

Original Article

Early clinical and biologic predictors of dupilumab response in pediatric moderate-to-severe atopic dermatitis

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Abstract: Aims: To identify early clinical, inflammatory, and skin barrier-related predictors of dupilumab response in pediatric patients with moderate-to-severe atopic dermatitis, and to develop a practical early prediction model to stratify short-term therapeutic outcomes, thereby facilitating individualized treatment optimization in routine clinical practice. Methods: In this retrospective cohort study, we enrolled 300 consecutive pediatric patients with moderate-to-severe atopic dermatitis who initiated dupilumab at the Children's Hospital, Zhejiang University School of Medicine, between January 2024 and December 2025. Patients were classified as non-responders ($n = 156$) or responders ($n = 144$) according to predefined response criteria during follow-up. The primary outcome was early rapid response by week 16. Baseline demographic, clinical, inflammatory, and skin barrier variables were collected, together with dynamic changes at weeks 2 and 4. Multivariable logistic regression was used to identify independent predictors and construct an Early Clinical-Biologic Prediction Score (CEPS) model. The model's discrimination, subgroup performance, longitudinal interactions, and week-16 risk-stratified outcomes were evaluated. Results: Responders had significantly lower baseline disease severity, inflammatory burden, and barrier dysfunction, with lower Eczema Area and Severity Index (EASI) score, SCORing Atopic Dermatitis (SCORAD), pruritus and sleep-loss Numerical Rating Scale (NRS), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), eosinophil count, and LDH (all $P \leq 0.001$). These between-group differences widened over time, as responders showed substantially greater improvement by weeks 2 and 4 across all major clinical and biomarker measures (all $P < 0.001$). By multivariable analysis, the CEPS model showed stable discrimination across prespecified subgroups (AUC range, 0.84-0.89). CEPS-based stratification further identified a clear gradient in week-16 outcomes, including EASI-75/EASI-90 achievement, symptom improvement, barrier recovery, and lower rescue treatment use, unscheduled visits, and treatment intensification (all $P < 0.001$). Conclusion: Early clinical, inflammatory, and skin barrier changes after dupilumab initiation provide robust prediction of subsequent treatment response in moderate-to-severe atopic dermatitis.

Keywords: Atopic dermatitis, dupilumab, moderate-to-severe disease, treatment response, early predictors

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disorder characterized by intense pruritus, recurrent eczematous lesions, sleep disturbance, and substantial impairment in quality of life [1, 2]. In patients with moderate-to-severe disease, the burden extends well beyond the skin, including considerable psy-

chological distress, social dysfunction, and increased healthcare use [3-5]. Although the clinical phenotype of AD is well recognized, marked interindividual variability exists in disease severity, disease course, and treatment response. This heterogeneity poses a major challenge in the management of moderate-to-severe AD, since persistent uncontrolled inflammation may result in sustained symptoms,

cumulative morbidity, and uncertainty in therapeutic decision-making. Therefore, identifying factors that may facilitate more personalized treatment strategies remains an important unmet clinical need.

Advances in the understanding of AD pathobiology have established type 2 immune dysregulation, particularly involving the interleukin (IL)-4 and IL-13 pathways, as a central driver of disease activity [6-9]. Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor alpha subunit and thereby blocking both IL-4 and IL-13 signaling, has substantially changed the treatment landscape for moderate-to-severe AD [10, 11]. Randomized clinical trials and observational studies have consistently demonstrated that dupilumab improves objective disease severity, pruritus, sleep disturbance, and patient-reported outcomes [12, 13], while maintaining a favorable safety profile. However, despite its overall efficacy, treatment response in clinical practice remains variable and not readily predictable. Some patients achieve rapid and durable disease control, whereas others show slower improvement, partial response, or limited benefit. This variability has important implications for treatment optimization, patient counseling, and the rational use of biologic therapy.

Accordingly, considerable effort has been devoted to identifying predictors of dupilumab response in AD. Candidate markers have included baseline clinical characteristics, disease duration, serum immunoglobulin E, blood eosinophil count, lactate dehydrogenase, and other inflammatory indicators [14-16], but the findings have been inconsistent and their clinical applicability remains limited. One important reason is that most proposed predictors are static pretreatment variables with insufficient discriminatory ability or laboratory values with limited reproducibility across different populations. By contrast, early-on treatment changes may more directly reflect biological sensitivity to dupilumab and may therefore predict subsequent therapeutic outcome better. In the context of precision medicine, the ability to identify likely responders or nonresponders early in the treatment course could facilitate timely adjustment of therapy and improve long-term disease control.

Therefore, there is a clear need to establish practical and clinically translatable early indicators of dupilumab response in pediatric patients with moderate-to-severe AD. In the present study, we aimed to identify early predictive factors associated with dupilumab response through a comprehensive evaluation of baseline characteristics together with early clinical, inflammatory, and skin barrier-related changes after treatment initiation. Our goal was to provide evidence for a more individualized therapeutic approach and to improve early clinical decision-making by clarifying the relationship between these early indicators and subsequent treatment outcome.

Materials and methods

Case selection

This retrospective cohort study was conducted at the Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China, and included consecutive pediatric patients with moderate-to-severe atopic dermatitis (AD) who initiated dupilumab treatment between January 2024 and December 2025. Potentially eligible cases were identified through the institutional electronic medical record system. Patients were included if they were younger than 18 years at the initiation of dupilumab therapy, had a diagnosis of AD confirmed by experienced dermatologists according to standard diagnostic criteria, had moderate-to-severe disease at baseline based on routine clinical assessment, and had complete baseline demographic, clinical, and laboratory data together with sufficient follow-up for efficacy evaluation. Patients were excluded if they had missing key baseline data, inadequate follow-up for treatment assessment, an inconclusive diagnosis, significant comorbid chronic inflammatory, immunologic, allergic, or dermatologic disorders that could confound the evaluation of disease severity or treatment response, or had poor adherence/non-compliance with follow-up, which precluded reliable outcome determination. A total of 300 patients met the eligibility criteria and were included in the final analysis. The primary outcome of this study was week-16 treatment response, defined as achievement of $\geq 75\%$ improvement in Eczema Area and Severity Index (EASI) score (EASI-75) or equivalent predefined clinical response crite-

ria. Based on this endpoint, patients were classified into a non-responder group ($n = 156$) and a responder group ($n = 144$) (**Figures 1 and 2**). Subsequently, to characterize further the heterogeneity in response kinetics, patients in the responder group were additionally stratified into early rapid responders and delayed responders according to early treatment dynamics, defined by the magnitude of improvement in disease severity at week 2 and sustained response patterns during follow-up. The study protocol was approved by the institutional ethics committee of the Children's Hospital, Zhejiang University School of Medicine, and the requirement for informed consent was waived because of the retrospective nature of the study and the use of de-identified data.

Data collection

Systematic data collection on the institutional electronic medical record system was used to extract baseline and early follow-up data on a standardized data collection form. Variables that were recorded at initiation of treatment included the same key clinical/biologic variables that were again measured at weeks 2 and 4 following the initiation of dupilumab, and absolute/relative changes in prespecified predictors of early treatment dynamics, such as changes in the SCORing Atopic Dermatitis (SCORAD), pruritus and sleep-loss NRS, Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), pruritus NRS reduction, and sleep-loss NRS reduction. Furthermore, the week-16 outcome data were measured to assess the treatment response and risk stratification measured by the Early Clinical-Biologic Prediction Score (CEPS) model, reduction in EASI, EASI-75/EASI-90 score, SCORAD improvement, pruritus and sleep-loss, enhancement of DLQI, reduced POEM, and the use of topical corticosteroids. Data were reviewed by at least two investigators and entry discrepancies or missing entries checked against original medical records prior to data analysis.

Outcome measure

The primary outcome of this study was treatment response to dupilumab at week 16. Based on predefined response criteria that were

applied consistently throughout follow-up, all enrolled patients were first classified into two groups: responders and non-responders. To further characterize response kinetics among those who achieved treatment response, the responder group was subsequently subdivided into early rapid responders and delayed responders according to prespecified early improvement patterns observed during follow-up. This hierarchical classification strategy was used for predictor analyses aimed at identifying factors associated not only with overall treatment response, but also with the timing and pace of response among responders. In addition to this response classification, we evaluated clinically meaningful outcomes across several domains. Secondary outcomes included: (1) early temporal changes in disease severity, symptom burden, and inflammatory activity at weeks 2 and 4, assessed using EASI, SCORAD, peak pruritus NRS, sleep-loss NRS, POEM, DLQI, absolute eosinophil count, and serum LDH; (2) baseline skin barrier and epidermal function parameters, including stratum corneum hydration, skin surface pH, xerosis, excoriation, lichenification, night-time awakening frequency, and rescue topical corticosteroid use; and (3) development and assessment of an early prediction model (CEPS) for identifying early rapid responders, including evaluation of model discrimination, subgroup performance, and longitudinal responder-time interactions. Week-16 clinical outcomes and healthcare utilization were also assessed according to CEPS-based risk stratification, including percentage reductions in EASI and SCORAD, achievement of EASI-75 and EASI-90, meaningful symptom improvement, POEM reduction, decreased need for rescue topical corticosteroids, fewer unscheduled dermatology visits, and lower rates of treatment intensification or switching.

Statistical analysis

All statistical analyses were conducted to identify predictors of dupilumab response at baseline and during early treatment, and to evaluate the performance of the CEPS. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range), and categorical variables as number (percentage). Comparisons between responders and non-responders were performed using indepen-

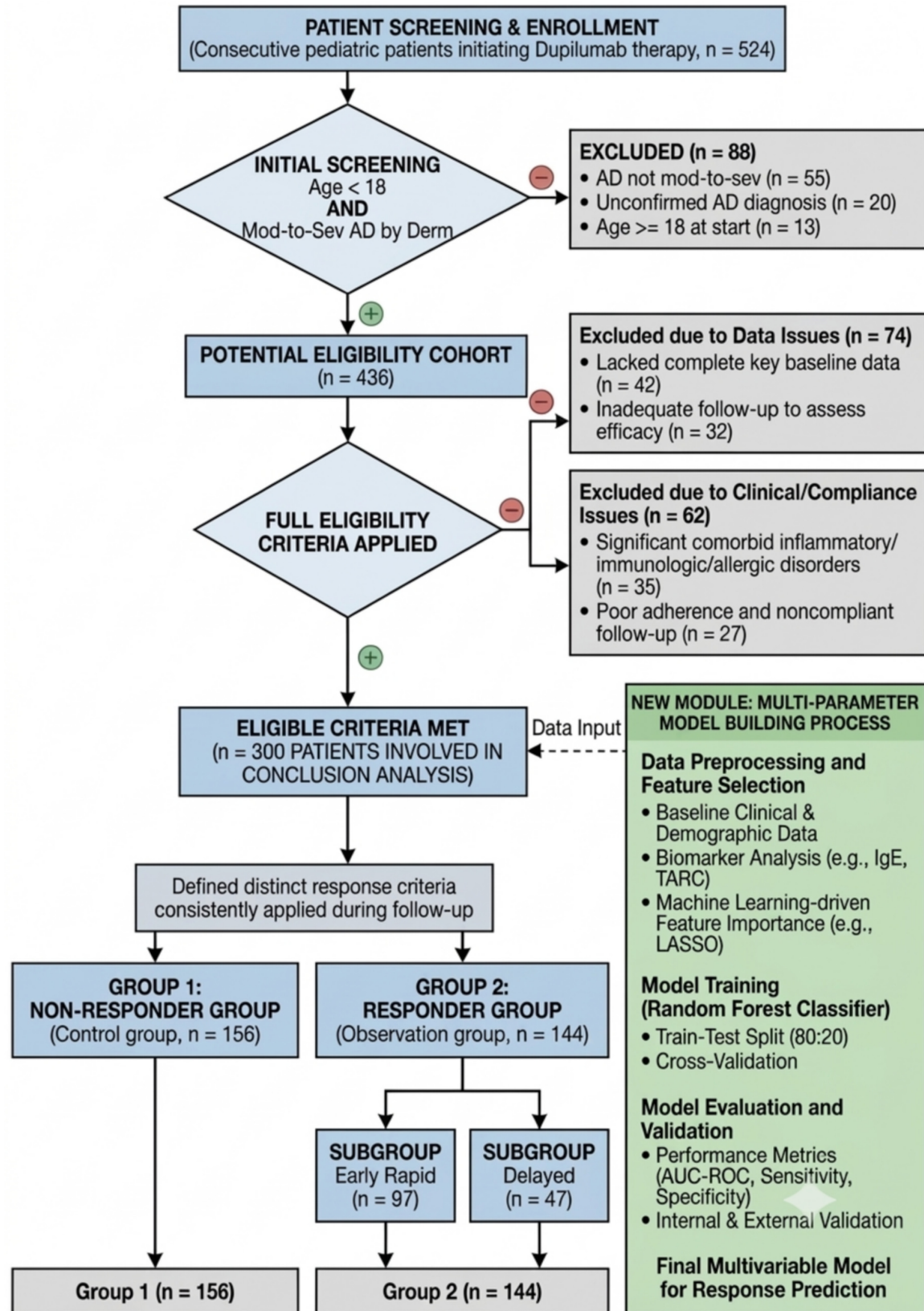


Figure 1. Flow chart of patient selection and grouping. Note: AD, Atopic Dermatitis; IgE, Immunoglobulin E; TARC, Thymus and Activation-Regulated Chemokine; CCL17, Chemokine (C-C motif) Ligand 17.

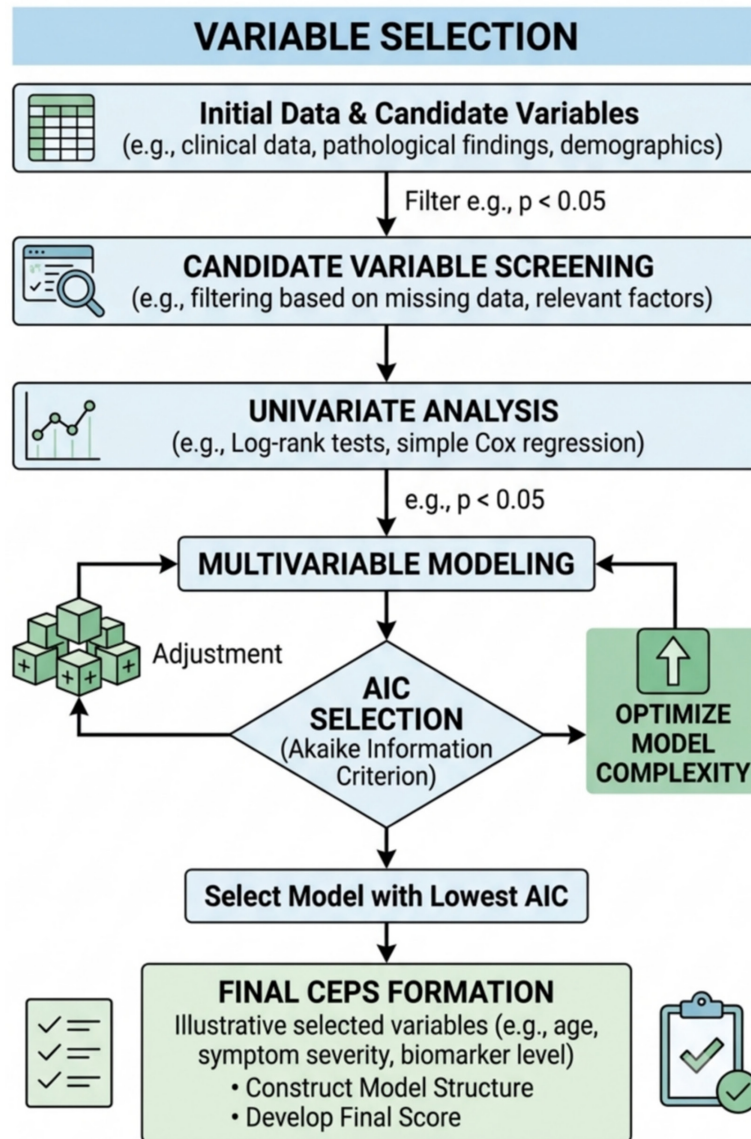


Figure 2. Flowchart of CEPS model construction. Note: CEPS, Early Clinical-Biologic Prediction Score; AIC, Akaike Information Criterion.

Information Criterion (AIC) to identify independent predictors, with effect estimates reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The final model informed the CEPS, whose discriminative performance was evaluated using receiver operating characteristic (ROC) curves and the area under the curve (AUC). To reduce potential optimism arising from model development and evaluation within the same cohort, internal validation was additionally performed using bootstrap resampling (1,000 repetitions) to estimate the optimism-corrected discriminative performance of the model. Calibration of the final model was also assessed using calibration plots and the Hosmer-Lemeshow goodness-of-fit test. Subgroup analyses were conducted across clinically relevant strata to assess model stability, and the CEPS-based risk stratification categorized patients into low-, middle-, and high-probability groups for comparison of week-16 clinical, patient-reported, biomarker, and healthcare utilization outcomes. All tests were two-sided, and a P value <0.05 was considered significant.

dent-samples t tests or Mann-Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. Repeated measures at baseline and weeks 2 and 4 were analyzed using linear mixed-effects models to assess the fixed effects of time, responder group, and time $\times$ group interactions for key clinical, biomarker, and barrier-related outcomes. For model construction, univariate analyses were first conducted to screen candidate predictors associated with week-16 response. Subsequently, a multivariable logistic regression model was built using a step-wise selection approach based on the Akaike

Results

Baseline demographic and general clinical characteristics

The two groups were well-balanced in terms of age, sex, family history of atopy, and smoking history (all $P>0.05$). However, compared to responders, non-responders had a significantly higher BMI-for-age z score ($P<0.001$), longer disease duration ($P = 0.036$), and earlier age at disease onset ($P = 0.001$). In addition, prior systemic immunosuppressant exposure ($P = 0.010$) and prior phototherapy ($P = 0.024$) were

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Table 1. Baseline demographic and general clinical characteristics

Variable	Non-responders (n = 156)	Responders (n = 144)	Statistic	P value
Age, years	10.20 ± 3.24	10.65 ± 2.82	t = 1.289	0.198
Male sex, n (%)	92 (59.0)	81 (56.3)	$\chi^2 = 0.228$	0.633
BMI-for-age z score	0.68 ± 0.08	0.54 ± 0.21	t = 8.133	<0.001
Disease duration, years	12.73 ± 4.14	11.68 ± 4.52	t = 2.101	0.036
Age at AD onset, years	11.79 ± 4.76	13.78 ± 3.55	t = -3.253	0.001
Family history of atopy, n (%)	69 (44.2)	78 (54.2)	$\chi^2 = 2.958$	0.085
Prior systemic immunosuppressant exposure, n (%)	101 (64.7)	72 (50.0)	$\chi^2 = 6.668$	0.010
Prior phototherapy, n (%)	48 (30.8)	28 (19.4)	$\chi^2 = 5.077$	0.024
Concomitant allergic rhinitis, n (%)	73 (46.8)	84 (58.3)	$\chi^2 = 3.996$	0.046
Concomitant asthma, n (%)	39 (25.0)	51 (35.4)	$\chi^2 = 3.869$	0.049
Smoking history, n (%)	41 (26.3)	27 (18.8)	$\chi^2 = 2.423$	0.120

more frequent in non-responders. By contrast, concomitant allergic rhinitis ($P = 0.046$) and asthma ($P = 0.049$) were more common among responders (**Table 1**).

Early temporal trajectories of clinical scores and biomarkers

At baseline, responders already showed lower disease severity and inflammatory burden, with significant between-group differences in EASI, SCORAD, peak pruritus NRS, sleep-loss NRS, POEM, DLQI, absolute eosinophil count, and LDH (all $P < 0.001$). These differences became more pronounced during follow-up. By week 2, responders exhibited substantially greater improvement in objective disease severity, patient-reported symptoms, and quality-of-life impairment, whereas non-responders showed only modest early changes (all $P < 0.001$). This divergence was sustained and further amplified by week 4, when responders demonstrated consistently steeper reductions across all clinical scores and biomarker measures than non-responders (all $P < 0.001$) (**Table 2**).

Early temporal trajectories of skin barrier and symptom-related scores

Non-responders exhibited persistently worse skin barrier function and greater symptom burden than responders during early follow-up. In particular, stratum corneum hydration remained significantly lower, whereas skin surface pH remained significantly higher, in non-responders at baseline, week 2, and week 4 (all $P < 0.01$). In parallel, non-responders consistently showed higher xerosis, excoriation, and

lichenification scores, more frequent night-time awakening, and greater rescue topical corticosteroid use than responders at all evaluated time points (all $P < 0.01$). Moreover, these between-group differences widened over time, suggesting that responders achieved earlier and more substantial improvement in both barrier recovery and symptom control following dupilumab treatment (**Table 3**).

Univariate analysis of baseline and early (week 2/4) predictors of early rapid versus delayed week 16 response

Among the 144 patients who were classified as responders according to the predefined week-16 response criteria, 97 were further categorized as early rapid responders and 47 as delayed responders based on their early treatment kinetics. In this subgroup analysis, early rapid responders had lower BMI-for-age z scores, shorter disease duration, less prior systemic immunosuppressant exposure, and less prior phototherapy than delayed responders (all $P \leq 0.05$). They also exhibited lower baseline disease severity and symptom burden, as reflected by lower EASI, SCORAD, peak pruritus Numerical Rating Scale (NRS), sleep-loss NRS, POEM, and DLQI scores (all $P \leq 0.05$). In addition, early rapid responders showed a less pronounced inflammatory and barrier-disruption phenotype, with lower eosinophil counts and LDH levels but higher stratum corneum hydration at baseline (all $P \leq 0.005$). By contrast, age, sex, allergic rhinitis, and asthma were not significantly associated with response kinetics (all $P > 0.05$), although age at onset and asthma

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Table 2. Early temporal trajectories of clinical scores and biomarkers

Variable	Time point	Non-responders (n = 156)	Responders (n = 144)	P value
EASI score	Week 0	29.29 ± 7.93	25.24 ± 7.82	<0.001
	Week 2	26.13 ± 7.85	20.66 ± 5.88	<0.001
	Week 4	24.37 ± 7.06	17.10 ± 3.89	<0.001
SCORAD score	Week 0	69.97 ± 12.38	62.38 ± 10.31	<0.001
	Week 2	60.28 ± 10.20	47.38 ± 10.43	<0.001
	Week 4	54.19 ± 10.28	39.10 ± 10.26	<0.001
Peak pruritus NRS	Week 0	8.83 ± 1.25	8.08 ± 1.13	<0.001
	Week 2	7.88 ± 1.47	6.97 ± 1.34	<0.001
	Week 4	7.43 ± 1.79	6.62 ± 1.56	<0.001
Sleep-loss NRS	Week 0	7.37 ± 1.70	6.70 ± 1.41	<0.001
	Week 2	6.94 ± 1.68	5.48 ± 0.95	<0.001
	Week 4	6.24 ± 1.42	5.21 ± 0.60	<0.001
POEM score	Week 0	23.13 ± 4.36	20.88 ± 4.08	<0.001
	Week 2	20.67 ± 3.84	16.83 ± 2.57	<0.001
	Week 4	18.22 ± 4.69	11.81 ± 4.78	<0.001
DLQI score	Week 0	18.15 ± 4.30	16.28 ± 4.81	<0.001
	Week 2	16.25 ± 4.44	11.60 ± 4.78	<0.001
	Week 4	14.74 ± 4.40	8.99 ± 3.66	<0.001
Absolute eosinophil count, ×10 ⁹ /L	Week 0	0.76 ± 0.49	0.51 ± 0.54	<0.001
	Week 2	0.88 ± 0.49	0.59 ± 0.51	<0.001
	Week 4	0.85 ± 0.50	0.59 ± 0.51	<0.001
LDH, U/L	Week 0	289.74 ± 66.02	235.73 ± 50.87	<0.001
	Week 2	265.19 ± 64.16	222.57 ± 47.15	<0.001
	Week 4	275.75 ± 61.17	206.65 ± 41.62	<0.001

Note: EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; LDH, lactate dehydrogenase.

showed borderline significance. More importantly, early-on treatment changes provided the strongest discrimination. Greater improvements in week-2 EASI, SCORAD, pruritus, sleep loss, POEM, and DLQI, as well as larger week-4 reductions in EASI and LDH and greater recovery of stratum corneum hydration, were all significantly associated with an early rapid response phenotype (all $P < 0.001$) (**Table 4**).

Multivariate logistic regression model for early prediction

For transparency of model development, all variables identified in univariate analyses (**Table 4**), including demographic characteristics, baseline clinical severity measures, inflammatory biomarkers (eosinophil count and LDH), skin barrier measures, and early treatment dynamic changes, were initially considered for multivariable modeling. A stepwise multivariable logistic regression based on the

Akaike Information Criterion (AIC) was then applied to derive the most parsimonious predictive model. During this process, although LDH and eosinophil count were significantly associated with early rapid response in univariate analyses, they were not retained in the final model because their predictive effects were substantially attenuated after inclusion of early treatment dynamic variables and they did not provide additional independent predictive information. Multicollinearity assessment further suggested overlap between these inflammatory markers and early clinical improvement measures, particularly week-2 Δ EASI and pruritus NRS reduction, indicating shared information reflecting underlying disease activity and treatment responsiveness. Consequently, the final CEPS model retained baseline stratum corneum hydration and key early dynamic predictors, including week-2 Δ EASI (adjusted OR: 0.821, $P < 0.001$; per 10% greater reduction from baseline) and week-2 pruritus

Table 3. Skin barrier and symptom-related indicators

Variable	Time point	Non-responders (n = 156)	Responders (n = 144)	P value
Stratum corneum hydration, AU	Week 0	21.51 ± 7.19	27.94 ± 7.59	<0.001
	Week 2	22.45 ± 8.02	29.13 ± 7.18	<0.001
	Week 4	24.19 ± 7.58	34.86 ± 7.38	<0.001
Skin surface pH	Week 0	6.15 ± 0.44	5.57 ± 0.45	<0.001
	Week 2	6.01 ± 0.40	5.66 ± 0.41	<0.001
	Week 4	6.03 ± 0.38	5.23 ± 0.37	<0.001
Xerosis severity score	Week 0	3.14 ± 0.55	2.38 ± 0.61	0.006
	Week 2	2.53 ± 0.70	1.79 ± 0.67	0.001
	Week 4	2.29 ± 0.73	1.36 ± 0.59	0.029
Excoriation score	Week 0	2.52 ± 0.68	2.03 ± 0.65	<0.001
	Week 2	2.30 ± 0.68	1.40 ± 0.63	<0.001
	Week 4	1.99 ± 0.71	1.26 ± 0.63	<0.001
Lichenification score	Week 0	3.14 ± 0.55	2.38 ± 0.61	<0.001
	Week 2	2.53 ± 0.70	1.79 ± 0.67	<0.001
	Week 4	2.29 ± 0.73	1.36 ± 0.59	<0.001
Night-time awakening frequency/week	Week 0	2.52 ± 0.68	2.03 ± 0.65	<0.001
	Week 2	2.30 ± 0.68	1.40 ± 0.63	<0.001
	Week 4	1.99 ± 0.71	1.26 ± 0.63	<0.001
Rescue topical corticosteroid use, days/week	Week 0	5.56 ± 1.47	4.69 ± 1.79	<0.001
	Week 2	4.44 ± 1.97	4.00 ± 1.81	0.043
	Week 4	3.83 ± 1.79	3.42 ± 1.64	0.043

Note: AU, arbitrary units; SD, standard deviation.

NRS reduction (adjusted OR: 0.130, $P < 0.001$), while other variables, including LDH and eosinophil count, were excluded by the AIC-based selection procedure due to lack of incremental contribution to model fit (**Table 5**). These results indicate that early clinical response variables, rather than baseline inflammatory biomarkers, provide the dominant predictive signal for the CEPS model.

Subgroup performance of CEPS for identifying early rapid responders

Before subgroup analyses, internal validation using bootstrap resampling (1,000 repetitions) was performed to assess possible optimism in model performance. The CEPS model showed an apparent AUC of 0.872, and the optimism-corrected AUC was 0.856 (95% CI, 0.811-0.901), supporting the robustness of the model's overall discrimination. The discriminative performance of the CEPS model was consistent across clinically relevant subgroups, with AUC values ranging from 0.84 to 0.89. Specifically, the model showed comparable accu-

racy in male and female patients (AUC, 0.85 [95% CI, 0.76-0.94] vs 0.89 [0.80-0.98]; P for interaction = 0.681), as well as in patients aged <12 years and those aged ≥12 years (AUC, 0.86 [0.75-0.97] vs 0.88 [0.80-0.96]; P for interaction = 0.742). Similar findings were observed after stratification by baseline disease severity and inflammatory burden: the AUC remained stable in patients with baseline EASI <30 versus ≥30 (0.86 [0.77-0.95] vs 0.88 [0.79-0.97]; P for interaction = 0.593) (**Figure 3**).

Mixed-effects model evaluating time × responder status interactions for key outcomes

Across all assessed variables, including EASI, SCORAD, pruritus NRS, there were significant main effects of time and responder group (all $P < 0.001$), indicating overall improvement over time and consistently lower disease burden among responders. More importantly, the time × responder group interaction was significant for all outcomes (all $P < 0.001$), demonstrating that responders showed a steeper decline in

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Table 4. Univariate analysis of baseline and early (week 2/4) predictors of early rapid versus delayed week 16 response

Predictor	Early Rapid Responders (n = 97)	Delayed Responders (n = 47)	Wald/ χ^2	P value
Age	11.58 $\pm$ 3.09	11.77 $\pm$ 2.98	0.348	0.728
Male sex	52 (53.6%)	29 (61.7%)	0.843	0.359
BMI-for-age z score	0.59 $\pm$ 0.27	1.04 $\pm$ 0.09	11.120	<0.001
Disease duration	12.02 $\pm$ 6.42	15.91 $\pm$ 5.05	3.647	<0.001
Age at AD onset	5.37 $\pm$ 2.81	4.26 $\pm$ 2.63	2.279	0.024
Prior systemic immunosuppressant exposure	41 (42.3%)	31 (66.0%)	7.107	0.008
Prior phototherapy	14 (14.4%)	14 (29.8%)	4.765	0.029
Concomitant allergic rhinitis	61 (62.9%)	23 (48.9%)	2.535	0.111
Concomitant asthma	39 (40.2%)	12 (25.5%)	2.981	0.084
Baseline EASI	25.41 $\pm$ 7.32	31.67 $\pm$ 8.31	4.601	<0.001
Baseline SCORAD	59.76 $\pm$ 9.58	67.82 $\pm$ 8.40	4.922	<0.001
Baseline peak pruritus NRS	7.83 $\pm$ 1.30	8.51 $\pm$ 1.36	2.891	0.004
Baseline sleep-loss NRS	5.97 $\pm$ 1.97	7.42 $\pm$ 1.97	4.148	<0.001
Baseline POEM	19.23 $\pm$ 4.56	21.96 $\pm$ 4.69	3.336	0.001
Baseline DLQI	14.68 $\pm$ 4.24	17.90 $\pm$ 5.71	3.807	<0.001
Baseline absolute eosinophil count	0.49 $\pm$ 0.31	0.64 $\pm$ 0.31	2.687	0.008
Baseline LDH	244.44 $\pm$ 63.40	286.21 $\pm$ 50.74	3.943	<0.001
Baseline stratum corneum hydration	29.56 $\pm$ 6.05	24.22 $\pm$ 6.93	4.737	<0.001
Week-2 Δ EASI	-35.26 $\pm$ 8.35%	-17.16 $\pm$ 4.79%	13.791	<0.001
Week-2 Δ SCORAD	-29.33 $\pm$ 9.11%	-13.14 $\pm$ 6.14%	11.016	<0.001
Week-2 pruritus NRS reduction	-2.81 $\pm$ 0.86	-1.32 $\pm$ 0.61	10.607	<0.001
Week-2 sleep-loss NRS reduction	-2.19 $\pm$ 0.53	-0.86 $\pm$ 0.57	13.778	<0.001
Week-2 Δ POEM	-6.31 $\pm$ 1.89	-3.20 $\pm$ 1.42	9.969	<0.001
Week-2 Δ DLQI	-4.97 $\pm$ 1.76	-2.76 $\pm$ 1.40	7.489	<0.001
Week-4 Δ EASI	-57.08 $\pm$ 11.46%	-33.51 $\pm$ 7.40%	12.844	<0.001
Week-4 Δ LDH	-43.78 $\pm$ 21.05	-16.71 $\pm$ 16.79	7.704	<0.001
Week-4 increase in stratum corneum hydration	+27.93 $\pm$ 12.50%	+14.47 $\pm$ 8.42%	6.678	<0.001

Note: AD, atopic dermatitis; BMI, body mass index; EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; LDH, lactate dehydrogenase.

disease severity, symptom burden, inflammatory activity, and barrier dysfunction over the early treatment period than non-responders (Table 6).

Discussion

In this retrospective cohort study, we identified multiple early clinical, inflammatory, and skin barrier-related predictors of dupilumab response in patients with moderate-to-severe atopic dermatitis (AD). Based on these findings, we developed a practical early prediction framework, the CEPS, to estimate week-16 treatment outcome. Overall, our results support three key observations. First, patients who

achieved early rapid response exhibited a distinct baseline phenotype characterized by lower inflammatory burden, relatively milder barrier dysfunction, and less severe clinical symptoms. Second, early on-treatment changes - particularly reductions in EASI and pruritus within the first two weeks - provided stronger discriminatory power than baseline characteristics alone. Third, the CEPS model demonstrated stable discriminative performance across clinically relevant subgroups and showed a consistent gradient in predicting week-16 outcomes, including disease severity reduction, symptom improvement, skin barrier recovery, and healthcare utilization. Collectively, these findings suggest that multidimen-

Table 5. Multivariate logistic regression model for early prediction

Predictor	Coding/unit	Adjusted OR	95% CI	β coefficient	P value
Baseline stratum corneum hydration	Per 1 AU increase	1.666	0.763-3.639	0.511	0.200
Week-2 Δ EASI	Per 10% greater reduction	0.821	0.778-0.866	0.198	<0.001
Week-2 pruritus NRS reduction	Per 1-point greater reduction	0.130	0.058-0.293	2.039	<0.001
Week-4 increase in stratum corneum hydration	Per 10% increase	1.021	0.964-1.080	0.020	0.482

Note: OR, odds ratio; CI, confidence interval; β , regression coefficient; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; AU, arbitrary units; Δ , change from baseline. Week-2 Δ EASI indicates the percentage reduction in EASI from baseline at week 2; Week-2 pruritus NRS reduction indicates the reduction in Numeric Rating Scale score at week 2.

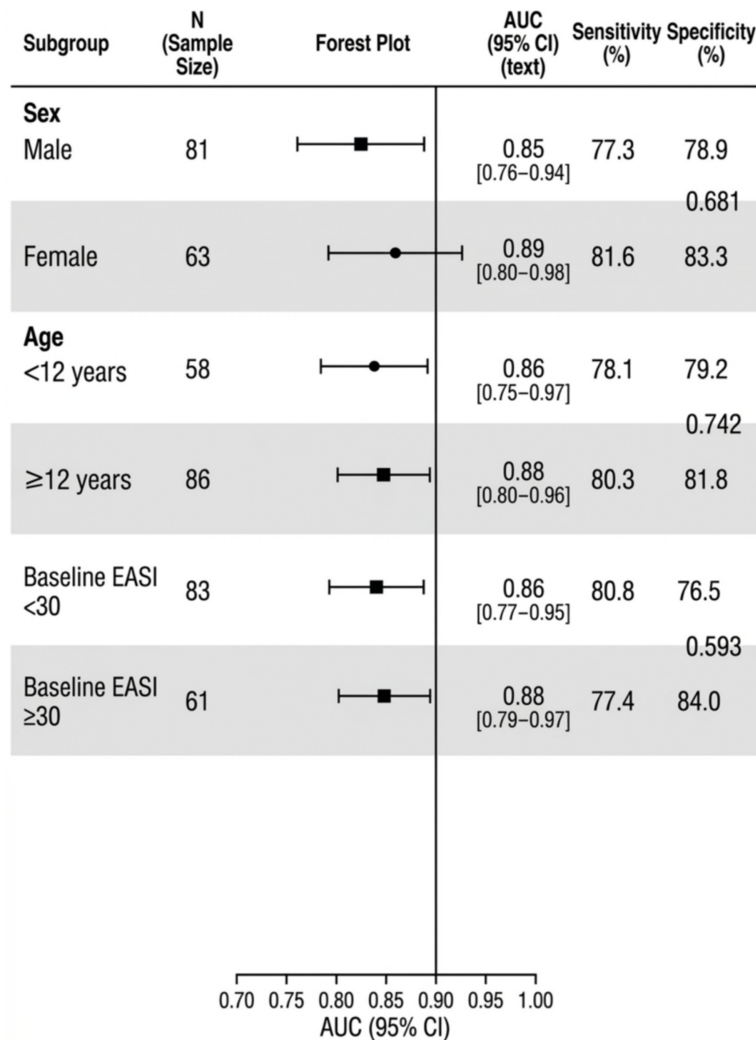


Figure 3. Subgroup performance of CEPS for identifying early rapid responders. Note: CEPS, Early Clinical-Biologic Prediction Score; AUC, area under the curve; CI, confidence interval; EASI, Eczema Area and Severity Index.

sional early treatment dynamics after dupilumab initiation can serve as robust predictors of subsequent therapeutic response and may support more precise, individualized management of AD.

may all influence these baseline measures and weaken their independent predictive performance. Clinically, this suggests that while baseline profiling remains useful for initial risk stratification, overreliance on pretreatment

The baseline disease severity and inflammatory burden were already lower in later responders, suggesting that pretreatment disease status retains prognostic value. Previous studies have reported inconsistent associations between baseline characteristics and dupilumab response, with some but not all demonstrating predictive value for baseline EASI, serum IgE, eosinophil counts, or LDH, although these associations appear less stable across cohorts [17]. Our findings are consistent with the broader view that deterministic pretreatment variables capture only a limited proportion of underlying therapeutic susceptibility and are often insufficient when used alone to generate clinically reliable predictions. One possible explanation is that baseline severity and eosinophilia - both central features of AD pathobiology and closely linked to the mechanism of action of dupilumab - reflect only part of the disease heterogeneity. In addition, disease chronicity, prior treatment exposure, patient-related factors, and heterogeneous inflammatory endotypes

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Table 6. Mixed-effects model evaluating time × responder status interactions for key outcomes

Outcome variable	Fixed effect: time (β , P)	Fixed effect: responder group (β , P)	Interaction: time × group (β , P)
EASI	-3.84, <0.001	-4.92, <0.001	-2.11, <0.001
SCORAD	-5.33, <0.001	-7.24, <0.001	-3.02, <0.001
Pruritus NRS	-0.62, <0.001	-0.89, <0.001	-0.47, <0.001

Note: EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; NRS, Numeric Rating Scale; β , regression coefficient. Mixed-effects models included fixed effects for time, responder group, and time × group interaction.

markers may lead to overly simplified expectations regarding treatment response.

Most baseline variables were less effective than early dynamic clinical changes for distinguishing rapid from delayed responders. This finding is consistent with a growing body of literature suggesting that the earliest treatment-induced changes may provide a more direct readout of biological sensitivity than static baseline characteristics. In our cohort, reductions in EASI and pruritus at week 2 were among the strongest predictors of clinical improvement, indicating that early improvements in objective disease severity and symptom burden carry important prognostic information. Mechanistically, this is biologically plausible, as IL-4/IL-13 blockade can rapidly suppress type 2 inflammatory signaling, inhibit itch-associated neuroimmune activation, and interrupt the itch-scratch cycle before complete lesion clearance is achieved [18-22]. Early symptomatic improvement may therefore reflect more than simple symptom relief; rather, it may represent an integrated signal of downstream immunologic modulation and epidermal functional recovery. Clinically, these findings suggest that the first two weeks after dupilumab initiation constitute a critical window for response assessment and patient counseling. Lack of early improvement during this period may warrant closer monitoring and reconsideration of therapeutic strategy.

The CEPS demonstrated balanced discriminative performance across subgroups stratified by sex, age, baseline disease severity, and inflammatory burden. This consistency is particularly noteworthy, since predictive models often perform well in the overall cohort but show reduced robustness in clinically heterogeneous subgroups. Limitations such as small sample size, restricted phenotypic characterization, and insufficient subgroup analyses have frequently constrained previous studies

on atopic dermatitis prediction, thereby limiting generalizability. In contrast, our subgroup analyses suggest that the predictive signal captured by CEPS was not restricted to any specific demographic or severity-defined subset. One possible explanation is that the model integrates complementary domains, including clinical severity, symptom dynamics, inflammatory activity, and skin barrier recovery, thereby reducing dependence on any single dimension. However, such subgroup stability should still be interpreted with caution, since the absence of significant interaction does not necessarily confirm full transportability. Overall, these findings suggest that multidomain early-response models may offer greater robustness than single biomarker- or single score-based approaches; nevertheless, external validation is required before clinical use.

The clinical relevance of CEPS-based risk stratification was also evident, as patients were clearly differentiated according to week-16 efficacy outcome, patient-reported benefits, need for rescue treatment, unscheduled visits, and treatment intensification. This is particularly important because predictive models are most valuable when they can be translated into clinically interpretable risk strata, rather than relying solely on favorable statistical metrics such as AUC. Although previous studies in atopic dermatitis have primarily focused on individual predictors or associations with specific endpoints, few have linked early predictive classifications to a broad spectrum of subsequent clinical outcomes and healthcare use measures. The graded response pattern observed in our cohort suggests that CEPS captures not only the probability of rapid clinical response but also the overall therapeutic trajectory under dupilumab treatment. Mechanistically, this may reflect the coordinated effects of early suppression of type 2 inflammation and restoration of skin barrier function, which together facilitate downstream improve-

ments in symptom control, quality of life, treatment burden, and healthcare demand. These findings may help clinicians identify patients who are likely to achieve optimal disease control, as opposed to those who require closer follow-up, earlier treatment adjustment, or additional therapeutic support. They also caution against relying solely on symptomatic improvement for evaluating treatment efficacy without considering multidimensional outcomes.

There are also important implications of our findings for the field of precision medicine in moderate-to-severe atopic dermatitis. At present, the therapeutic landscape is increasingly focused on individualized biologic selection and optimization during the early stages of treatment. However, clinically applicable tools for predicting treatment response remain limited. Published candidate predictors have been difficult to translate into routine practice, as most are based on single biomarkers, costly assays, or findings that vary across different populations. In contrast, CEPS is built on routinely available clinical, laboratory, and skin barrier-related indicators obtained during early follow-up visits, which enhances its feasibility and real-world applicability. Notably, one of the key strengths of this framework is that it integrates disease biology with treatment kinetics, thereby better reflecting the multidimensional nature of therapeutic response. Nevertheless, such tools should not be for the sole criteria for clinical decision-making; rather, they should complement and support clinical judgment. Importantly, adaptive monitoring and individualized management should be guided by early predictive signals, but not lead to premature treatment discontinuation or escalation, since disease trajectories may continue to evolve beyond the initial treatment period in some patients.

Several limitations should be acknowledged. First, this was a retrospective single-center study, which may have introduced selection bias, unmeasured confounding, and limited generalizability. Second, the study included a moderate-sized cohort, and the model was both developed and evaluated using the same institutional dataset; no independent external validation cohort was available. Therefore, potential model optimism cannot be fully

excluded despite internally consistent results. Third, several candidate biomarkers, such as serum IgE, additional type 2 inflammatory cytokines, and molecular endotyping data, were not systematically available and therefore could not be incorporated into the analysis. Fourth, the observational design precludes causal inference regarding the relationships between early changes in biomarkers or skin barrier function and subsequent clinical response. Fifth, intangible factors such as treatment adherence, topical therapy intensity, and other behavioral variables may have influenced early response patterns and week-16 outcome. Finally, although CEPS demonstrated good performance in subgroup analyses, further external validation across different age groups, ethnicities, care settings, and treatment regimens is required before its broader clinical application.

In conclusion, this study demonstrated that early clinical outcomes, combined with dynamic changes in inflammatory and skin barrier biomarkers, provide superior predictive value for dupilumab response in patients with moderate-to-severe atopic dermatitis compared to baseline characteristics alone.

Disclosure of conflict of interest

None.

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