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Original Article

Development of a clinical indicator-based severity scoring system for pediatric atopic dermatitis and evaluation of dupilumab treatment outcomes

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Abstract: Objective: To develop and validate a pediatric atopic dermatitis (AD) severity scoring system based on routinely available clinical indicators and to evaluate the efficacy and safety of dupilumab in children with moderate-to-severe AD. Methods: Clinical data from 236 children with AD treated between January 2023 and January 2025 were retrospectively analyzed and randomly split into training and internal validation cohorts (7:3). An external validation cohort included 42 patients treated between February and June 2025. AD severity was classified using the SCORAD index. Factors associated with disease severity were identified by logistic regression, and a scoring system was developed and evaluated using receiver operating characteristic (ROC) and calibration curves. In addition, children with moderate-to-severe AD treated with dupilumab were assessed for changes in clinical scores at baseline and weeks 4, 12, and 16, with adverse events recorded. Results: The scoring system (0-9 points) included onset age ≤2 years, xerosis, spiny lichen, vitamin D insufficiency/deficiency, and eosinophil count ≥0.455×10^9/L. The areas under the ROC curve were 0.885 in the internal validation cohort and 0.824 in the external validation cohort, with good calibration. Dupilumab treatment significantly improved EASI, SCORAD, PP-NRS scores. At week 16, EASI50, EASI75, and EASI90 were achieved in 86.52%, 65.17%, and 33.71% of patients, respectively. Adverse events were mild and infrequent. Conclusions: A simple and practical severity scoring system for pediatric AD was developed and validated. Dupilumab demonstrated favorable efficacy and acceptable safety in children with moderate-to-severe AD.

Keywords: Atopic dermatitis, children, severity scoring system, dupilumab, clinical efficacy

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by recurrent eczematous lesions, marked skin dryness, and intense pruritus, and represents a major contributor to the global burden of skin diseases [1]. The global prevalence of AD is approximately 4% in children and 2% in adults [2]. In recent years, the incidence of AD in China has shown a continuous upward trend. A nationwide epidemiological survey conducted in 12 provinces and municipalities in China in 2016 reported a prevalence of AD as high as 12.9% among children [3]. Although the pathogenesis of AD has not been fully elucidated, evidence suggests that epidermal barrier dysfunction and immune dysregulation play critical roles in disease development [4]. Assessment of disease severity is a key step in guiding therapeutic decision-making for AD. Currently, commonly used severity assessment tools include the Scoring Atopic Dermatitis (SCORAD) index and the Eczema Area and Severity Index (EASI); however, these instruments are designed primarily for clinical trials and may be limited in routine clinical practice due to their complexity and time-consuming nature [5]. In addition, previous studies have suggested that indicators such as *Staphylococcus aureus* skin colonization density, thymic stromal lymphopoietin levels, serum activation-regulated chemokines, and transepidermal water loss are associated with AD severity [6, 7], yet these assessments are not routinely available in clinical settings. Therefore, the development of a simple and

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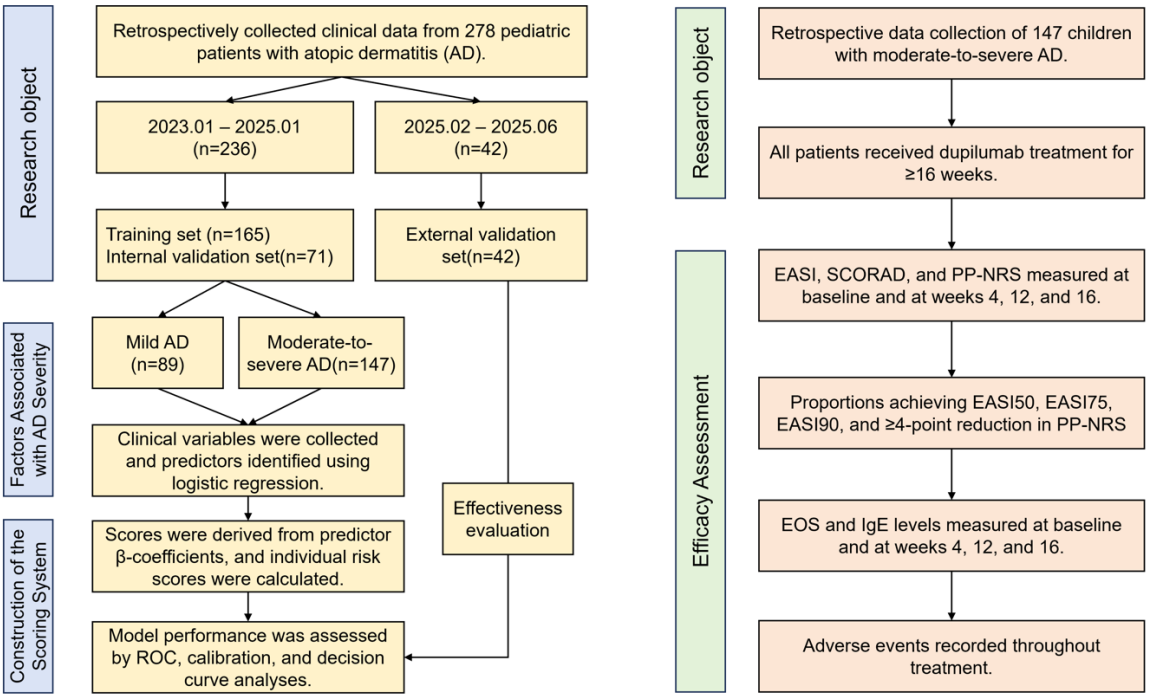

Figure 1. Study flowchart. EASI: eczema area and severity index; SCORAD: scoring atopic dermatitis; PP-NRS: peak pruritus numerical rating scale.

practical AD severity scoring system based on commonly available clinical indicators is of substantial clinical value.

In terms of treatment, the management of pediatric AD, particularly moderate-to-severe disease, remains challenging. Topical corticosteroids may lead to local or systemic adverse effects with long-term use; phototherapy is not recommended for children younger than 12 years; and immunosuppressive agents such as cyclosporine carry potential risks of hepatotoxicity and nephrotoxicity [8, 9]. In recent years, dupilumab, a biologic agent that blocks the interleukin (IL)-4 and IL-13 signaling pathways, has emerged as a novel therapeutic option for moderate-to-severe AD [10]. Multiple clinical trials have demonstrated that dupilumab provides favorable efficacy and safety in adults, adolescents, and children with AD [11, 12]. However, evidence regarding the use of dupilumab in Chinese pediatric patients with AD remains limited. Therefore, this study retrospectively analyzed the clinical data of pediatric patients with AD (**Figure 1**) to develop a disease severity scoring system based on routinely available clinical indicators and to evaluate the effectiveness of dupilumab in Chinese children younger than 12 years with moderate-to-severe AD. This will support individualized severity assessment and standardized management of pediatric AD.

Materials and methods

Construction of the AD severity scoring system

Research subjects: Clinical data of 236 pediatric patients with AD treated at Affiliated Maternity and Child Health Care Hospital of Nantong University between January 2023 and January 2025 were retrospectively analyzed. These patients were randomly divided into a training cohort and an internal validation cohort at a ratio of 7:3. In addition, 42 pediatric patients with AD treated between February 2025 and June 2025 were included as an external validation cohort. All enrolled patients met the diagnostic criteria for AD proposed by Hanifin and Rajka and were aged 1-12 years. This study was approved by the Ethics Committee of the Affiliated Maternity and Child Health Care Hospital of Nantong University.

Data collection: Baseline demographic and clinical data were collected, including sex, age,

age at disease onset, family history of atopy, SCORAD index, xerosis, spiny lichen, immunoglobulin E (IgE), vitamin A, vitamin E, vitamin D, eosinophil count (EOS), eosinophil-derived neurotoxin (EDN), galectin-10 (Gal-10), interleukin (IL)-4, IL-13, IL-31, and interferon-γ (IFN-γ).

All laboratory indicators were measured using venous blood samples collected within 24 hours of enrollment. Serum IgE levels were determined by radioimmunoassay. Gal-10, EDN, IL-4, IL-13, IL-31, and IFN-γ were measured using enzyme-linked immunosorbent assay (ELISA). Vitamin A and vitamin E levels were assessed by high-performance liquid chromatography, and vitamin D levels were determined by liquid chromatography-tandem mass spectrometry. EOS was obtained using an automated hematology analyzer.

Patients were classified into mild and moderate-to-severe groups according to SCORAD scores, with scores <25 defined as mild, 25-50 as moderate, and >50 as severe. The definitions of laboratory values were based on clinical guideline criteria: vitamin A ≥0.3 mg/L was considered sufficient, >0.2 to <0.3 mg/L insufficient, and ≤0.2 mg/L deficient; vitamin D ≥30 ng/mL was considered sufficient, >20 to 30 ng/mL insufficient, and ≤20 ng/mL deficient; vitamin E >7 mg/L was considered sufficient, 5-7 mg/L insufficient, and <5 mg/L deficient. A total IgE level below 165.3 U/mL was defined as normal.

Statistical analysis: Statistical analyses were performed using SPSS Statistics version 26.0. Continuous variables with a normal distribution were presented as mean ± standard deviation and were compared using Student's t test or analysis of variance, as appropriate. Non-normally distributed continuous variables were expressed as median and interquartile range and were compared using nonparametric tests. Categorical variables were presented as numbers and percentages and were compared using the chi-square test.

Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values for retained continuous variables, which were subsequently transformed into categorical variables based on clinical relevance. Logistic regression analysis was performed to identify factors associated with AD severity. Scores were assigned according to the β regression coefficients of the selected variables, and the sum of individual scores constituted the overall severity score for each patient. The performance of the scoring system was evaluated using the area under the ROC curve (AUC) and calibration curves. A two-sided *P* value <0.05 was considered significant.

Clinical efficacy analysis of dupilumab treatment

Research object: Clinical data of children with moderate-to-severe AD who received dupilumab treatment at Affiliated Maternity and Child Health Care Hospital of Nantong University between January 2023 and January 2025 were retrospectively collected. These patients were selected from the training and internal validation cohorts.

The inclusion criteria were as follows: (1) age between 1 and 12 years; (2) SCORAD score ≥25; (3) inadequate response to, intolerance of, or unwillingness to continue conventional therapies, including topical corticosteroids and systemic agents; (4) receipt of at least one dose of dupilumab.

The exclusion criteria were as follows: (1) active tuberculosis infection, immune system diseases, or active hepatitis B infection; (2) known hypersensitivity to any component of dupilumab; (3) the presence of other uncontrolled severe systemic diseases.

Treatment regimen: For children younger than 6 years, dosing was weight-based: patients weighing 5 to <15 kg received an initial dose of 200 mg, followed by 200 mg every 4 weeks; those weighing 15 to <30 kg received an initial dose of 300 mg, followed by 300 mg every 4 weeks.

For children aged 6-12 years, patients weighing 15 to <30 kg received an initial dose of 600 mg, followed by 300 mg every 4 weeks; those weighing 30 to <60 kg received an initial dose of 400 mg, followed by 200 mg every 2 weeks. All patients received treatment for at least 16 weeks.

Data collection: The EASI, SCORAD, Peak Pruritus Numeric Rating Scale (PP-NRS), EOS count, serum IgE levels, and adverse events

Table 1. Comparison of three datasets

Variable	Training set (n = 165)	Internal validation set (n = 71)	External validation set (n = 42)	Statistic value	P
Severity				0.854[a]	0.652
Mild	62 (37.58)	27 (38.03)	19 (45.24)		
Moderate-to-severe	103 (62.42)	44 (61.97)	23 (54.76)		
Sex				0.341[a]	0.843
Male	102 (61.82)	46 (64.79)	25 (59.52)		
Female	63 (38.18)	25 (35.21)	17 (40.48)		
Onset age ≤2 years				1.713[a]	0.425
No	45 (27.27)	24 (33.80)	15 (35.71)		
Yes	120 (72.73)	47 (66.20)	27 (64.29)		
Family history of atopy				0.868[a]	0.648
No	84 (50.91)	35 (49.30)	18 (42.86)		
Yes	81 (49.09)	36 (50.70)	24 (57.14)		
Comorbid atopic diseases				0.620	0.733
No	100 (60.61)	44 (61.97)	23 (54.76)		
Yes	65 (39.39)	27 (38.03)	19 (45.24)		
Xerosis				0.678[a]	0.712
No	62 (37.58)	30 (42.25)	18 (42.86)		
Yes	103 (62.42)	41 (57.75)	24 (57.14)		
Spiny lichen				0.870[a]	0.647
No	97 (58.79)	43 (60.56)	28 (66.67)		
Yes	68 (41.21)	28 (39.44)	14 (33.33)		
IgE				1.520[a]	0.468
Normal	38 (23.03)	15 (21.13)	13 (30.95)		
Elevated	127 (76.97)	56 (78.87)	29 (69.05)		
Vitamin A				2.590[a]	0.629
Sufficient	69 (41.82)	31 (43.66)	21 (50.00)		
Insufficient	58 (35.15)	25 (35.21)	16 (38.10)		
Deficient	38 (23.03)	15 (21.13)	5 (11.90)		
Vitamin E				1.432[a]	0.839
Sufficient	93 (56.36)	41 (57.75)	27 (64.29)		
Insufficient	58 (35.15)	25 (35.21)	11 (26.19)		
Deficient	14 (8.48)	5 (7.04)	4 (9.52)		
Vitamin D				7.537[a]	0.110
Sufficient	68 (41.21)	23 (32.39)	20 (47.62)		
Insufficient	62 (37.58)	23 (32.39)	10 (23.81)		
Deficient	35 (21.21)	25 (35.21)	12 (28.57)		
Age, year	6 (4, 8)	5 (3, 9)	8 (6, 9)	4.241[b]	0.120
EOS, ×10^9/L	0.39 (0.19, 0.63)	0.32 (0.18, 0.56)	0.32 (0.17, 0.57)	2.498[b]	0.287
EDN, ng/ml	193.58±50.61	206.3±45.29	202.42±43.95	1.907[c]	0.150
Gal-10, pg/ml	28.8±8.98	26.37±8.75	30.13±7.74	2.909[c]	0.056
IL-4, pg/ml	18.84±8.31	18.04±8.55	20.52±6.71	1.225[c]	0.295
IL-13, pg/ml	14.73±6.18	15.37±6.99	13.36±5.21	1.381[c]	0.253
IL-31, pg/ml	34.38±9.22	36.23±8.51	36.83±8.82	1.840[c]	0.161
IFN-γ, pg/ml	39.94±10.4	38.66±8.42	41.26±6.55	1.037[c]	0.356

Note: a: the statistical value of the chi-square test; b: the statistical value of the non-parametric test; c: the statistical value of the one-way ANOVA; IgE: immunoglobulin E; EOS: eosinophils; EDN: eosinophil-derived neurotoxin; Gal-10: galectin-10; IL: interleukin; IFN-γ: interferon-γ.

were recorded at baseline and at weeks 4, 12, and 16 after treatment initiation.

The primary efficacy endpoints were the proportions of patients achieving at least a 50% (EASI50), 75% (EASI75), and 90% (EASI90) reduction in EASI score. The secondary efficacy endpoint was the proportion of patients achieving a reduction of ≥4 points in PP-NRS.

Statistical analysis: Statistical analyses were performed using SPSS Statistics version 26.0. Continuous variables with a normal distribution are presented as mean ± standard deviation and were analyzed using one-way repeated-measures analysis of variance. Non-normally distributed continuous variables are expressed as median and interquartile range and were analyzed using nonparametric tests. Pairwise comparisons were adjusted using the Bonferroni correction, with an adjusted significance level of $\alpha' = 0.05/6 = 0.008$.

The proportions of patients achieving the primary and secondary efficacy endpoints were compared using the chi-square test, and Bonferroni correction was applied for pairwise multiple comparisons, with an adjusted significance level of $\alpha' = 0.05/3 = 0.017$. Except for multiple-comparison adjustments, all statistical tests were two-sided, and a *P* value <0.05 was considered significant.

Results

AD severity scoring system

Comparison of the three cohorts: A total of 278 pediatric patients with AD were included in this study, comprising 165 patients in the training cohort, 71 in the internal validation cohort, and 42 in the external validation cohort. The baseline characteristics of patients in the three cohorts are summarized in **Table 1**.

Univariate analysis in the training cohort: The 165 patients in the training cohort were classified into a mild group (n = 62) and a moderate-to-severe group (n = 103) according to SCORAD scores. Comparisons of clinical characteristics between the two groups revealed significant differences in age at disease onset, xerosis, spiny lichen, vitamin D status, and EOS (**Table 2**).

Factors associated with AD severity: Multicollinearity among candidate predictors was assessed using variance inflation factors (VIF). Categorical variables, including vitamin D status (sufficient, insufficient, and deficient), were entered into the model as single categorical predictors. No significant multicollinearity was observed among the included variables (all VIFs <5).

ROC curve analysis was performed to determine the optimal cutoff value for the continuous variable EOS. The cutoff corresponding to the maximum Youden index was identified as 0.455×10^9/L. Accordingly, EOS was dichotomized as $<0.455\times10^9$/L (coded as 0) and $\geq0.455\times10^9$/L (coded as 1).

AD severity was then included as the dependent variable (0 = mild, 1 = moderate-to-severe), and onset age ≤2 years (0 = no, 1 = yes), xerosis (0 = no, 1 = yes), spiny lichen (0 = no, 1 = yes), vitamin D status (0 = sufficient, 1 = insufficient, 2 = deficient), and EOS (0 = <0.455, 1 = ≥0.455) were entered as independent variables in a logistic regression model. The analysis identified onset age ≤2 years, xerosis, spiny lichen, vitamin D insufficiency, vitamin D deficiency, and EOS ≥0.455×10^9/L as significant factors associated with AD severity (**Table 3**).

Development of the AD severity scoring system: Significant variables identified from the logistic regression analysis were assigned weighted scores. The β coefficient of each variable was divided by the smallest β coefficient (1.149), and the resulting values were rounded to the nearest integer to determine the corresponding score for each indicator (**Table 4**). Based on this approach, an AD severity scoring system was successfully developed as follows: onset age ≤2 years (1 point), xerosis (1 point), spiny lichen (1 point), vitamin D insufficiency (1 point), vitamin D deficiency (2 points), and EOS ≥0.455×10^9/L (3 points), yielding a total score ranging from 0 to 9.

Scores were calculated for all patients with AD using the established scoring system, and ROC curves and calibration curves were applied to evaluate its clinical performance. As shown in **Figure 2**, the optimal diagnostic cutoff value of the scoring system was determined to be 3.5

Table 2. Single factor analysis of the training set

	Mild (n = 62)	Moderate-to-severe (n = 103)	Statistic value	P
Sex			0.593[a]	0.441
Male	36 (58.06)	66 (64.08)		
Female	26 (41.94)	37 (35.92)		
Onset age ≤2 years			13.264[a]	<0.001
No	27 (43.55)	18 (17.48)		
Yes	35 (56.45)	85 (82.52)		
Family history of atopy			0.213[a]	0.644
No	33 (53.23)	51 (49.51)		
Yes	29 (46.77)	52 (50.49)		
Comorbid atopic diseases			0.220	0.639
No	39 (62.90)	61 (59.22)		
Yes	23 (37.10)	42 (40.78)		
Xerosis			12.618[a]	<0.001
No	34 (54.84)	28 (27.18)		
Yes	28 (45.16)	75 (72.82)		
Spiny lichen			11.873[a]	<0.001
No	47 (75.81)	50 (48.54)		
Yes	15 (24.19)	53 (51.46)		
IgE			1.079[a]	0.299
Normal	17 (27.42)	21 (20.39)		
Elevated	45 (72.58)	82 (79.61)		
Vitamin A			3.803[a]	0.149
Sufficient	20 (32.26)	49 (47.57)		
Insufficient	26 (41.94)	32 (31.07)		
Deficient	16 (25.81)	22 (21.36)		
Vitamin E			0.552[a]	0.759
Sufficient	33 (53.23)	60 (58.25)		
Insufficient	24 (38.71)	34 (33.01)		
Deficient	5 (8.06)	9 (8.74)		
Vitamin D			14.756[a]	0.001
Sufficient	37 (59.68)	31 (30.10)		
Insufficient	18 (29.03)	44 (42.72)		
Deficient	7 (11.29)	28 (27.18)		
Age, years	7 (5, 9)	6 (4, 8)	-1.612[b]	0.107
EOS, ×10^9/L	0.20 (0.12, 0.32)	0.58 (0.35, 0.78)	-7.093[b]	<0.001
EDN, ng/ml	185.26±43.77	198.59±53.91	-1.647[c]	0.102
Gal10, pg/ml	28.07±7.42	29.24±9.81	-0.813[c]	0.418
IL-4, pg/ml	17.95±6.95	19.38±9.02	-1.067[c]	0.287
IL-13, pg/ml	13.7±4.86	15.35±6.8	-1.671[c]	0.097
IL-31, pg/ml	33.19±8.86	35.1±9.4	-1.292[c]	0.198
IFN-γ, pg/ml	41.9±7.95	38.76±11.5	1.892[c]	0.060

Note: a: the statistical value of the chi-square test; b: the statistical value of the non-parametric test; c: the statistical value of the t test; IgE: immunoglobulin E; EOS: eosinophils; EDN: eosinophil-derived neurotoxin; Gal-10: galectin-10; IL: interleukin; IFN-γ: interferon-γ.

points based on the maximum Youden index. Considering clinical applicability, patients with a total score ≥4 points were classified as having moderate-to-severe AD, whereas those with

Table 3. Logistic regression

Variable	β	S.E.	Wald χ^2	P	OR	95 CI
Onset age ≤2 years	1.149	0.515	4.980	0.026	3.155	1.150-8.652
Xerosis	1.553	0.496	9.825	0.002	4.727	1.790-12.483
Spiny lichen	1.274	0.492	6.717	0.010	3.575	1.364-9.368
Vitamin D insufficiency	1.557	0.529	0.8664	0.003	4.744	1.682-13.376
Vitamin D deficiency	1.817	0.664	7.481	0.006	6.154	1.674-22.630
EOS ≥0.455×10^9/L	3.266	0.565	33.459	<0.001	26.216	8.668-79.292

Note: EOS: eosinophils.

Table 4. Coefficient and score of the evaluation index

Index	β coefficient	β/minimum β	Score
Onset age ≤2 years	1.149	1.000	1
Xerosis	1.553	1.352	1
Spiny lichen	1.274	1.109	1
Vitamin D insufficiency	1.557	1.355	1
Vitamin D deficiency	1.817	1.579	2
EOS ≥0.455×10^9/L	3.266	2.842	3

Note: EOS: eosinophils.

a score <4 points were classified as having mild AD. Among patients classified as having moderate-to-severe AD, an exploratory, descriptive stratification was further performed to improve clinical interpretability. Based on the distribution of total scores within this subgroup, scores of 4-6 were descriptively considered indicative of moderate AD, while scores of 7-9 were descriptively considered indicative of severe AD. The AUC in the training set was 0.902 (95% CI: 0.855-0.949), with a sensitivity of 79.6% and a specificity of 87.1%. The calibration curve demonstrated a mean absolute error of 0.015, indicating good agreement between the predicted AD severity and SCORAD-based classification. These results suggest that the proposed severity scoring system exhibited good calibration and discriminatory ability.

Validation of the AD severity scoring system: The AD severity scoring system was validated using both the internal and external validation cohorts. The distribution of patients stratified by the predefined cutoff across the training, internal validation, and external validation cohorts is summarized in **Table 5**. As shown in **Figure 3**, the AUC was 0.885 (95% CI: 0.812-0.957) in the internal validation cohort, with a sensitivity of 70.5% and a specificity of 92.6%. In the external validation cohort, the AUC was 0.824 (95% CI: 0.700-0.948), with a sensitivity of 69.6% and a specificity of 89.5%. Calibration curves for both validation cohorts demonstrated good agreement between the predicted AD severity and SCORAD-based classification, indicating that the scoring system maintains stable predictive performance and good calibration across different datasets.

Clinical efficacy of dupilumab in children with moderate-to-severe AD

Baseline characteristics: From January 2023 to January 2025, a total of 147 children with moderate-to-severe AD who met the inclusion and exclusion criteria received at least one injection of dupilumab. Among them, 93 were male (63.27%) and 54 were female (36.73%), with a median age of 6 years (interquartile range: 4-8 years). 82 patients (55.79%) had a family history of allergy, and 63 patients (42.86%) had comorbid atopic diseases.

Prior to dupilumab initiation, all patients had received at least 3 months of conventional therapy, including topical corticosteroids and antihistamines, with inadequate clinical response. During dupilumab treatment, all patients concomitantly used emollients for skin care. During the 16-week follow-up period, some patients discontinued treatment or were lost to follow-up due to time constraints and financial burden. Of the 147 enrolled patients, 116, 94, and 89 patients completed treatment at weeks 4, 12, and 16, respectively.

Changes in clinical scores after treatment: At weeks 4, 12, and 16 after treatment initiation,

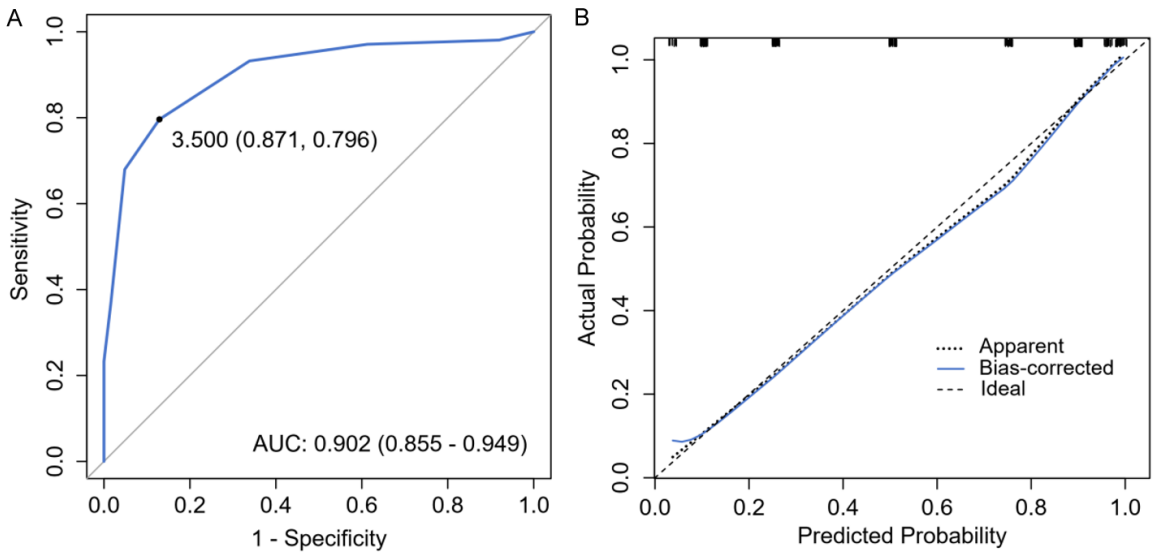

Figure 2. ROC curve and calibration plot for the training set. A: ROC curve; B: calibration plot.

Table 5. Distribution of patients by the AD severity scoring system and SCORAD classification across cohorts

Dataset	Score ≥4 (n)	Score <4 (n)	Moderate-to-severe by SCORAD (n)	Mild by SCORAD (n)	PPV (%)	NPV (%)	Accuracy (%)
Training set (n = 165)	90	75	103	62	91.1%	72.0%	82.4%
Internal validation set (n = 71)	33	38	44	27	93.9%	65.8%	78.9%
External validation set (n = 42)	18	24	23	19	88.9%	70.8%	78.6%

Note: PPV: positive predictive value; NPV: negative predictive value.

EASI, SCORAD, and PP-NRS scores were significantly improved compared with baseline values (all P<0.008). In addition, all scores at weeks 4, 12, and 16 were significantly lower than those at the preceding time point (all P< 0.008). The changes in clinical scores before and after treatment are summarized in **Table 6**.

The proportions of patients achieving EASI50, EASI75, EASI90, and a PP-NRS reduction ≥4 points at weeks 4, 12, and 16 are shown in **Figure 4**. Compared to week 4, the proportions of patients achieving EASI50, EASI75, EASI90, and a PP-NRS reduction ≥4 points at weeks 12 and 16 were significantly higher (all P<0.017).

Changes in laboratory parameters after treatment: After dupilumab treatment, there was no significant change in EOS counts compared to baseline. However, serum IgE levels at week 16 were significantly reduced compared to pre-treatment levels (P<0.008) (**Figure 5**).

Adverse events: During the 16-week treatment and follow-up period, a total of 10 patients (6.80%) experienced adverse events. Among them, 6 patients (4.08%) discontinued dupilumab treatment due to worsening of skin lesions and pruritus. Injection-site reactions, including swelling and mild pruritus, were observed in 3 patients (2.04%); all cases resolved after topical corticosteroid treatment without treatment discontinuation. In addition, 1 patient (0.68%) developed mild conjunctivitis during treatment, which improved after topical ophthalmic therapy, allowing continuation of dupilumab treatment.

Discussion

Current national and international guidelines recommend a stepwise treatment strategy for AD based on disease severity, and accurate assessment of severity is essential for developing individualized treatment plans. In the present study, we quantified routinely collected

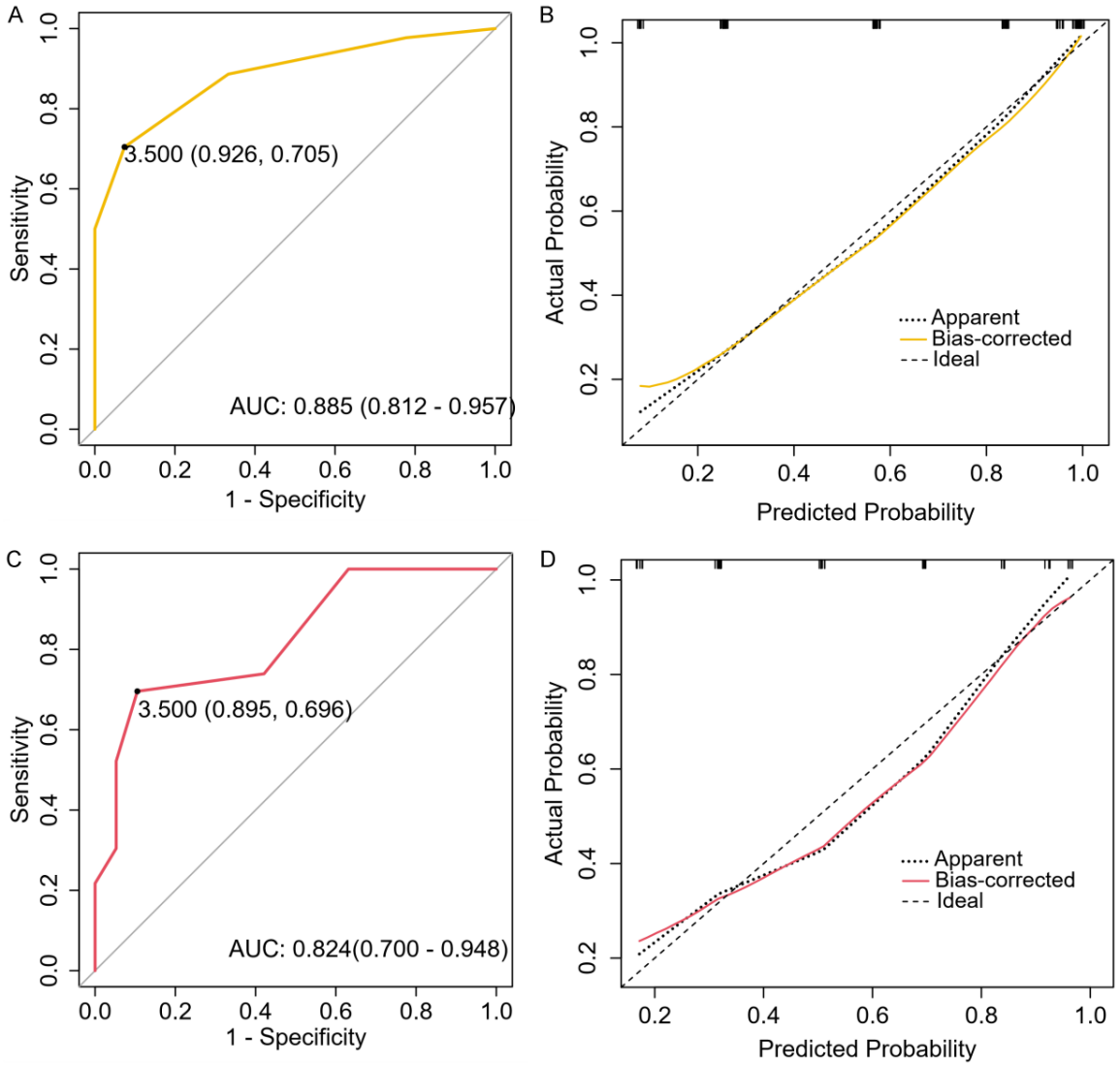

Figure 3. ROC curve and calibration plot for the validation set. A: The ROC curve for the internal validation set; B: The calibration plot for the internal validation set; C: ROC curve for the external validation set; D: calibration plot for the external validation set.

Table 6. Changes in clinical scores across treatment timepoints

Clinical score	Baseline (n = 147)	Week 4 (n = 116)	Week 12 (n = 94)	Week 16 (n = 89)	Wald χ^2	P
EASI	20 (11, 28)	10 (6, 15)[a,b]	5 (3, 9)[a,b]	3 (2, 6)[a,b]	122.969	<0.001
SCORAD	44 (34, 53)	28 (20, 37)[a,b]	21 (14, 30)[a,b]	16 (8, 25)[a,b]	121.017	<0.001
PP-NRS	7 (6, 9)	5 (4, 6)[a,b]	3 (2, 4)[a,b]	2 (1, 3)[a,b]	171.898	<0.001

Note: EASI: eczema area and severity index; SCORAD: scoring atopic dermatitis; PP-NRS: peak pruritus numerical rating scale; a: vs. baseline; b: vs. previous timepoint; Bonferroni-adjusted P<0.008.

clinical data to identify factors associated with disease severity in children with AD and subsequently developed a simple and practical severity scoring system.

This scoring system comprises six readily available clinical indicators: onset age ≤2 years (1 point), xerosis (1 point), spiny lichen (1 point), vitamin D insufficiency (1 point), vitamin D defi-

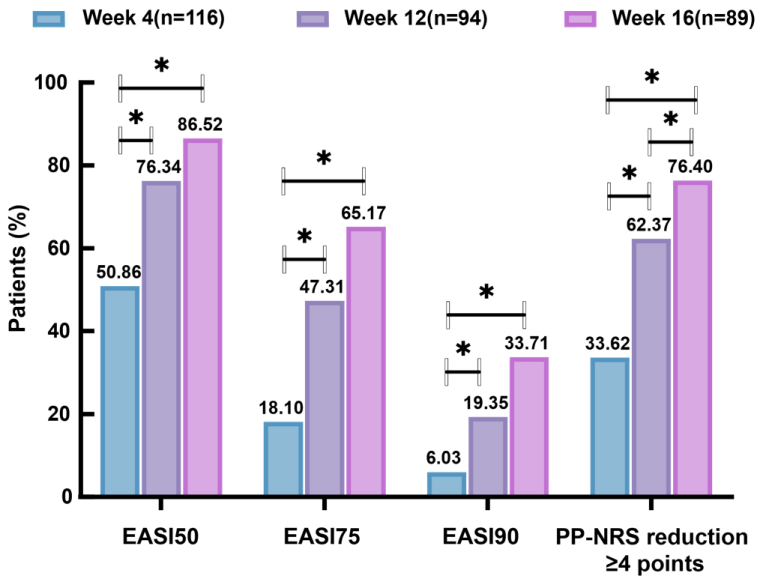

Figure 4. Comparison of efficacy endpoint achievement across time points. Note: EASI50, EASI75, EASI90: a ≥50%, ≥75%, or ≥90% reduction in the eczema area and severity index; PP-NRS: peak pruritus numerical rating scale. Bonferroni-adjusted significance levels: *P<0.017.

ciency (2 points), and eosinophil count ≥0.455×10^9/L (3 points), yielding a total score ranging from 0 to 9. Using the optimal cutoff value determined by the maximum Youden index (≥4 points), the system enables rapid stratification of pediatric patients into mild and moderate-to-severe AD. Validation analyses demonstrated stable discriminatory performance across cohorts, with an AUC of 0.885 in the internal validation cohort and 0.824 in the external validation cohort. In addition, calibration analyses showed good agreement between predicted severity and SCORAD-based classification, supporting the reliability of the scoring system for clinical severity grading. However, the present scoring system was developed using a binary outcome (mild vs moderate-to-severe AD) based on logistic regression. The cutoff score of ≥4 points was intended to distinguish mild from moderate-to-severe disease. Further subdivision of disease severity would require a multiclass modeling framework and larger sample sizes and therefore warrants investigation in future studies.

Several validated instruments are available for assessing AD severity, including SCORAD and EASI, which are widely used in clinical trials. However, these tools involve relatively complex calculations and detailed lesion assessments, limiting their feasibility in routine clinical practice, particularly in primary care settings. In addition, accurate evaluation of erythema and lesions located on socially sensitive areas may be challenging in certain populations, potentially affecting severity classification [13, 14]. Patient-reported outcome measures require dedicated questionnaires and may not be routinely available in resource-limited setting. In contrast, the proposed scoring system is based entirely on objective clinical findings and routinely collected laboratory values. Rather than replacing established instruments, it is intended to complement existing severity assessments by providing a simple and rapid method for initial severity stratification in real-world clinical practice.

Our findings indicate that children with disease onset at ≤2 years of age tend to have more severe AD. This result is consistent with the findings reported by Holm et al. [15]. During early childhood, the skin barrier is not yet fully mature, allowing allergens and microorganisms to penetrate more easily into the deeper layers of the skin. Moreover, the immune system in young children is still undergoing rapid development, with immature regulatory T-cell function, which may amplify inflammatory responses and accelerate disease progression [16].

Xerosis and spiny lichen are common clinical phenotypes of AD. The filaggrin (FLG) gene mutation c.3321delA is the most prevalent FLG mutation in the Chinese population, present in approximately 15% of patients with AD, and is strongly associated with a dry skin phenotype [17]. As one manifestation of this phenotype, xerosis is widely regarded as a clinical expression of FLG deficiency. Spiny lichen is a chronic disorder of follicular keratinization, and FLG mutations have been detected in approximately 35% of affected individuals [18]. Epidemiological studies have shown that Spiny lichen is not only associated with the presence of AD but also closely related to disease severity [19].

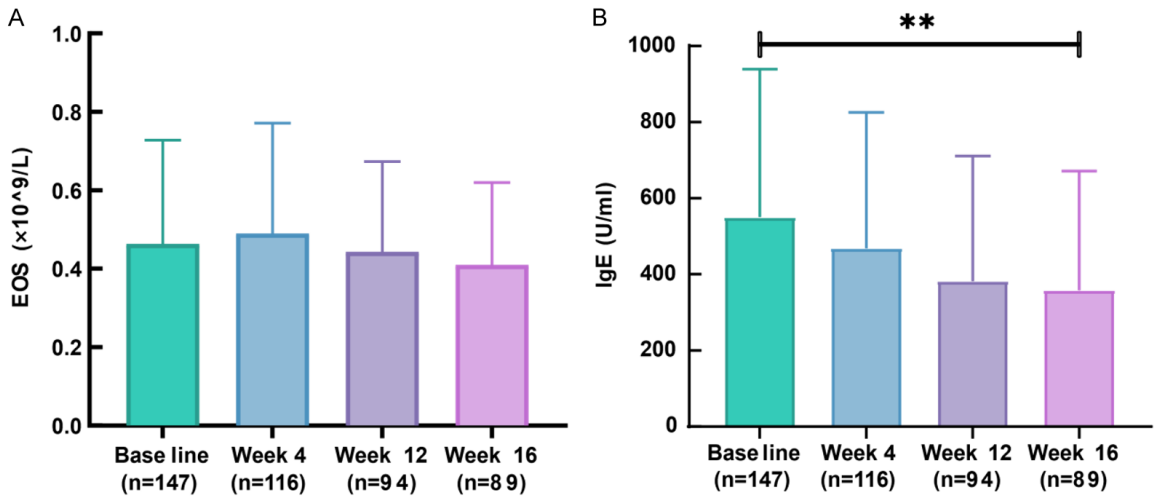

Figure 5. Changes in laboratory values across treatment timepoints. A: EOS; B: IgE. Note: EOS: eosinophils; IgE: immunoglobulin E; Bonferroni-adjusted significance levels: **P<0.008.

Vitamin D, as a key immuno-barrier regulatory factor, plays a central role in keratinocyte differentiation, antimicrobial peptide synthesis, and the expression of structural proteins [20]. Vitamin D insufficiency may compromise skin barrier integrity, disrupt cutaneous microecological homeostasis, and increase susceptibility to exaggerated inflammatory responses. Previous studies have demonstrated that serum vitamin D levels are significantly lower in children with AD than in healthy controls and are inversely correlated with disease severity [21]. Consistently, our findings showed that the rate of vitamin D insufficiency or deficiency was markedly higher among children with moderate-to-severe AD compared to those with mild disease.

Eosinophils (EOS), as components of the innate immune system, participate in host defense by producing and releasing chemokines and other immunomodulatory mediators [22]. AD is characterized predominantly by a Th2-skewed immune response, in which eosinophils are recruited and activated under the influence of Th2-associated cytokines, subsequently releasing pro-inflammatory mediators that perpetuate and amplify cutaneous inflammation [23]. Elevated eosinophil levels therefore indicate a greater inflammatory burden and are commonly associated with increased disease severity.

This study further evaluated the therapeutic efficacy of dupilumab in children with moderate-to-severe AD and demonstrated favorable clinical effectiveness. Following treatment, all clinical severity scores showed significant reductions, which is consistent with findings from previous clinical trials [24]. Notably, significant improvements were already observed at week 4, and a progressive enhancement in treatment response was evident from week 4 to week 16. This pattern suggests a time-dependent and cumulative therapeutic effect, with sustained benefits achieved through continued treatment. At week 16, the proportions of patients achieving EASI50, EASI75, and EASI90 were 86.52%, 65.17%, and 33.71%, respectively, indicating substantial improvement in skin lesions. Pruritus control was also satisfactory, with 76.40% of patients achieving a reduction of ≥4 points in PP-NRS. A multicenter study from Italy reported that 74.54% of children aged 6–11 years achieved EASI75 after 16 weeks of dupilumab treatment [25]. Similarly, a phase III randomized controlled trial demonstrated that, at week 16, 91.0%, 41.8%, and 50.8% of patients receiving dupilumab plus topical corticosteroids achieved EASI50, EASI90, and PP-NRS reduction ≥4 points, respectively [26]. Overall, the efficacy outcomes observed in the present study were comparable to those reported in previous real-world studies and clinical trials.

Analysis of laboratory values showed that EOS levels did not change significantly over time, despite a non-significant transient increase at week 4 followed by a gradual decline. Serum

IgE levels were significantly lower than baseline at week 16. Similar patterns of EOS and IgE changes have been reported by Paller et al. [27] in children aged 6 months to 5 years with moderate-to-severe AD. Consistently, the phase III LIBERTY AD PRESCHOOL trial demonstrated that dupilumab combined with topical corticosteroids could induce a temporary elevation in circulating EOS counts, without being associated with clinical deterioration or an increased incidence of safety events [28]. This phenomenon may be explained by the pharmacologic mechanism of dupilumab. By blocking IL-4 and IL-13 signaling, dupilumab inhibits eosinophil chemotaxis and the expression of vascular cell adhesion molecule-1 (VCAM-1), thereby reducing eosinophil migration from the circulation into peripheral tissues. However, dupilumab does not suppress eosinophil production or release from the bone marrow, which may result in a transient accumulation of eosinophils in the peripheral blood during the early phase of treatment [29, 30].

In our study, dupilumab was generally well-tolerated. Six patients (4.08%) discontinued dupilumab treatment due to worsening skin lesions and pruritus, while only one patient (0.68%) developed mild conjunctivitis, which resolved after symptomatic treatment. Previous studies have reported a wide range of conjunctivitis incidence associated with dupilumab, varying from 0.8% to 21% [31, 32]. A longer disease duration and facial involvement of AD have been identified as risk factors for the development of conjunctivitis during dupilumab therapy [33]. The relatively low incidence of conjunctivitis observed in our cohort may be attributable to differences in ethnicity and age, as well as the early implementation of preventive and therapeutic interventions.

This study has several limitations. First, as a single-center retrospective study, the sample size was relatively limited, and the number of included variables was constrained, which may have introduced selection bias. Therefore, the proposed severity scoring system requires further validation in multicenter studies with larger and more diverse populations. Second, due to suboptimal treatment adherence among pediatric patients, some follow-up data on dupilumab efficacy were missing. In addition, the follow-up duration was limited to 16 weeks, and further studies with longer observation periods are warranted to evaluate the long-term efficacy and safety of dupilumab.

Conclusion

This study developed and preliminarily validated a simple and practical severity scoring system for pediatric atopic dermatitis based on routinely available clinical indicators, which may serve as a useful tool for clinical risk stratification. In addition, the findings suggest that dupilumab demonstrates favorable clinical efficacy and an acceptable safety profile in children with moderate-to-severe atopic dermatitis, with outcomes generally consistent with those reported in previous studies.

Disclosure of conflict of interest

None.

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