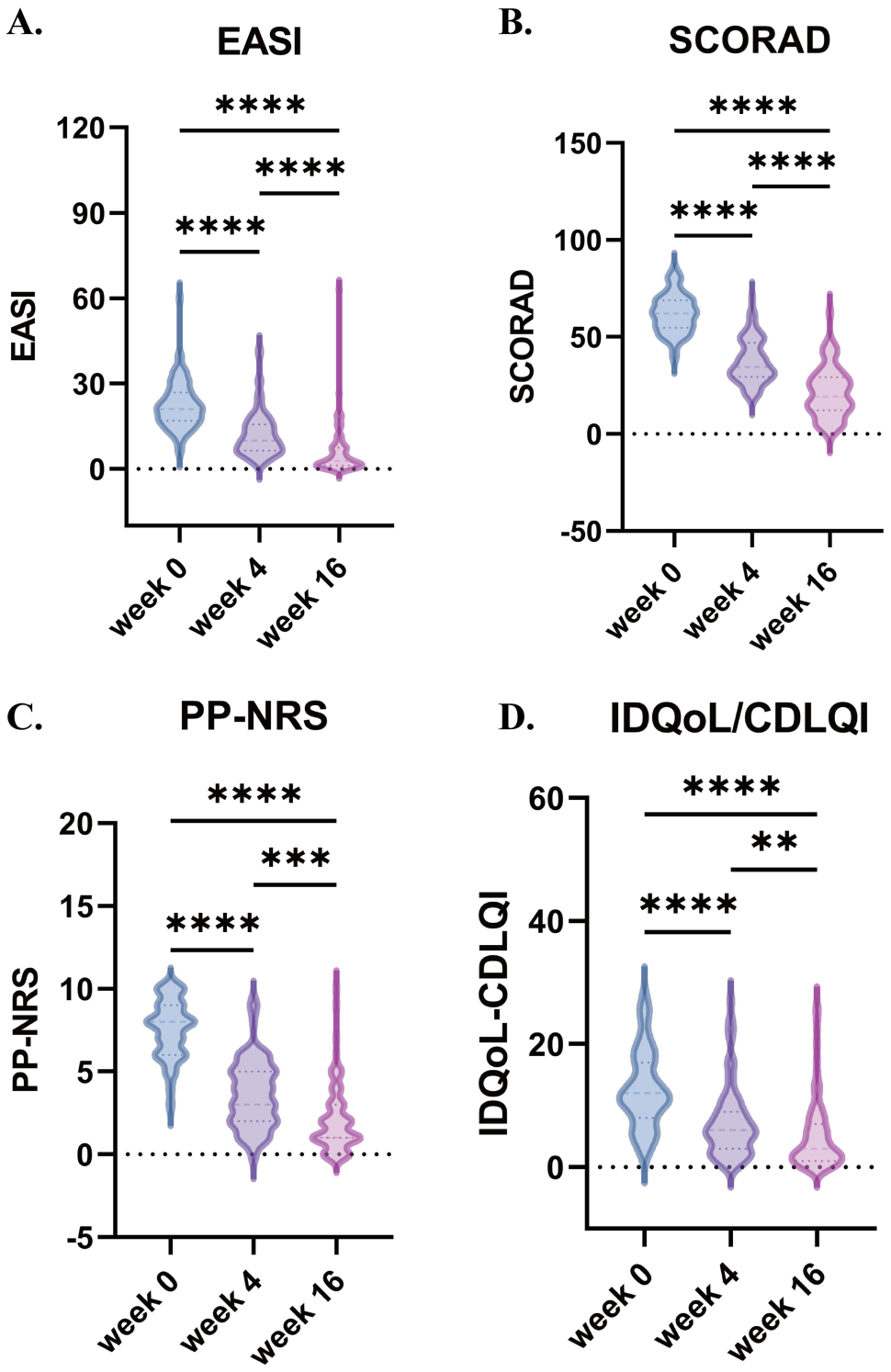

Figure 1 The change of the eczema area and severity index (EASI) (**A**), Scoring Atopic Dermatitis (SCORAD) (**B**), peak pruritus-numerical rating scale (PP-NRS) (**C**), Infants' Dermatitis Quality of Life Index (IDQoL) or Children's Dermatology Life Quality Index (CDLQI) (**D**) at weeks 0, 4, or 16 of dupilumab treatment in atopic dermatitis patients. **p < 0.01; ***p < 0.001; ****p < 0.0001.

The Association Between the Percentage Reduction of Inflammatory Indexes and the Percentage Reduction of Clinical Scores

Then we analyzed whether the percentage reductions in NLR, PLR, ELR, ENR, MLR, SIRI, SII, and AISI were associated with the reductions in clinical parameters (Table 3). The percentage reduction in ELR at weeks 4 and 16

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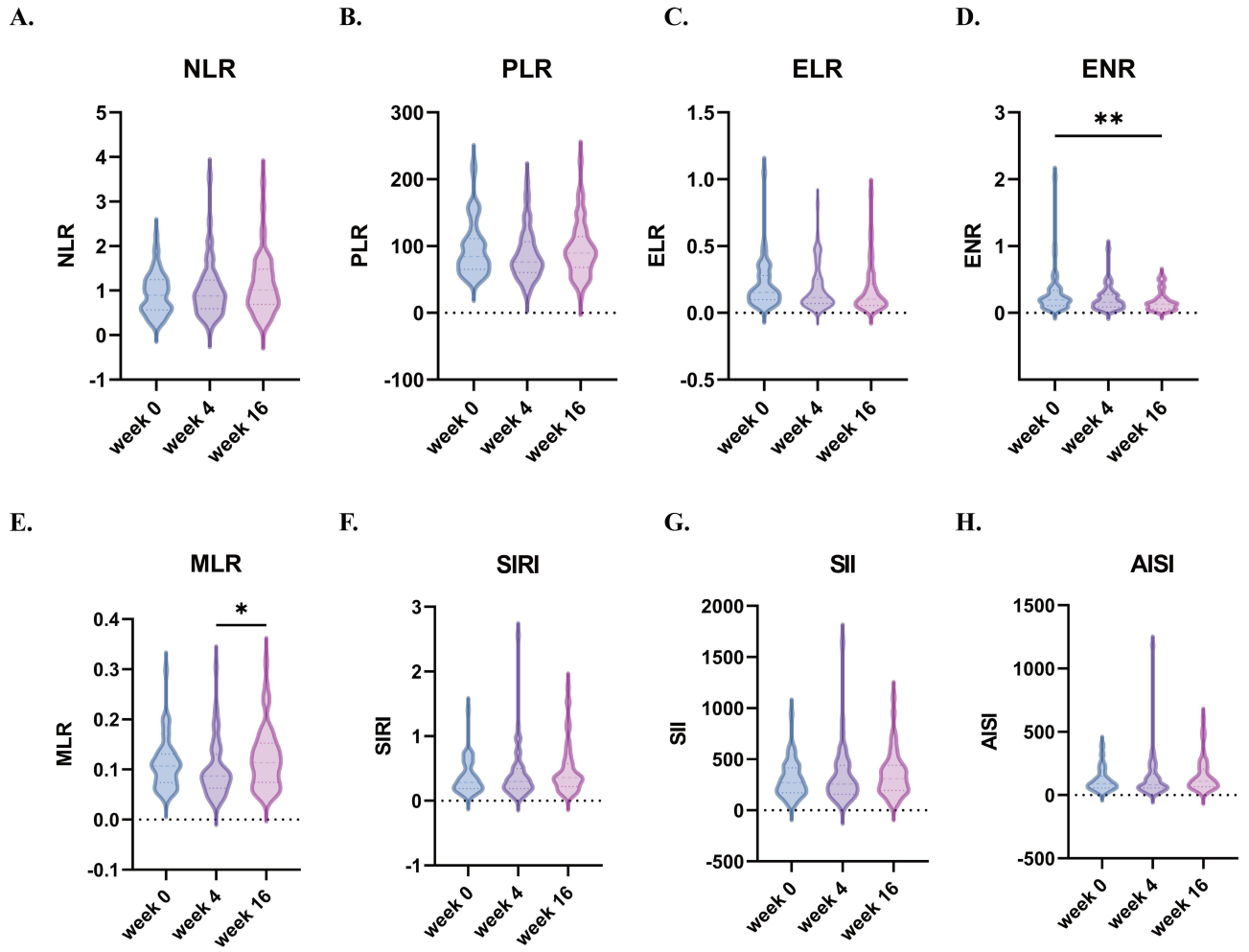

Figure 2 The change of neutrophil-to-lymphocyte ratio (NLR) (**A**), platelet-to-lymphocyte ratio (PLR) (**B**), eosinophil-to-lymphocyte ratio (ELR) (**C**), eosinophil-to-neutrophil ratio (ENR) (**D**), monocyte-to-lymphocyte ratio (MLR) (**E**), systemic inflammation response index (SIRI) (**F**), systemic inflammation index (SII) (**G**), and aggregate inflammation systemic index (AISI) (**H**) at weeks 0, 4, or 16 of dupilumab treatment in atopic dermatitis patients. *p < 0.05; **p < 0.01.

was positively correlated with the percentage reductions in EASI and PP-NRS. The percentage reduction in ENR at weeks 4 and 16 was positively correlated with the percentage reduction in EASI. The percentage reduction in PP-NRS at week 4 was associated with PLR, MLR and AISI. At week 16, the percentage reduction in PP-NRS was positively correlated with ENR. Additionally, at week 16, the percentage reduction in IDQoL/CDLQI was positively correlated with ELR, SIRI and AISI.

The Correlation Between Inflammatory Indexes and Clinical Scores with the Efficacy of Dupilumab Treatment

At week 16, patients in the <6 years group who achieved EASI75 were classified as the good response group, while the others were classified as the poor response group. Compared to the good response group, ELR was significantly elevated in the poor response group (Figure 3A and Table S1). Next, we conducted a binary logistic regression analysis to identify factors associated with the efficacy of dupilumab (Table 4). Univariate logistic regression analysis revealed that gender (P = 0.116) and ELR (P = 0.026) were closely related to whether patients achieved EASI75. All variables from the univariate logistic regression with P < 0.2 (gender, ELR) were included in the multivariate logistic regression model. We further confirmed that ELR (OR = 0.006, 95% CI: 0.000–0.689) were associated with the efficacy of dupilumab. The results suggested that ELR was an independent risk factor for predicting poor response after 16 weeks of dupilumab treatment in patients with AD younger than 6 years old; specifically, higher baseline ELR levels were associated with

Table 3 The Correlation Between the Percentage Reduction of Inflammatory Indexes and the Percentage Reduction of Clinical Scores at Weeks 4 and 16 of Treatment with Dupilumab in Children with Atopic Dermatitis

Inflammatory Indexes	Clinical Scores	Week4		Week16	
		Rho	p	Rho	p
NLR	EASI	0.087	0.487	−0.026	0.828
	SCORAD	0.095	0.511	−0.031	0.821
	PP-NRS	0.195	0.117	0.006	0.960
	IDQoL/CDLQI	0.082	0.518	0.203	0.082
PLR	EASI	0.104	0.406	−0.026	0.823
	SCORAD	0.175	0.223	0.017	0.899
	PP-NRS	0.275	**0.026**	0.005	0.964
	IDQoL/CDLQI	−0.016	0.898	0.048	0.687
ELR	EASI	0.402	**0.001**	0.238	**0.039**
	SCORAD	0.255	0.074	0.243	0.069
	PP-NRS	0.273	**0.026**	0.363	**0.001**
	IDQoL/CDLQI	0.197	0.115	0.363	**0.001**
ENR	EASI	0.286	**0.020**	0.245	**0.034**
	SCORAD	0.177	0.220	0.252	0.059
	PP-NRS	0.112	0.369	0.323	**0.005**
	IDQoL/CDLQI	0.137	0.276	0.167	0.155
MLR	EASI	0.209	0.093	−0.035	0.765
	SCORAD	0.186	0.195	0.016	0.903
	PP-NRS	0.322	**0.008**	0.075	0.525
	IDQoL/CDLQI	0.209	0.095	0.164	0.162
SIRI	EASI	0.131	0.294	0.013	0.914
	SCORAD	0.105	0.468	−0.056	0.682
	PP-NRS	0.221	0.075	0.025	0.832
	IDQoL/CDLQI	0.116	0.357	0.259	**0.026**
SII	EASI	0.086	0.494	0.040	0.735
	SCORAD	0.127	0.381	−0.032	0.814
	PP-NRS	0.212	0.088	−0.004	0.973
	IDQoL/CDLQI	0.058	0.646	0.222	0.054
AISI	EASI	0.128	0.304	0.050	0.670
	SCORAD	0.135	0.349	−0.033	0.808
	PP-NRS	0.253	**0.040**	0.012	0.916
	IDQoL/CDLQI	0.103	0.416	0.252	**0.031**

Notes:Values in boldface are significant ($p < 0.05$).

Abbreviations: EASI, eczema area and severity index; SCORAD, Scoring Atopic Dermatitis; PP-NRS, peak pruritus numerical rating scale; IDQoL, Infants' Dermatitis Quality of Life Index; CDLQI, Children's Dermatology Life Quality Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; ENR, eosinophil-to-neutrophil ratio; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic inflammation index; AISI, aggregate inflammation systemic index.

a lower likelihood of reaching EASI75. ROC curve analysis indicated that ELR can predict the failure to achieve EASI75 in atopic dermatitis patients after 16-week dupilumab treatment (AUC = 0.654, 95% CI: 0.518–0.791; Figure 3B), with a cutoff value of 0.139, yielding a sensitivity of 58.93% and a specificity of 69.57%.

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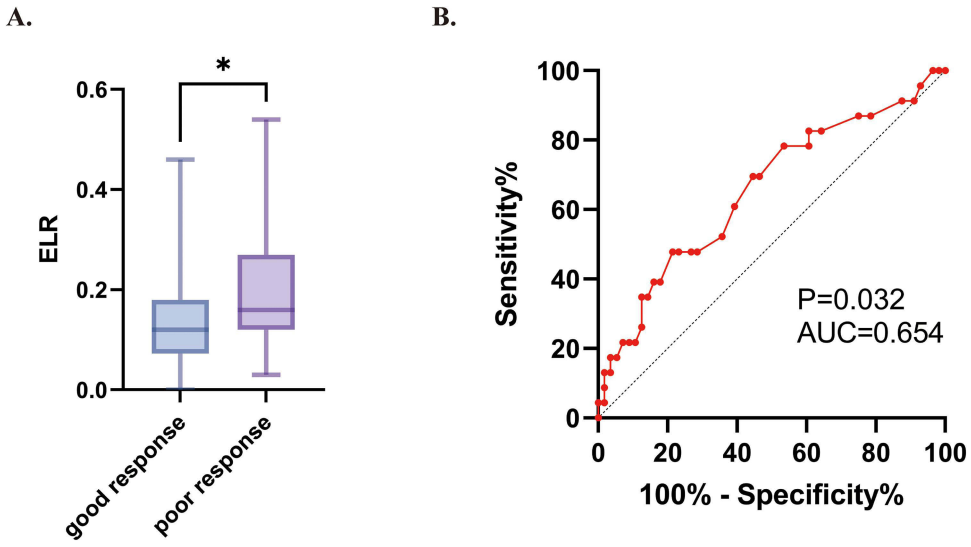

Figure 3 (**A**) Difference in ELR value between good-response group and poor-response group. (**B**) ROC curve for response to dupilumab treatment in patients with atopic dermatitis aged <6 years. *p < 0.05.

Discussion

Dupilumab is the first biologic agent approved for the treatment of moderate to severe AD. It works by binding to IL-4Rα, thereby blocking the IL-4/IL-13 signaling pathway and downstream JAK-STAT signaling, which inhibits type 2 immune responses. The US Food and Drug Administration (FDA) approved dupilumab for the treatment of moderate to severe AD in children aged 6 years and older in May 2020. Subsequently, in June 2022, the age indication for dupilumab was expanded to include children aged 6 months to 5 years, making it the first biologic agent approved for the treatment of moderate to severe AD across all age groups, from infants to adults.[17] Several Phase III clinical trials conducted in

Table 4 The Predictive Factors for EASI75 at Week 16 of Dupilumab Treatment Assessed by Binary Logistic Regression Analysis in Patients Aged <6 Years

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Sex(male)	0.438(0.156,1.227)	0.116	0.459(0.159,1.326)	0.150
Age(months)	0.987(0.958,1.016)	0.373		
Disease duration (months)	0.992(0.962,1.024)	0.632		
IgE	1.000(0.999,1.000)	0.807		
BMI	0.967(0.777,1.205)	0.767		
NLR	0.857(0.347,2.115)	0.737		
PLR	0.998(0.985,1.011)	0.738		
ELR	0.005(0.000,0.538)	**0.026**	0.006(0.000,0.689)	**0.035**
ENR	0.562(0.099,3.183)	0.515		
MLR	3.969(0.015,1.020)	0.626		
SIRI	1.455(0.376,5.625)	0.587		
SII	1.000(0.998,1.003)	0.886		
AISI	1.002(0.997,1.007)	0.481		

Notes: Values in boldface are significant (p < 0.05).
Abbreviations: BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; ENR, eosinophil-to-neutrophil ratio; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic inflammation index; AISI, aggregate inflammation systemic index.

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North America and Europe have demonstrated that dupilumab significantly improves the signs, symptoms, and quality of life of AD patients across different age groups (infants, children, and adolescents) over a 16-week period.[18–20] However, due to limitations in clinical research, there has been a lack of real-world data on the use of dupilumab in pediatric patients in China. As of May 2023, dupilumab has been approved in China for the treatment of moderate to severe AD in patients aged 6 months to 5 years. With ongoing studies, the efficacy and safety of dupilumab in Chinese children under 6 years of age have been validated.[21–23]

Dupilumab treatment reduced levels of inflammatory biomarkers, reflecting reduction of systemic general and type 2 inflammation, such as serum lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC)/CCL17, and total IgE.[24] Several biomarkers related to disease severity or predictive of dupilumab efficacy of AD have also been proposed, such as LDH, interleukin (IL)-22, CD25/soluble interleukin (sIL)-2Rα, IL-31 and IL-36β.[25–27] But these biomarkers often require additional detection, or the complex combination brings limitations to the application. Therefore, it is essential to identify more effective and convenient biomarkers. Inflammatory indicators derived from routine blood tests indicate the body ‘s inflammatory state, which is helpful for early diagnosis, severity classification and efficacy prediction of the disease.[14] Inflammatory indicators including ELR, NLR, and PLR have been reported to be related to disease severity, and reflecting the inflammatory response in AD patients.[9,10] ELR, the combination of SIRI, SII, AISI were found that may serve as biomarkers for assessing the efficacy of biologics treatment in AD.[12,14]

To our knowledge, this study is the first to investigate the efficacy of dupilumab in pediatric patients in China, including those under 6 years of age, in relation to peripheral blood cell counts derived inflammatory indices. In this study, we not only assessed the dynamic changes of these indices during treatment but also explored the relationship between inflammatory indices and clinical scores. The results revealed significant associations between baseline ELR, ENR and baseline EASI, as well as between baseline ENR and baseline PP-NRS. Furthermore, a reduction in ELR during dupilumab treatment for atopic dermatitis was positively correlated with reductions in EASI or PP-NRS at weeks 4 and 16. The results are consistent with previous reports indicating that ELR is associated with disease severity and pruritus.[8,12] Additionally, multivariate logistic regression analysis revealed that ELR was an independent risk factor for predicting the efficacy of dupilumab. Our study demonstrated that changes in ELR were significantly correlated with changes of EASI in the early stage of treatment (4 weeks), and mid to late treatment (16 weeks). Furthermore, ELR served as an independent biomarker for predicting poor response in pediatric patients with atopic dermatitis under 6 years of age. Therefore, ELR can reflect the improvement of clinical symptoms following dupilumab therapy for atopic dermatitis and is an effective indicator for evaluating treatment efficacy in children under 6 years of age.

Eosinophils play a role in allergic reactions, inflammation, and anti-infection responses. In AD lesions, granules secreted by eosinophils, including major basic protein (MBP), eosinophil peroxidase (EPO), and eosinophil cationic protein (ECP), can induce keratinocyte damage and promote the release of alarmins.[12] Eosinophils also secrete various factors such as TNF, transforming growth factor, IL-1, IL-3, IL-4, IL-5, IL-8, and GM-CSF, which enhance the inflammatory process and influence T cell differentiation.[28] In patients with AD, circulating eosinophil counts and eosinophil granule protein levels are elevated and correlated with disease activity. This may be attributed to cytokines and chemokines that can generate, recruit, and activate eosinophils.[29] In clinical studies of dupilumab treatment for AD, we often observe a transient increase in eosinophils, typically occurring at 4 weeks post-treatment, followed by a return to baseline levels by week 8.[30] However, it is noteworthy that these studies primarily focus on adults and adolescents. Previous research has indicated that eosinophil counts and ELR are higher in patients with asthma and atopy.[31] In moderate to severe AD patients, NLR, PLR, and ELR are significantly elevated compared to those with mild AD. However, almost all hematological ratios in pediatric AD patients (0–18 years) are significantly lower than those in adult AD patients. Weissmann suggests that this may be due to an increase in acute neutrophilic inflammatory responses in adults or an increase in lymphocyte apoptosis, leading to higher neutrophil counts and lower lymphocyte counts in adults compared to children.[32] Interestingly, in our study, we further subdivided children under 18 years of age and found that, except for ENR, all hematological ratios in children over 6 years of age were higher than those in children under 6 years with AD. It is evident that hematological parameters vary with age, showing higher ratios with increasing age. This may be related to the continuous development of immune organs and the gradual maturation of immune cell functions. Additionally, our data indicated that among patients aged 6–17 years, the ELR exhibited an initial increase followed by a decrease. In contrast to previous reports, we did not observe a transient increase in ELR at 4 weeks in the group of children under 6 years;

instead, ELR demonstrated a gradual decline over the course of treatment. Undoubtedly, these inflammatory markers, particularly the ELR, contribute to the management, follow-up, and efficacy prediction for AD patients, but attention should be paid to their application across different age groups.

This study has several limitations. First, it was a retrospective study, making it difficult to avoid confounding factors and biases. Second, the sample size of children over 6 years of age was relatively small, which may limit the generalizability of the finding due to the decrease of statistical power. A larger sample size is needed to further confirm these results of this subgroup. Finally, the follow-up duration in our study was relatively short; longer follow-up is warranted to explore the dynamic relationship between long-term efficacy and inflammatory markers.

Conclusion

Baseline ELR was positively correlated with baseline EASI, so does the change of ELR and EASI during dupilumab treatment. Baseline ELR could be used as an independent biomarker to predict the efficacy of 16-week dupilumab treatment in children with atopic dermatitis under 6 years of age. In summary, ELR is an effective and convenient indicator, which could be helpful for the evaluation and management of children with AD in clinical practice. Longer follow-up time is required to validate the predictive role of ELR in the long-term efficacy of AD.

Abbreviations

BMI, body mass index; EASI, eczema area and severity index; SCORAD, Scoring Atopic Dermatitis; PP-NRS, peak pruritus numerical rating scale; IDQoL, Infants' Dermatitis Quality of Life Index; CDLQI, Children's Dermatology Life Quality Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; ENR, eosinophil-to-neutrophil ratio; MLR, monocyte-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic inflammation index; AISI, aggregate inflammation systemic index; AUC, area under the curve.

Data Sharing Statement

The data set presented in this study can be obtained through the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study involving human subjects was reviewed and approved by the Ethics Committee of Children 's Hospital Affiliated to Chongqing Medical University. Written informed consent was obtained from the legal guardians / collateral relatives of individuals (s) and minors (s). This study complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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