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ORIGINAL PAPER

Factors associated with comorbidity development in atopic dermatitis: a cross-section study

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Abstract
Identifying the characteristics of atopic dermatitis (AD) patients with its comorbidity has become increasingly crucial. We aimed to investigate the relevant factors associated with comorbidities in adults with AD. We analyzed cross-sectional data through univariate and multivariate regression analyses, encompassing 439 adult cases of AD from the Clinical Research and Homogenization Diagnosis and Treatment Project for Type 2 Inflammatory Dermatosis. It was found that 231 patients developed at least one comorbidity. 161 cases had a positive family history of atopy, 292 exhibited elevated IgE levels. A family history of allergic rhinitis or sinusitis was found to be associated with concurrent diseases (OR (95% CI): 2.92 (1.41–6.06) in model 1; 2.71 (1.27–5.77) in model 2; 3.59 (1.75–7.37) in model 3; 3.38 (1.62–7.05) in model 4; 3.60 (1.83–7.08) in model 5; 3.56 (1.78–7.12) in model 6). The linkage between elevated IgE levels and concurrent diseases with different classifications was negative (OR (95% CI): 0.51 (0.33–0.79) in model 1; 0.51 (0.33–0.80) in model 2; 0.51 (0.33–0.79) in model 3; 0.52 (0.33–0.81) in model 4; 0.45 (0.29–0.71) in model 5; 0.47 (0.30–0.73) in model 6). Scores for familial atopy (OR (95% CI): 1.56 (1.00-2.44) in model 2; 1.59 (1.03–2.48) in model 4; 1.84 (1.19–2.84) in model 6) were positively associated with comorbidities. Factors associated with comorbidity development in AD included a family history of allergic rhinitis or sinusitis, elevated IgE levels and scores indicating familial atopy. These relevant factors might contribute to improved discrimination and early intervention for comorbidities in individuals with AD.

Keywords Atopic dermatitis · Comorbidity · Family health · Immunoglobulin E

Introduction

Atopic dermatitis (AD) is the most common recrudescent, chronic, inflammatory skin disorder that occurs with or without an increase in immunoglobulin E (IgE) and eosinophil levels; It is characterized by bothersome pruritus and polymorphic eczematous lesions. The prevalence of AD in children and adolescents ranges from 13.5 to 41.9%, while in adults, it varies from 3.4 to 33.7% [1, 2]. Therapy for AD includes basic moisturizers and emollients, and systemic and topical drugs [3, 4]. However, the treatment regimen is ineffective for the control and prediction of certain concurrent diseases associated with AD, whose significance is often underestimated.

The thorough exploration of AD, has shown that it often coexists with allergic rhinitis (AR), asthma, eosinophilic esophagitis and food allergy (FA), a phenomenon known as the atopic march. It is well-known that an individual with a family history of allergic asthma and allergic rhino-conjunctivitis is susceptible to AD or other atopic disorders, such as atopic diathesis [5]. Besides, researchers have discovered the link between AD and non-atopic illnesses, such as autoimmune diseases (including alopecia areata, vitiligo, chronic urticaria, inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis), hypertension, diabetes mellitus, psychiatric diseases (including anxiety, depression, and attention hyperactivity disorder), infections (including cutaneous and extracutaneous infections), osteoporosis, nasal polyposis etc [6–9]. They may potentially share similar pathogenic

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factors, and pathways, and contribute to the development of certain illnesses.

Most research has focused on certain comorbidities in AD; and evidence regarding multiple concurrent diseases considered as an entity is limited. Usually, family atopy was categorized as being present or absent, and there is a scarcity of scoring systems. Also, there is insufficient clinical evidence on the relationship between relevant factors, such as initial onset site, elevated immunoglobulin E levels, and comorbidities associated with AD. Moreover, both dermatologists and patients probably underestimate the effects of these associations on the treatment and prevention of comorbidities in medical decision-making. Therapeutic approaches might vary slightly for various comorbidities [3, 4].

Thus, we analyzed the common features in the adult population to identify potential influential factors. Subsequently, we built clinical binomial logistic regression models to predict comorbidity development.

Methods

Data source

Data from the AD population was randomly obtained from the database for the Clinical Research and Homogenization, Diagnosis and Treatment Project for Type 2 Inflammatory Dermatosis, National Clinical Research Center for Dermatological and immunologic Disease, which was established in April 2021, and is an ongoing, non-interventional, observational registry of patients with AD, eczema, bullous pemphigoid or prurigo nodularis in China. This project was approved by the Ethics Committee and informed consent was obtained from all the study participants.

In December 2022, we extracted data for over 600 cases using the nextlnt function of the SecureRandom library. After excluding data with obvious errors and inconsistencies, we screened 565 cases of AD, including 439 adults and 126 adolescents, during our analysis. We selected 439 adult cases of AD for further analyses, taking into account differences between adults and adolescents, for whom the collected information included the gender, birth date, onset sites, rash-distribution, comorbidities, elevated IgE (yes or no), serum IgE levels, mean pruritus scores, and pruritus severity, assessed weekly through the numerical rating scale(NRS), investigator's global assessment (IGA) score, eczema area and severity index (EASI), affected body surface area (BSA) (%), dermatology life quality index (DLQI), AD control tool (ADCT), patient-oriented eczema measure (POEM), and hospital anxiety and depression scale (HADS), etc.

Table 1 Atopic family history scores

Scores	Description
0 points	No family history of following diseases, eczema, asthma, AR or sinusitis, chronic urticaria, AC or FA
1 point	Possessing a family history of one of above 6 diseases
2 points	Possessing a family history of two of above 6 diseases
3 points	Possessing a family history of three of above 6 diseases
4 points	Possessing a family history of four of above 6 diseases
5 points	Possessing a family history of five of above 6 diseases
6 points	Possessing a family history of above all 6 diseases

Family history was referred to a medical history of collateral relative by blood three generations

To assess the factors associated with comorbidity development, we defined 3 groups based on different outcome events. Outcome 1 (named as the 'all comorbidities group') referred to AD patients that developed at least one of concurrent diseases, including asthma, AR or sinusitis, allergic conjunctivitis (AC), FA, drug allergy, xerodema or ichthyosis, chronic urticaria, contact dermatitis, psoriasis, alopecia areata, inflammatory bowel disease, coronary heart disease, diabetes, hypertension, depression or anxiety disorder, attention deficit hyperactivity disorder, and skin infections. Considering the internal associations between comorbidities, we reorganized outcome 2 based on whether the individual with AD had at least one of four allergic disorders, i.e., asthma, AR or sinusitis, AC, and FA. Furthermore, we defined outcome 3 based on whether patients suffered from at least one of three atopic diseases (asthma, AR or sinusitis, and AC) in this study, because the prevalence FA was lower in adults than in children.

Positive familial atopy was defined as a family history of at least one of following six diseases, eczema, asthma, AR or sinusitis, chronic urticaria, AC, and FA. In this study, family history was referred to as the medical history of collateral family members related by blood within three generations. Besides, we determined atopic family history scores, which were the sum of the familial atopy conditions described above (0–6 points) (Table 1). Disease inactivity is indicated by ADCT scores < 7 points; otherwise, it is considered that an individual has active disease. The severity of the EASI could be classified as mild when EASI scores were equal to or less than 7, moderate when EASI scores were between 7 and 21, and severe when scores exceeded 21. IGA scores less than or equal to 2 was mild, those equal to 3 was moderate, and those equal to 4 or 5 was severe. POEM scores below 7 were considered mild, those between 8 and 16 were considered moderate, and scores exceeding 16 were considered severe. Scores less than or equal to 5 were mild,

those ranging from 6 to 10 were moderate, and those otherwise were considered severe in DLQI.

Statistical analysis

Categorical values were described as numbers and percentages, and continuous variables were described as medians and quartiles. Categorical variables were analyzed using the χ^2 test. The non-parametric test was used for numerical variables. We analyzed the relationship between potential indicators and comorbidities of AD via univariable and multi-variable logistic regression analysis with SPSS 17.0. Results were presented as odds ratios (OR) with 95% confidence intervals (CIs). Results were defined as statistically significant if $P < 0.05$. Plyr, ggsci [10], ggplot2, rcompanion, ResourceSelection, VGAM, rms, reshape and cowplot packages in R (4.2.3) were used to plot and build binomial logistic regression models.

Results

Clinical features

We analyzed 439 cases of AD and their clinical characteristics were as follows. Gender-based differences were not significant, with males accounting for 50.57% of the study population. Patients generally complained of pruritus (429), and a smaller number of patients experienced a burning sensation (65) and pain (59). The trunk (238), lower extremities (229), and upper extremities (220) were the most common initial onset sites in adults with AD. The top three areas where rashes were distributed included the upper extremities (338), lower extremities (326) and the trunk (324). 72 patients were positive for an allergen, 139 exhibited elevated eosinophils, and 292 had elevated IgE levels. Besides, most patients had the active disease (395, 89.98%). Over half the patients (231, 52.62%) were born in Spring and Autumn (i.e. born in SA) (Fig. 1a).

The severity grade percentage varied with different assessments. The percentage of patients with mild, moderate, and severe EASI scores were 37.81% (166), 38.27% (168), and 23.92% (105), respectively. The percentage of patients with mild, moderate, and severe POEM scores accounted for 12.30% (54), 52.62% (231), and 35.08% (154) of the study population, respectively. In terms of IGA values, the percentage were 22.55% (99), 51.48% (226), and 25.97% (114) for the mild, moderate, and severe categories, respectively. The DLQIs were 33.03% (145), 19.13% (84), and 47.84% (210) for mild, moderate, and severe categories, respectively (Fig. 1b).

More than half the patients (231, 52.62%) developed at least one comorbidity. The percentage of patients with two concomitant comorbidities was 10.48% (46), while, 2.96% (13) had 3 or 4 comorbidities. The proportion of patients who had at least one comorbidity in the outcome 2 and outcome 3 groups accounted for 47.15% (207) and 38.50% (169) of the study population, respectively. The top 3 comorbidities health included AR or sinusitis (151, 34.40%), FA (59, 13.44%), and asthma (22, 5.01%) (Fig. 1c).

The differences in IgE levels and scores of individuals with familial atopy were statistically significant (Table 2). Categorical variables, including elevated IgE levels, familial atopy, and family history of AR or sinusitis showed statistical differences in different outcomes (Table 3).

Evaluating potentially associated factors via logistic regression analysis

In order to investigate the potential were differences between familial atopy and its scores, we categorized them into different subgroups for each outcome. In the multi-variable logistic regression analysis, we built models 1, 3, and 5, corresponding to outcomes 1, 2, and 3, respectively, and encompassing the variable of family atopy. Models 2, 4, and 6 corresponded to outcomes 1, 2, and 3 encompassing the scores for familial atopy.

Univariate and multivariate regression analysis with outcome 1

In the univariable analysis, 8 variables were significantly associated with the development of AD-associated comorbidities (Table 4). In the multivariable analysis, only a few variables remained statistically significant. These included elevation of IgE (OR (95% CI): 0.51 (0.33–0.79) in model 1; 0.51 (0.33–0.80) in model 2), onset in the lower extremities (OR (95% CI): 1.85 (1.22–2.81) in model 1; 1.86 (1.23–2.82) in model 2), scores for familial atopy (OR (95% CI): 1.56 (1.00-2.44)), and family history of AR or sinusitis (OR (95% CI): 2.92 (1.41–6.06) in model 1; 2.71 (1.27–5.77) in model 2), y2y6 duration (OR (95% CI): 3.38 (1.58–7.25) in model 1; 3.38 (1.58–7.25) in model 2) (Fig. 1d; Table 4). However, no statistical differences were observed for familial atopy (OR (95% CI): 1.67 (0.98–2.86)) in this multivariable analysis.

Univariate and multivariate regression analysis with outcome 2

The results of univariable analysis are shown in Table 4. Notably, elevated IgE levels (OR (95% CI): 0.51 (0.33–0.79) in model 3; 0.52 (0.33–0.81) in model 4), age of

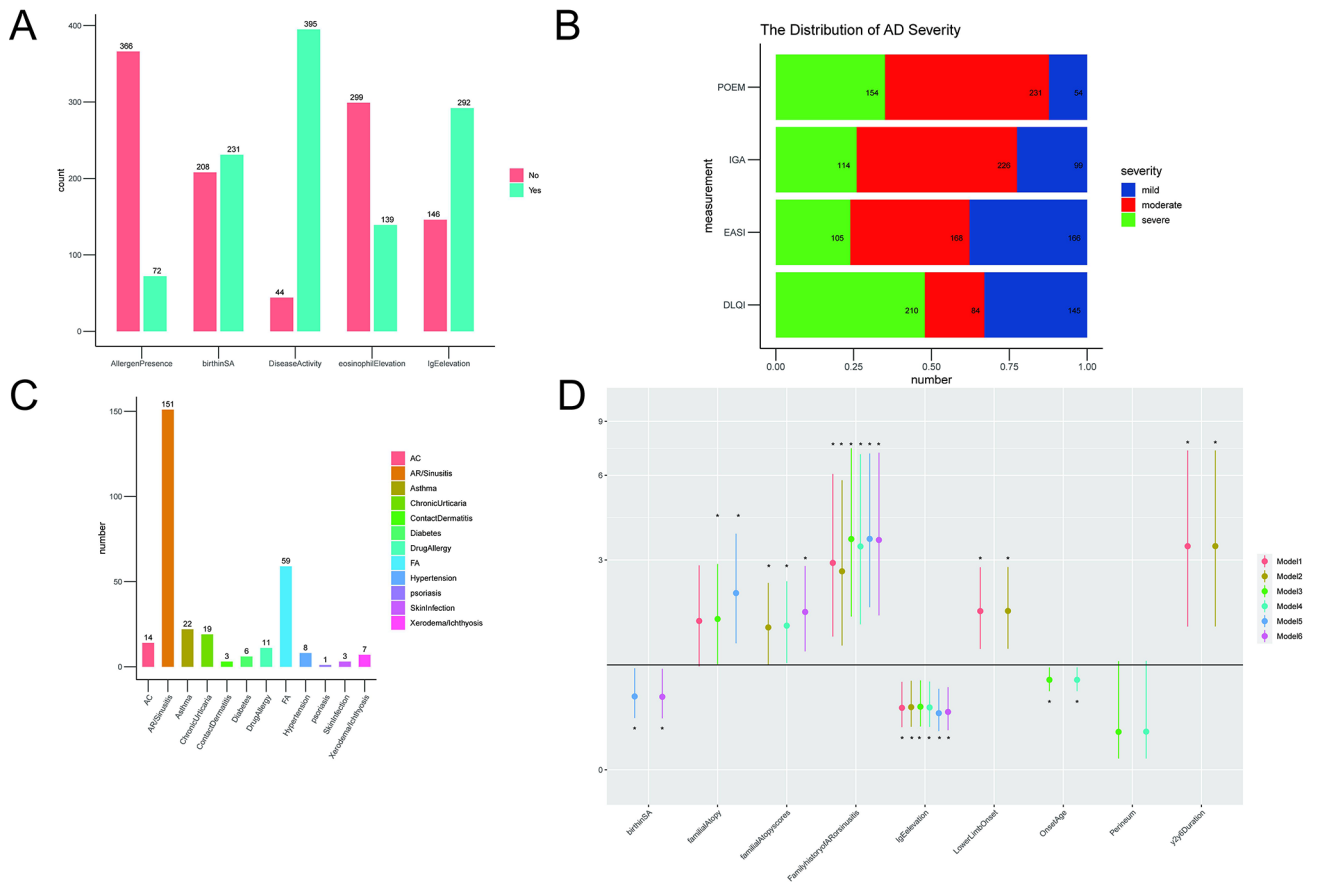

Fig. 1 (**a**). Characteristics of AD patients. (**b**). The severity of AD population in different measurements. (**c**). The distribution of AD comorbidities. Some diseases didn't show for zero case, such as alopecia areata, inflammatory bowel disease, coronary heart disease, depression or anxiety disorder, attention deficit hyperactivity disorder. d. Multivariable logistic analysis in six models. Model 1, 3 and 5 corresponded to outcome 1, 2 and 3, encompassing variable of family atopy. Model 2, 4, 6 corresponded to outcome 1, 2 and 3 respectively, containing scores of familial atopy. * $P < 0.05$. y2y6Duration means that patients had AD presentation from 2 to 6 years old

onset (OR (95% CI): 0.81 (0.68–0.97) in model 3; 0.81 (0.68–0.97) in model 4), scores of familial atopy (OR (95% CI): 1.59 (1.03–2.48)), familial atopy (OR (95% CI): 1.71 (1.01–2.90)), and family history of AR or sinusitis (OR (95% CI): 3.59 (1.75–7.37) in model 3; 3.38 (1.62–7.05) in model 4) were statistically significant in multivariable analysis (Fig. 1d).

Univariate and multivariate regression analysis with outcome 3

The results of univariable analysis are shown in Table 4. In the multivariable analysis, elevated IgE levels (OR (95% CI): 0.45 (0.29–0.71) in model 5; 0.47 (0.30–0.73) in model 6), familial atopy (OR (95% CI): 2.22 (1.31–3.76)) or scores of familial atopy (OR (95% CI): 1.84 (1.19–2.84)), family history of AR or sinusitis (OR (95% CI): 3.60 (1.83–7.08) in model 5; 3.56 (1.78–7.12) in model 6) and birth in spring and autumn (OR (95% CI): 0.62 (0.41–0.96) in model 5; 0.62 (0.41–0.95) in model 6) exhibited statistical differences (Fig. 1d; Table 4). Notably, both univariable and multivariable logistic regression analysis results showed that birth in the spring and autumn (birth in SA) seasons was related to comorbidities from outcome 3.

Binomial logistic regression models

After excluding missing data using the R language, we proceeded with the data for 401 individuals model development. Additionally, we analyzed and identified important factors from various elements through a step-by-step approach using R language, and the results were similar to those calculated using SPSS. Then, we plotted nomograms displaying 100% of the developing comorbidities (outcome 1), allergic comorbid conditions (outcome 2) and atopic comorbidities (outcome 3). The nomograms included points

Table 2 Baseline demographics and disease characteristics

Characteristic	*n*	Classification	all	*P* value
Age (years, median[range])	439		34.00(24.00–48.00)	
		outcome 1 (yes)	34.00(25.00–48.00)	0.640
		outcome 2 (yes)	34.00(25.00–48.00)	0.554
		outcome 3 (yes)	35.00(25.00–48.00)	0.373
Height (cm, median[range])	439		166.00(161.00-172.00)	
		outcome 1 (yes)	165.00(160.00-172.00)	0.475
		outcome 2 (yes)	165.00(160.00-172.00)	0.455
		outcome 3 (yes)	165.00(160.00-172.00)	0.401
Weight (kg, median[range])	439		62.00(54.00–72.00)	
		outcome 1 (yes)	63.00(55.00–72.00)	0.888
		outcome 2 (yes)	62.00(54.00–72.00)	0.855
		outcome 3 (yes)	63.00(53.00–72.00)	0.808
BMI (Kg/m^2, median[range])	439		22.49(22.20-24.91)	
		outcome 1 (yes)	22.55(20.24-24.91)	0.525
		outcome 2 (yes)	22.49(20.20–25.10)	0.839
		outcome 3 (yes)	22.27(20.07–25.13)	0.932
BSA (%, median[range])	439		18.00(8.00–36.00)	
		outcome 1 (yes)	18.00(7.00–33.00)	0.505
		outcome 2 (yes)	19.00(7.00–33.00)	0.533
		outcome 3 (yes)	19.00(7.00-35.15)	0.845
ESAI (median[range])	439		10.00(4.50–20.60)	
		outcome 1 (yes)	10.80(4.50–21.60)	0.563
		outcome 2 (yes)	10.80(4.40–21.60)	0.459
		outcome 3 (yes)	9.70(3.68–20.73)	0.337
ADCT (median[range])	439		14.00(11.00–18.00)	
		outcome 1 (yes)	14.00(11.00–18.00)	0.586
		outcome 2 (yes)	14.00(11.00–18.00)	0.917
		outcome 3 (yes)	14.00(10.00–18.00)	0.337
POEM (median[range])	439		14.00(11.00–18.00)	
		outcome 1 (yes)	13.00(10.00–18.00)	0.262
		outcome 2 (yes)	13.00(10.00–17.00)	0.051
		outcome 3 (yes)	13.00(9.50–18.50)	0.576
DLQI (median[range])	439		10.00(2.00–15.00)	
		outcome 1 (yes)	11.00(1.00–16.00)	0.964
		outcome 2 (yes)	11.00(0.00–16.00)	0.465
		outcome 3 (yes)	10.00(0.00–16.00)	0.391
HADS (median[range])	439		12.00(6.00–18.00)	
		outcome 1 (yes)	12.00(7.00–18.00)	0.607
		outcome 2 (yes)	12.00(7.00–17.00)	0.989
		outcome 3 (yes)	12.00(6.00–18.00)	0.845
Mean pruritus scores by weekly NRS (median[range])	437		6.00 (4.00–7.00)	
		outcome 1 (yes)	6.00(5.00–7.00)	0.373
		outcome 2 (yes)	6.00(4.75-7.00)	0.854
		outcome 3 (yes)	6.00(4.00–7.00)	0.879
Pruritus severity by weekly NRS (median[range])	438		7.00(5.75-8.00)	
		outcome 1 (yes)	7.00(6.00–8.00)	0.765
		outcome 2 (yes)	7.00(6.00–8.00)	0.634
		outcome 3 (yes)	8.00(5.00-8.75)	0.660
IgE (median[range])	438		315.50(86.49-842.45)	
		outcome 1 (yes)	346.10(105.69–1180.00)	0.007*
		outcome 2 (yes)	351.29(107.00-1221.80)	0.003*
		outcome 3 (yes)	384.00(149.00-1388.45)	0.000*

Table 2 (continued)

Characteristic	*n*	Classification	all	*P* value
Scores of Familial Atopy (median[range])	438		0.00(0.00–1.00)	
		outcome 1 (yes)	0.00(0.00–1.00)	0.000*
		outcome 2 (yes)	0.50(0.00–1.00)	0.000*
		outcome 3 (yes)	1.00(0.00–1.00)	0.000*

* $P < 0.05$, data were described as median and quartiles because these continuous variables were non-normal distribution. *P* value was calculated by non-parametric test with different outcomes

assigned to factors in different models (Fig. 2). Notably, no statistical differences in familial atopy were observed in patients with allergic comorbid conditions (outcome 1). Elevated IgE levels and family history of AR or sinusitis were statistically different statistically in all models. Models were verified via calibration.

Discussion

The increasing prevalence of AD, has gradually attracted the attention of dermatologists towards concurrently occurring diseases. Thus, it is necessary to design appropriate preventive strategies for understanding the factors associated with concurrent disease development in individuals with AD. In this article, we indicated the presence or absence of familial atopy, scores of familial atopy, and family history of AR or sinusitis, and showed that these factors were positively associated with concurrent disease development. However, there was a negative association between elevated IgE levels and comorbidities. Binomial logistic regression models indicated that AD subjects with a family history of AR or sinusitis, who had higher scores of family atopy or familial atopy, non-elevated IgE levels, and onset in the lower limbs were more likely to have comorbid disorders. These patients, characterized by higher scores for family atopy, IgE levels within normal ranges, and positive allergen and family history of AR or sinusitis, had a higher likelihood of development of one of the conditions in outcome 2. Individuals in the outcome 3 group, exhibiting the development of disorders, showed certain features, including not being born in spring and autumn, having normal IgE levels, familial atopy or higher scores of family atopy, and a positive family history of AR or sinusitis.

Consistent with other studies [11, 12], this article identifies AR (151, 34.4%) as the most common comorbidity. Increasingly, scientific research indicates an increased risk of developing AD and AR in a population with a positive parental history of AD or other atopic diseases [13–15]. In comparison to health individuals, the prevalence of AD in a population in which the relatives had atopic dermatitis was about 3.1 times higher (12.4% vs. 4.0%) [16]. Besides, Ćosićkić Almira et al. [17] observed in a cohort study that familial atopy was a risk factor for both asthma and AR OR values were 7.0 (95%CI 2.8–17.0) and 4.0 (95%CI 1.6–9.5). Nevertheless, evidence regarding the relationship between familial atopy and individuals with AD and other comorbidities is limited.

In this study, we retrospectively investigated the connection between familial atopy and comorbidities, treating them as a collective entity. First, we introduced the concept of atopic family history scores, representing the sum of all positive family histories of 6 other atopic diseases. Significant differences were observed in the multi-variable logistic regression analysis of outcome 1. While family atopy, indicated by a yes or no showed no statistical differences, a similar trend was observed. However, this phenomenon was not evident in multi-variable logistic models of outcome 2 and outcome 3. The inconsistency may be attributed to the small sample size and inclusion familial history of partial atopic diseases in this context. Consequently, we hypothesized that atopic family history scores may be a unique and potentially superior factor contributing to the evaluation of the risk of comorbid diseases compared to simple family atopy classification. This may provide new clues for further research by refining the level and weight of familial atopy based on the degree of the relationship. Also, its authenticity and effectiveness need to be verified by more large-scale, multi-center, and prospective studies.

FA, AD, and asthma are commonly accompanied by strong familial clustering [18–20]. However, we only observed that a family history of AR or sinusitis was positively associated with comorbid diseases in all 6 models. These results can be attributed to a certain genetic background, similar external environment, and lifestyle. Notably, FA, AD, AR, and asthma are clinically considered as different but genetically interlinked disorders involving at least 16 common genes (*IL5*, *IL4*, *TSLP*, *IL10*, *RNASE3*, *IGHG4*, *IL13*, *CCL11*, *IFNG*, *RNASE2*, *FCER2*, *CD4*, *FOXP3*, *IL4R*, *KCNE4*, and *CCL26*) [21]. The relevance estimate value for AD and AR, was 0.62 [22]. Herein, a family history of AR or sinusitis could be used as a predictor of co-morbidity in AD patients.

Current evidence regarding the association between IgE, severity, and comorbidity in individuals with AD has been inconsistent. Unlike previous studies [23], this study found no notable associations between AD severity, as measured by various clinical indicators, and comorbidities. For instance, Nora Laske et al. [24] reported that extremely high

Table 3 Baseline demographics and disease characteristics (categorical variables)

Characteristic	Percentage	Outcome 1				Outcome 2				Outcome 3			
		no	yes	χ^2	*P* value	no	yes	χ^2	*P* value	no	yes	χ^2	*P* value
Gender, male, yes, n	50.57% (222/439)	110	112	0.848	0.357	123	99	1.179	0.277	140	82	0.461	0.497
Ig E elevation, yes, n	66.67% (292/438)	153	139	8.464	0.004*	168	124	7.332	0.007*	197	95	12.558	0.000*
Lower Limb Onset, yes, n	53.01% (229/432)	94	135	7.454	0.006*	112	117	2.928	0.087	135	94	1.416	0.234
y2y6 Duration, yes, n	9.74% (41/421)	12	29	6.214	0.013*	18	23	1.579	0.209	24	17	0.264	0.607
Family history of AR or sinusitis, yes, n	18.49% (81/438)	17	64	27.988	0.000*	17	64	40.799	0.000*	22	59	49.979	0.000*
Familial Atopy, yes, n	36.76% (161/438)	51	110	25.523	0.000*	58	103	29.336	0.000*	66	95	45.913	0.000*
Family history of eczema, yes, n	17.12% (75/438)	28	47	3.743	0.053	33	42	2.922	0.087	36	39	7.125	0.008*

*$P < 0.05$. Categorical variables were described as numbers. P value was calculated by χ^2 test. y2y6 Duration indicated patients ever had rashes when they were from 2 to 6 years old

levels of IgEs (over 10,000 kU/L) resulted in a higher proportion of individuals exhibiting allergy reactions (20% vs. 7%) and hypersensitivity to both airborne and food allergens (80% vs. 32%), compared to individuals with the moderate IgE levels (400-1000kU/L). However, elevated cord-blood IgE levels have been found to correlate negatively with AD in infants who were less than 12 months old [25]. In our study, raised IgE levels were similarly found to negatively correlated with comorbidity presence in the adult AD population. Several factors may explain the inconsistency in IgE associations. First, this study focused on adults, whose IgE levels may differ in stability from those in children. Additionally, the IgE data collected across three generations relied on self-reporting and family-reported information, which may introduce potential recall bias and limitations in data accuracy, especially for historical records lacking precise medical documentation. Future studies could benefit from a prospective design or standardized multigenerational medical records to obtain more reliable data. Moreover, IgE levels are also easily influenced by various external factors, such as air pollution, parasite infections, gender, and genetic factors, complicating consistent associations with AD comorbidities. Furthermore, our study classified IgE elevation simply as "yes" or "no", without stratifying by degree of elevation, potentially overlooking nuanced relationships. This limitation leads us to speculate on whether IgE may play a dual regulatory role in AD. IgE may play a transient protective role when its levels are within a certain range, and act as a risk factor for individuals with AD with comorbidities when present at levels beyond this range. This hypothesis offers a novel perspective for future research to investigate IgE's threshold effects in AD comorbidities.

Lio Peter A et al. [26] suggested that patient quality of life is affected by lesion sites, particularly in visible areas such as the head and neck (68%), hands (58%), and upper extremities (22%). Unfortunately, no statistical differences were observed between rash-distribution, other onset sites of the human body, and comorbidities apart from onset in the lower limbs. These differences might stem from variations in ethnicity, environmental exposure, or study design.

The identified indicators in our study may assist with early identification and intervention of comorbid conditions in AD patients, which is especially important for personalized precision medicine. Dermatologists need to consider these factors, particularly family history of AR or sinusitis and familial atopy scores, when making clinical decisions to prevent comorbidities in AD patients. In summary, factors associated with comorbidity development in AD patients included a family history of AR or sinusitis, elevated IgE levels, and familial atopy scores, all of which may improve discrimination and early intervention in AD patients with comorbidities.

Table 4 Results of univariable and multivariable logistic analysis

	Univariable logistic analysis			Multivariable logistic analysis					
	Outcome 1	Outcome 2	Outcome 3	Model 1 [OR (95%CI)]	Model 2 [OR (95%CI)]	Model 3 [OR (95%CI)]	Model 4 [OR (95%CI)]	Model 5 [OR (95%CI)]	Model 6 [OR (95%CI)]
Lower Limb Onset	1.70* (1.16-2.49)	1.39 (0.95-2.04)	1.27 (0.86-1.87)	1.85* (1.22-2.81)	1.86* (1.23-2.82)				
y2y6 Duration	2.39* (1.19-4.83)	1.51 (0.79-2.90)	1.19 (0.62-2.29)	3.38* (1.58-7.25)	3.38* (1.58-7.25)				
IgE elevation	0.55* (0.37-0.82)	0.58* (0.39-0.86)	0.48* (0.32-0.72)	0.51* (0.33-0.79)	0.51* (0.33-0.80)	0.51* (0.33-0.79)	0.52* (0.33-0.81)	0.45* (0.29-0.71)	0.47* (0.30-0.73)
Family history of AR or sinusitis	4.33* (2.44-7.69)	5.70* (3.21-10.13)	6.10* (3.56-10.46)	2.92* (1.41-6.06)	2.71* (1.27-5.77)	3.59* (1.75-7.37)	3.38* (1.62-7.05)	3.60* (1.83-7.08)	3.56* (1.78-7.12)
Onset Age	0.80* (0.68-0.94)	0.83* (0.71-0.98)	0.90 (0.77-1.06)			0.81* (0.68-0.97)	0.81* (0.68-0.97)		
Perineum	0.29* (0.09-0.90)	0.25* (0.07-0.88)	0.35 (0.10-1.26)			0.29 (0.08-1.05)	0.29 (0.08-1.05)		
Familial Atopy	2.82* (1.88-4.25)	3.00* (2.00-4.49)	4.02* (2.66-6.08)	1.67 (0.98-2.86)		1.71* (1.01-2.90)		2.22* (1.31-3.76)	
Familial Atopy scores	2.35* (1.67-3.30)	2.51* (1.80-3.52)	3.02* (2.15-4.26)		1.56* (1.00-2.44)		1.59* (1.03-2.48)		1.84* (1.19-2.84)
Family history of eczema	1.65 (0.99-2.75)	1.54 (0.94-2.55)	1.97* (1.19-3.24)						
Birth in SA	0.95 (0.65-1.38)	0.78 (0.53-1.13)	0.63* (0.43-0.93)					0.62* (0.41-0.96)	0.62* (0.41-0.95)

*$P < 0.05$. Model 1, 3 and 5 corresponded to outcome 1, 2 and 3, encompassing variable of family atopy. Model 2, 4, 6 corresponded to outcome 1, 2 and 3 respectively, containing scores of familial atopy. Birth in SA: birth in spring or autumn; y2y6 Duration indicated patients ever always had rashes when they were from 2 to 6 years old. Perineum: Patients had a rash-distribution in perineum when they go to a doctor

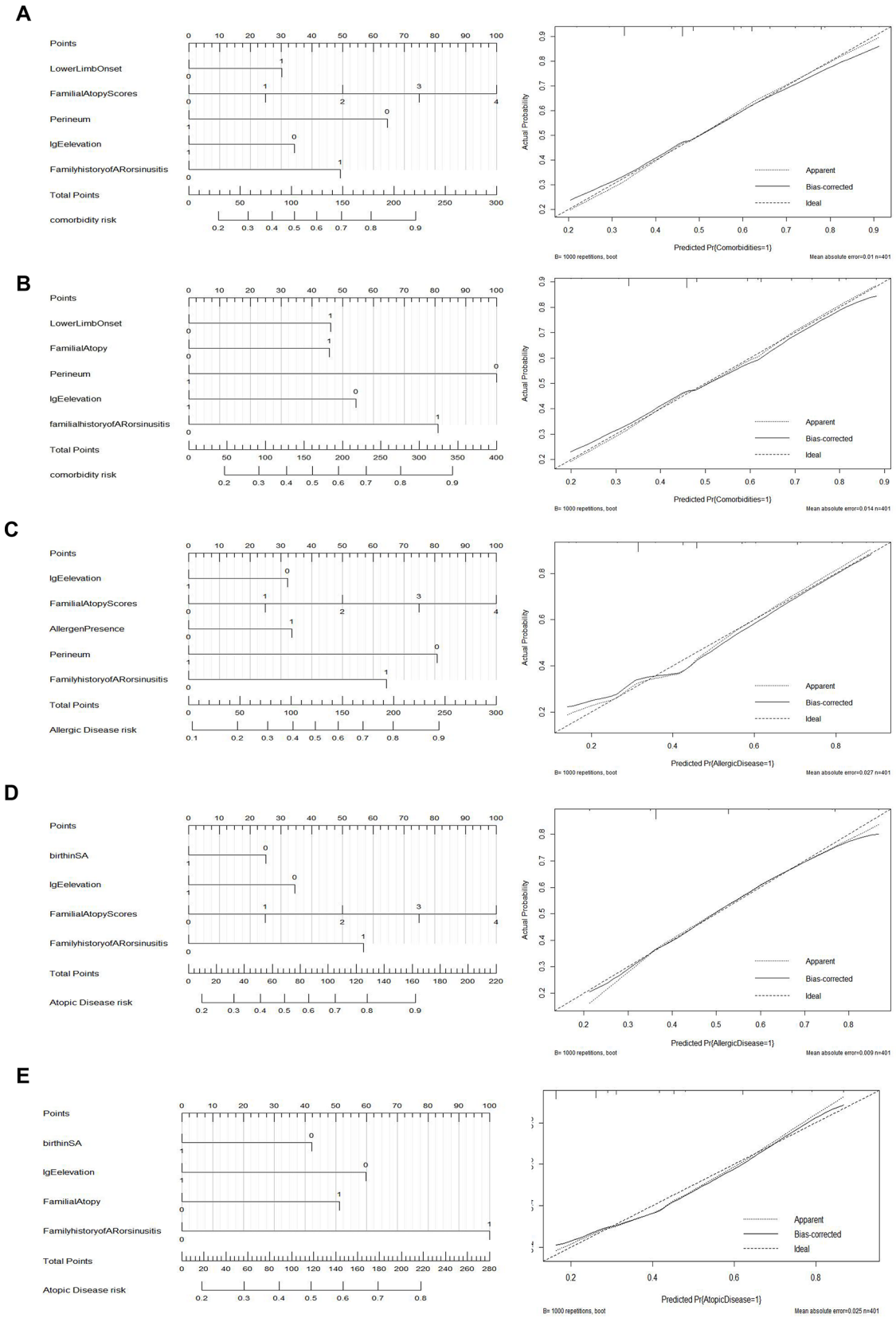

Fig. 2 Nomogram (on the left) and calibration curve (on the right) in different models. Both a and b, d and e were respectively analyzed with outcome of AD comorbidity and atopic diseases, corresponding to different forms of familial atopy. C was built by results of allergic disease in adults with AD

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Data availability Research data is available upon request under reasonable request.

Declarations

Ethical approval Additional ethical approval was not required for this study because data were obtained from studies conducted by the Clinical Research and Homogenization Diagnosis and Treatment Project for Type 2 Inflammatory Dermatosis. These studies were performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee (2021 scientific research 223).

Consent to participate Informed consent was obtained from all subjects.

Consent to publish Not applicable.

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References

1. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P et al (2021) Atopic dermatitis in the pediatric population: a cross-sectional, international epidemiologic study. Ann Allergy Asthma Immunol 126 4:417–28 e2. https://doi.org/10.1016/j.anai.2020.12.020
2. Maspero J, De Paula Motta Rubini N, Zhang J, Sanclemente G, Amador JR, El Sayed MH et al (2023) Epidemiology of adult patients with atopic dermatitis in AWARE 1: a second international survey. World Allergy Organ J 16 3:100724. https://doi.org/10.1016/j.waojou.2022.100724
3. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S et al (2022) European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. J Eur Acad Dermatol Venereol 36 9:1409–1431. https://doi.org/10.1111/jdv.18345
4. Adam DN, Gooderham MJ, Beecker JR, Hong CH, Jack CS, Jain V et al (2023) Expert consensus on the systemic treatment of atopic dermatitis in special populations. J Eur Acad Dermatol Venereol 37 6:1135–1148. https://doi.org/10.1111/jdv.18922
5. Lim JJ, Lim YYE, Ng JY, Malipeddi P, Ng YT, Teo WY et al (2022) An update on the prevalence, chronicity, and severity of atopic dermatitis and the associated epidemiological risk factors in the Singapore/Malaysia Chinese young adult population: a detailed description of the Singapore/Malaysia Cross-sectional Genetics Epidemiology Study (SMCGES) cohort. World Allergy Organ J 15 12:100722. https://doi.org/10.1016/j.waojou.2022.100722
6. Soares GB, Orfali RL, Averbach BL, Yosipovitch G, Aoki V (2023) Atopic dermatitis in Latin America: considerations on Epidemiology, Clinical and Laboratory Features, Ethnic/Racial variations, and Therapeutic Management. J Clin Med 12(10). https://doi.org/10.3390/jcm12103419
7. Silverberg JI (2019) Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol. 123 2:144–51; https://doi.org/10.1016/j.anai.2019.04.020
8. Thyssen JP, Halling AS, Schmid-Grendelmeier P, Guttman-Yassky E, Silverberg JI (2023) Comorbidities of atopic dermatitis-what does the evidence say? J Allergy Clin Immunol 151 5:1155–1162. https://doi.org/10.1016/j.jaci.2022.12.002
9. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH et al (2018) Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. Ann Allergy Asthma Immunol 121 5:604–12 e3. https://doi.org/10.1016/j.anai.2018.07.042
10. Xiao Nggsci (2023) Scientific Journal and Sci-Fi Themed Color Palettes for 'ggplot2
11. Degboe B, Atadokpede F, Nguessie C, Kouassi A, Elegbede N, Maffo N et al (2021) Comorbidities and Environmental Factors Associated with atopic dermatitis in children and adults in Dermatology-Venereology in Cotonou, Benin. Dermatol Res Pract 2021:1502721. https://doi.org/10.1155/2021/1502721
12. Wananukul S, Chatproedprai S, Tempark T, Phuthongkamt W, Chatchatee P (2015) The natural course of childhood atopic dermatitis: a retrospective cohort study. Asian Pac J Allergy Immunol 33 2:161–168. https://doi.org/10.12932/AP0498.33.2.2015
13. Lee JT, Lam ZC, Lee WT, Kuo LC, Jayant V, Singh G et al (2004) Familial risk of allergic rhinitis and atopic dermatitis among Chinese families in Singapore. Ann Acad Med Singap 33:171–174
14. Cantani A, Micera M (2011) A study on 300 asthmatic children, 300 controls and their parents confirms the genetic transmission of allergy and asthma. Eur Rev Med Pharmacol Sci 15 9:1051–1056
15. Kijima A, Murota H, Takahashi A, Arase N, Yang L, Nishioka M et al (2013) Prevalence and impact of past history of food allergy in atopic dermatitis. Allergol Int 62(1):105–112. https://doi.org/10.2332/allergolint.12-OA-0468
16. Huang YH, Huang LH, Kuo CF, Yu KH (2020) Familial aggregation of atopic dermatitis and co-aggregation of allergic diseases in affected families in Taiwan. J Dermatol Sci 100 1:15–22. https://doi.org/10.1016/j.jdermsci.2020.07.007
17. Cosickic A, Skokic F, Selimovic A, Mulic M, Suljendic S, Dedic N et al (2017) Development of respiratory allergies, asthma and allergic rhinits in children with atopic dermatitis. Acta Clin Croat 56(2):308–317. https://doi.org/10.20471/acc.2017.56.02.15
18. Tsai HJ, Kumar R, Pongracic J, Liu X, Story R, Yu Y et al (2009) Familial aggregation of food allergy and sensitization to food allergens: a family-based study. Clin Exp Allergy 39(1):101–109. https://doi.org/10.1111/j.1365-2222.2008.03111.x

19. Luoma R, Koivikko A, Viander M (1983) Development of asthma, allergic rhinitis and atopic dermatitis by the age of five years. A prospective study of 543 newborns. Allergy 38 5:339–346. https://doi.org/10.1111/j.1398-9995.1983.tb04128.x
20. Mathias RA (2014) Introduction to genetics and genomics in asthma: genetics of asthma. Adv Exp Med Biol 795:125–155. https://doi.org/10.1007/978-1-4614-8603-9_9
21. Gupta J, Johansson E, Bernstein JA, Chakraborty R, Khurana Hershey GK, Rothenberg ME et al (2016) Resolving the etiology of atopic disorders by using genetic analysis of racial ancestry. J Allergy Clin Immunol 138 3:676–699. https://doi.org/10.1016/j.jaci.2016.02.045
22. van Beijsterveldt CE, Boomsma DI (2007) Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. Eur Respir J 29 3:516–521. https://doi.org/10.1183/09031936.00065706
23. Kiiski V, Ukkola-Vuoti L, Vikkula J, Ranta M, Lassenius MI, Kopra J (2023) Effect of Disease Severity on Comorbid conditions in atopic dermatitis: Nationwide Registry-based investigation in Finnish adults. Acta Derm Venereol 103:adv00882. https://doi.org/10.2340/actadv.v103.4447
24. Laske N, Bunikowski R, Niggemann B (2003) Extraordinarily high serum IgE levels and consequences for atopic phenotypes. Ann Allergy Asthma Immunol 91 2:202–204. https://doi.org/10.1016/S1081-1206(10)62178-3
25. Edenharter G, Bergmann RL, Bergmann KE, Wahn V, Forster J, Zepp F et al (1998) Cord blood-IgE as risk factor and predictor for atopic diseases. Clin Exp Allergy 28 6:671–678. https://doi.org/10.1046/j.1365-2222.1998.00241.x
26. Lio PA, Wollenberg A, Thyssen JP, Pierce EJ, Rueda MJ, DeLozier AM et al (2020) Impact of atopic dermatitis lesion location on quality of life in adult patients in a real-world study. J Drugs Dermatol 19 10:943–948. https://doi.org/10.36849/JDD.2020.5422