RESEARCH PAPER

Association between Interleukin-31 Levels and Disease Severity in Pediatric Atopic Dermatitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritus and a predominance of the T helper 2 (Th2) immune response. Interleukin-31 (IL-31) functions as a pruritogenic cytokine, amplifies inflammation, and has been reported to correlate with disease activity. Histamine also plays an important role in the pathogenesis of allergic conditions, including AD. This study aims to evaluate the association between IL-31 levels and AD severity in children. A literature search was performed across four databases (PubMed, ScienceDirect, Cochrane/CENTRAL, and Google Scholar) to identify and screen observational studies and randomized controlled trials (RCTs) published between 2010 and 2025 that investigated the association between IL-31 levels and AD severity. A total of 7 studies were selected for review, and 4 were included in the meta-analysis. All analyses were performed using Review Manager (RevMan) version 5.4.1. Following the literature search and study selection, comparisons of IL-31 levels between severity groups were expressed as standardized mean differences (SMDs) with 95% confidence intervals (95% CIs). Study quality was evaluated using Risk of Bias 2 (RoB 2) or the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. The present study reveals that IL-31 levels were associated with the severity of AD in children, with severe AD demonstrating significantly higher IL-31 levels compared with mild atopic dermatitis, with a pooled SMD of 2.78 (95% CI: 0.47–5.10; $p < 0.00001$; $I^2 = 95\%$). To conclude, IL-31 may be used as an inflammatory biomarker to assess the severity of AD in children.

Keywords: Atopic Dermatitis, Children, Interleukin-31, Severity

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INTRODUCTION

Atopic dermatitis is a skin disorder marked by chronic itching (pruritus), often beginning in childhood and continuing into adulthood. It can increase the risk of other atopic conditions. AD remains a prevalent dermatological ailment worldwide, and its prevalence has been steadily increasing over the past decade [1]. In Indonesia, the estimated national prevalence is 6.8%, and pediatric AD represents 23.67% of 611 newly documented dermatologic cases [2]. The Indonesian Pediatric Dermatology Study Group has identified AD as the most prevalent pediatric skin condition among the ten most common skin diseases in the nation. Diagnosis is primarily based on well-established clinical criteria, which incorporate patient history and physical examination findings. The Hanifin–Rajka criteria remain a widely used diagnostic tool, consisting of three major and three minor criteria. Disease severity is assessed using the SCORAD index, which ranges from 0 to 103, and its severity is classified as follows: mild (AD score ≤25), moderate (25–50), and severe (>50)[1,3].

AD results from an immune reaction involving Th2 cells, which secrete proinflammatory mediators (cytokines), particularly IL-31, acting as a pruritogen by intensifying inflammation by increasing the production of cytokines and chemokines. Additionally, IL-31 disrupts skin barrier functions by inhibiting keratinocyte proliferation and differentiation [4]. Numerous studies have identified a link between IL-31 and the onset of itching in chronic inflammatory skin disorders. This cytokine, which was discovered relatively recently, is predominantly released by activated T cells with a Th2-dominant profile. Moreover, research has shown that IL-31 levels are elevated in patients with AD compared to healthy subjects. Furthermore, IL-31 serum concentrations have been found to correlate with AD symptoms [5]. Histamine plays a pivotal role in allergic responses, particularly in atopic dermatitis. During skin prick tests, the introduction of an allergen leads to the release of histamine, which subsequently causes blood vessels to dilate and capillary permeability to increase. These changes result in the formation of wheals, thereby highlighting histamine's

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essential function as a positive control in allergen skin-prick testing [6].

Measuring IL-31 concentrations may offer a more thorough evaluation of inflammation, itching, and skin barrier abnormalities in children with AD, which could pave the way for objective measures of disease severity. This study aims to gather and analyze scientific research on IL-31 concentration in pediatric patients with AD, and to explore the relationship between IL-31 levels and the severity of AD symptoms.

METHODS

Search strategy and eligibility criteria

The literature search followed PRISMA guidelines and included PubMed, ScienceDirect, Cochrane/CENTRAL, and Google Scholar databases. The keywords used included “Interleukin-31,” “atopic dermatitis,” “children,” and “severity.” The records were assessed using established inclusion criteria, including clinical and observational studies (cohort, cross-sectional, systematic reviews, and scholarly articles) published between 2010 and 2025, to examine the relationship between IL-31 levels and the severity of atopic dermatitis in children. Exclusion criteria were literature reviews and studies not published in English or Indonesian.

Study selection and data extraction

Two reviewers independently assessed titles and abstracts to exclude irrelevant studies. They then thoroughly examined full texts of potentially relevant articles. Using a standardized tool, they independently collected data from eligible publications, including year, inclusion criteria, sample size, age, gender, IL-31 levels, author's name, and assessed outcomes.

Risk of bias assessment and quality of evidence

The Cochrane Risk of Bias 2 (RoB 2) tool assessed bias across all trials (using RCTs), while ROBINS-I assessed the bias for a specific trial (non-randomized) in the study. Bias levels were categorized as low, moderate, or high risk, or "No information" if data were lacking. Two independent assessors reviewed methodological quality according to SIGN criteria, with disagreements resolved by a third reviewer. The SIGN checklist was applied to RCTs and non-RCTs to assess three domains: internal validity, overall assessment, and study description. Articles were rated as 1+ if they were meta-analyses, low risk (in RCT), or systematic reviews. RCTs with a high risk of bias were rated 1-. Studies with high methodological rigor and low risk of bias were rated 2+, while studies with a high risk of bias were rated 2-.

Data synthesis and statistical analysis

The analysis was performed using Review Manager 5.4.1. The outcomes were measured as mean or standardized mean differences, with 95% confidence intervals. Heterogeneity was assessed using the I^2 index. Significant heterogeneity was determined when the p-value was <0.10 and the I^2 value exceeded 50%. Small-study effects and publication bias were assessed using a funnel plot. Subgroup analyses were significant at $p < 0.05$.

RESULTS

Characteristics of the included studies

Figure 1 shows the PRISMA flow diagram for this review. The literature search found 15 articles in PubMed, 104 in ScienceDirect, 2 in Cochrane, and 544 in Google Scholar, totaling 665 records. Duplicates, year, and title/abstract screening reduced this to 57 full-text articles. After applying inclusion and exclusion criteria, 9 articles were excluded for non-English or Indonesian language, and 41 for not addressing the topic. As a result, a systematic review included 7 articles with 323 participants, while a meta-analysis involved only 4 studies. Table 1 summarizes the study characteristics. All articles, published between 2010 and 2025, used observational clinical designs (case–control, cohort, cross-sectional) and investigated the relationship between IL-31 levels and atopic dermatitis severity in children.

Table 1: Characteristics of the included studies.

Author, Year	Design	Study quality *	Countries of origin	Total study population	Mean age	Sex ratio (male:female)	Severity assessment tool	IL-31 sample type	IL-31 levels (pg/mL)
Ozceker et al, 2018[7]	Case-control	2+	Turkey	61 children diagnosed with atopic dermatitis	6.02 ± 3.62 years	36:25	SCORAD	Plasma	Mild: 340.8 ± 177.0 Moderate: 273.0 ± 171.9 Severe: 274.6 ± 150.3
Atallah et al, 2019[8]	Case-control	2+	Egypt	50 children with atopic	5.98 ± 2.35 years	30:20	SCORAD	Serum	Mild: 64.18 ± 6.18 Moderat

				dermatitis					e: 104.53 ± 8.94 Severe: 202.85 ± 8.57
Ezzat et al, 2011[9]	Case-control	2+	Egypt	50 children with atopic dermatitis	5.75 ± 2.11 years	30:20	SCORAD	Serum	Mild: 540 ± 210 Moderate: 1,300 ± 769 Severe: 2,400 ± 1,010
Raap et al, 2012[10]	Cross-sectional	2-	Germany	65 children with atopic dermatitis	34.9 ± 16.9 months	not reported	SCORAD	Serum	Mean values not reported
Duca et al, 2022[11]	Observational study	2-	Romania	31 children with moderate-to-severe atopic dermatitis	not reported specifically for the atopic dermatitis subgroup	not reported specifically for the atopic dermatitis subgroup	SCORAD	Serum	Mean values not reported
Siniewicz-Luzeńczyk et al, 2013[5]	Cross-sectional	2-	Poland	25 children aged 4 months to 17 years diagnosed with atopic dermatitis	4.2 years	9:16	SCORAD	Serum	Mean values not reported
Cheon et al, 2015[12]	Cross-sectional	2+	South Korea	91 children with atopic dermatitis	6.33 ± 3.70 years	44:47	SCORAD	Serum	Mild: 5.90 ± 1.87 Moderate: 6.01 ± 1.48 Severe: 6.18 ± 2.06

SCORAD: Scoring Atopic Dermatitis

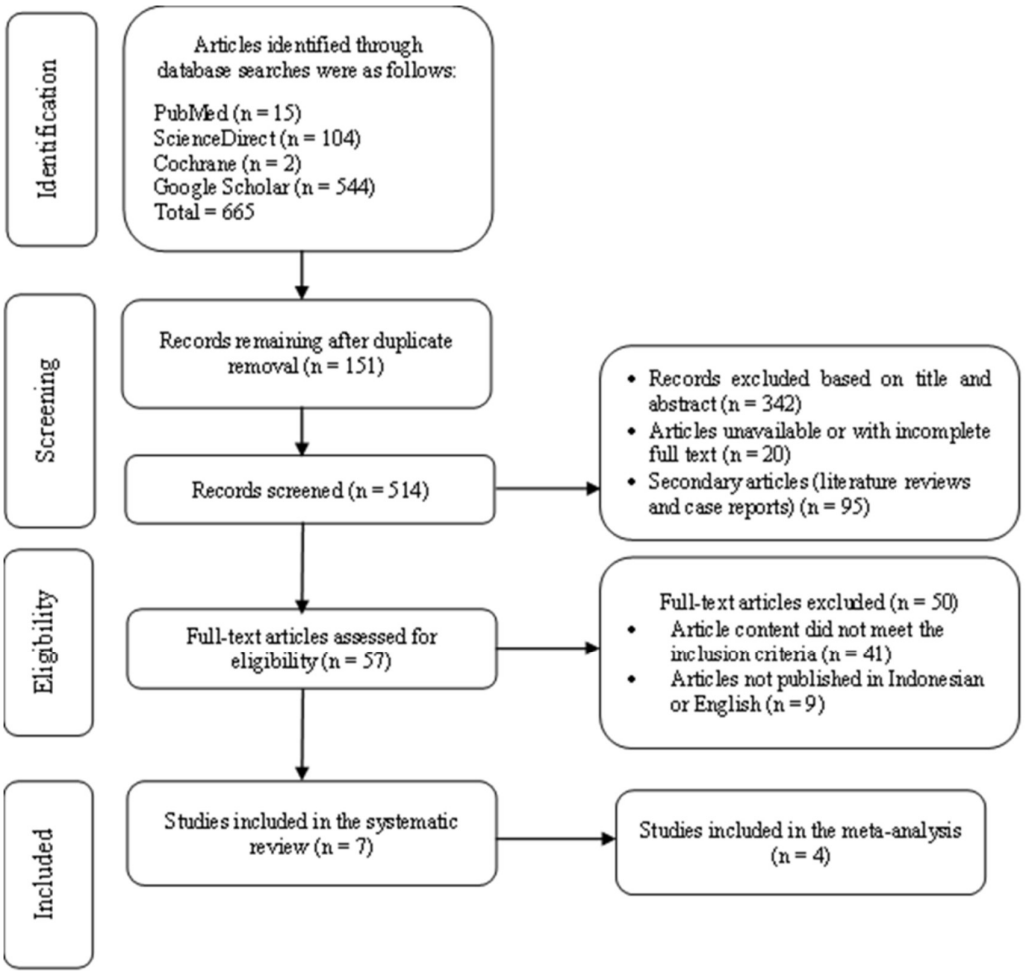

Figure 1: PRISMA flow diagram.

Risk of bias assessment and funnel plot

Figure 2 summarizes the results from the bias assessment using ROBINS-I. Three studies were of low risk, and four were of unclear risk. Figure 3 shows the funnel plot for the meta-analysis, indicating potential publication bias or heterogeneous results. However, with only a small number of studies, the graph was insufficient for a definitive assessment of bias.

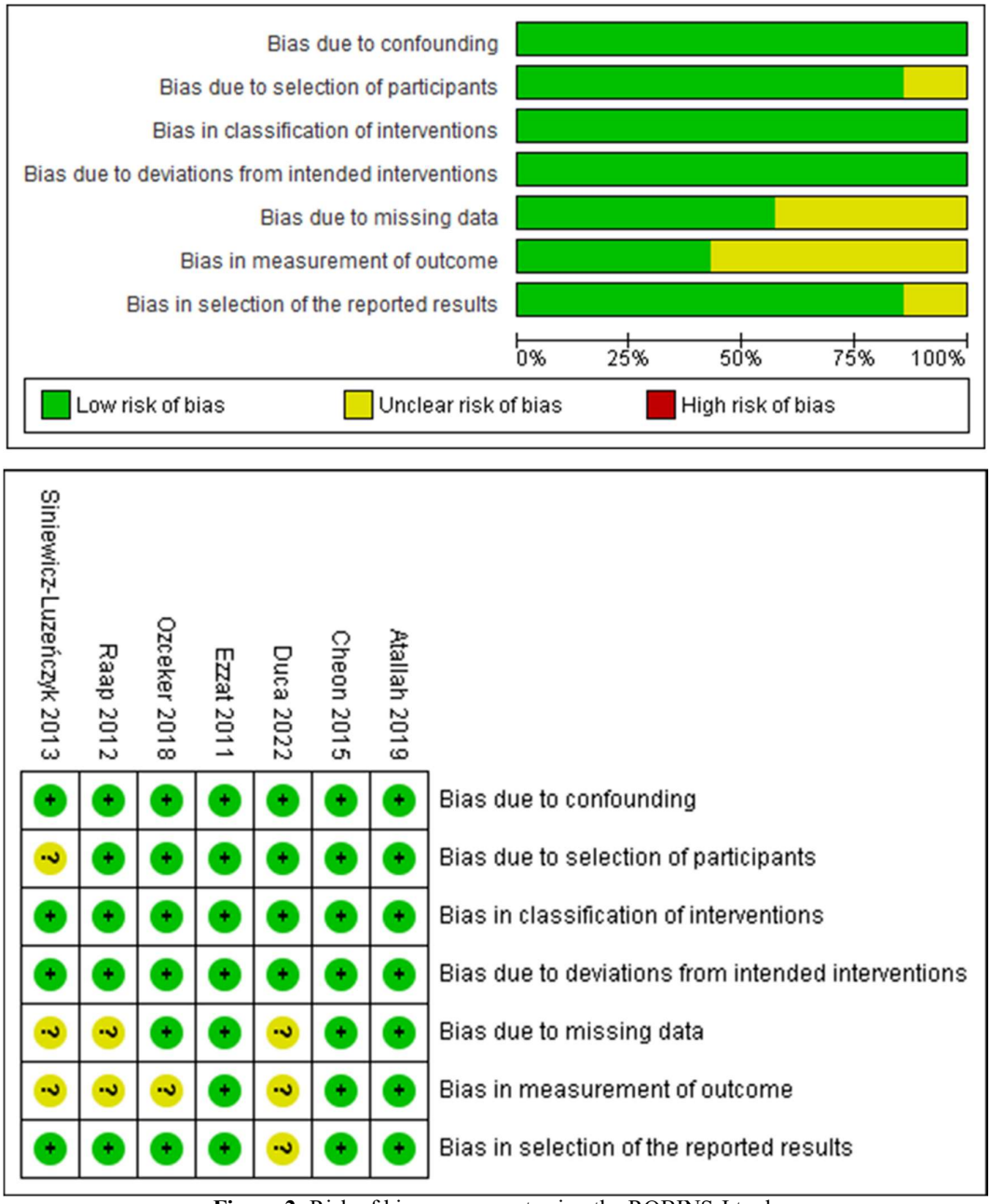

Figure 2: Risk of bias assessment using the ROBINS-I tool.

Summary of study findings

The summary-of-findings section (Table 2) presents comprehensive data from all the studies included. Various studies have shown conflicting results regarding the relationship between serum IL-31 levels and the severity of AD. Some studies found a substantial positive correlation between IL-31 levels and disease severity (references 8-11), while others reported no significant association (5,7,12).

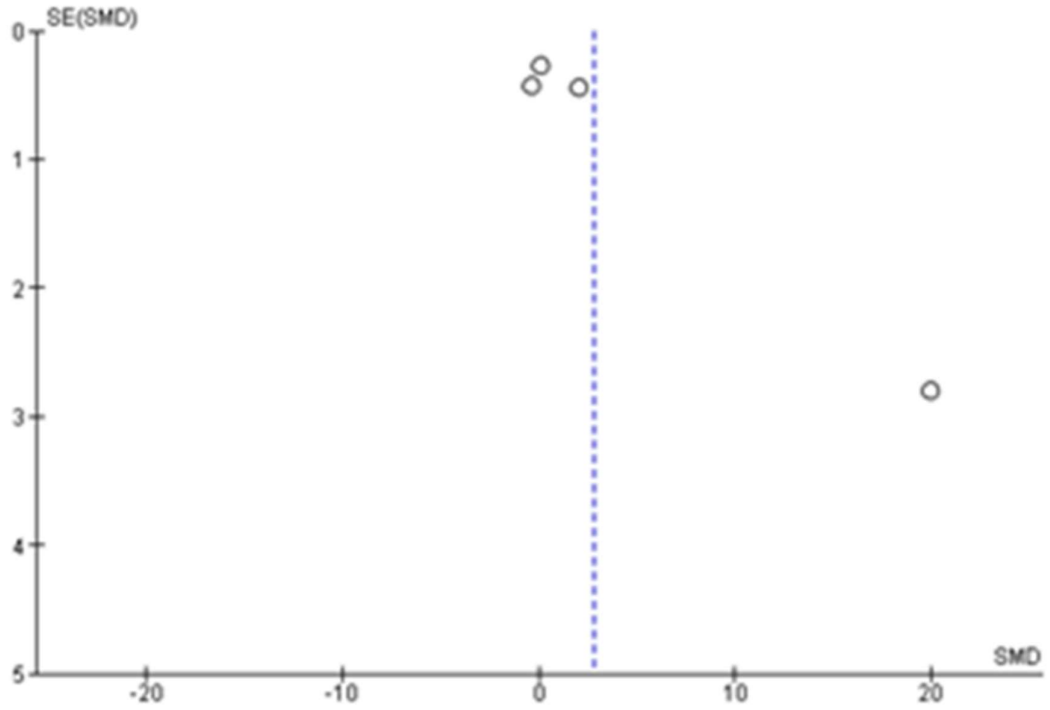

Figure 3: Funnel plot from the meta-analysis comparing IL-31 levels (left) in children with atopic dermatitis according to disease severity.

Association between IL-31 levels and AD severity

Figure 4 compares IL-31 levels across four studies. The specific results on the link between IL-31 levels and AD severity are shown in Table 2. The meta-analysis found that children with severe atopic dermatitis had higher IL-31 levels, and this relationship was statistically significant. The combined SMD was 2.78, with a 95% confidence interval ranging from 0.47 to 5.10 (95% CI: 0.47 to 5.10; $p < 0.001$; $I^2 = 95\%$).

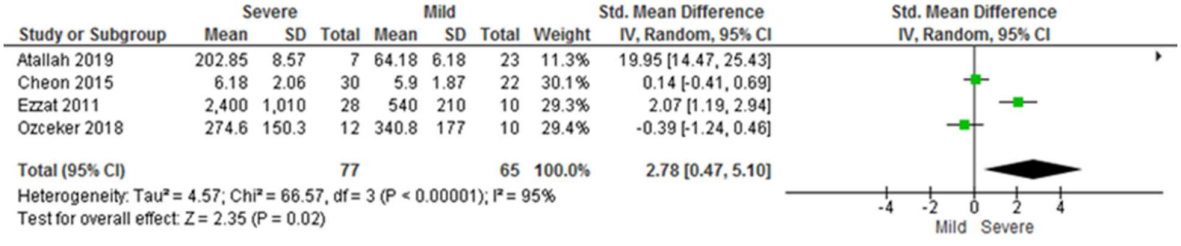

Figure 4: Analysis of differences in IL-31 levels according to severity in atopic dermatitis.

DISCUSSION

Atopic dermatitis is a chronic skin disease marked by itchy eczema flare-ups and periods of remission [13]. The severity of AD is evaluated using the SCORAD index and other objective and subjective symptoms. Atopic dermatitis is more prevalent in the pediatric population. The global incidence among children is 4.0% (102.78 million individuals), with regional variations ranging from 2.4% in Central Asia to 5.2% in central sub-Saharan Africa [15,16]. IL-31 is a newly identified cytokine associated with atopic dermatitis. Initially recognized for its role in inducing itching due to elevated levels in pruritic and allergic conditions, it mediates immune-nervous system interactions. Dillon et al. characterized IL-31 as a four-helix bundle cytokine in the gp130/IL-6 family in 2004 [17].

Meta-analysis showed children with severe atopic dermatitis had significantly higher IL-31 levels than those with mild disease, with a pooled standardized mean difference (SMD) of 2.78 (95% CI: 0.47 to 5.10; $p < 0.001$; $I^2 = 95\%$). This suggests higher IL-31 levels are linked to more severe atopic dermatitis.

Table 2: Studies on IL-31 levels and pediatric atopic dermatitis severity (PRISMA-based).

References (author, year)	Study location	Results
Ozceker et al, 2018[7]	Turkey	The median IL-31 level in the mild group was 336.5 pg/mL (IQR 223.5–462.5), in the moderate group 249 pg/mL (IQR 169–401), and in the severe group 313 pg/mL (IQR 154–356.8). Statistically, the differences in IL-31 levels among the groups were not significant ($p > 0.05$), indicating no strong evidence of a direct association between increasing atopic dermatitis severity and IL-31 levels in this study sample.
Atallah et al, 2019[8]	Egypt	Serum IL-31 levels increased progressively with the severity of atopic dermatitis as assessed by the SCORAD score. In the mild disease group, the mean IL-31 level was 64.18 ± 6.18 pg/mL with a median of 32.56 pg/mL, whereas in the moderate group it increased to 104.53 ± 8.94 pg/mL with a median of 108.05 pg/mL. The severe group exhibited the highest levels, with a mean of 202.85 ± 8.57 pg/mL and a median of 204 pg/mL. Statistical analysis demonstrated a highly significant difference in IL-31 levels among the groups ($H = 17.544$; $p < 0.001$), with significant differences between the mild and moderate groups ($p = 0.048$), the mild and severe groups ($p < 0.001$), and the moderate and severe groups ($p = 0.007$). These results demonstrated a positive association between increasing serum IL-31 levels and the severity of atopic dermatitis.
Ezzat et al, 2011[9]	Egypt	Serum IL-31 levels were significantly higher in the group with severe disease compared with the moderate or mild severity groups. In addition, serum IL-31 levels were positively correlated with the calculated severity scores (LSS, SSS, and the SCORAD index).
Raap et al, 2012[10]	Germany	Serum IL-31 levels were significantly correlated with the SCORAD score ($p < 0.01$), supporting an association between IL-31 and inflammatory severity in children with extrinsic atopic dermatitis.
Duca et al, 2022[11]	Romania	IL-31 levels were positively correlated with disease severity and activity in children with atopic dermatitis.
Siniewicz-Luzeńczyk et al, 2013[5]	Poland	There was no statistically significant correlation between serum IL-31 levels and disease severity or itch intensity. Serum IL-31 levels showed an inverse correlation with disease severity as assessed by the SCORAD index ($p = 0.1$).
Cheon et al, 2015[12]	South Korea	Serum IL-31 levels were not associated with atopic dermatitis groups or with disease severity as assessed by the SCORAD index. IL-31 levels did not differ significantly among the three groups, regardless of atopic dermatitis severity.

SCORAD: Scoring Atopic Dermatitis

Studies on the relationship between IL-31 levels and AD severity in children have yielded inconsistent results. Some reports show a significant positive correlation between serum IL-31 concentrations and disease severity, while others find no significant association or even contradictory results. Atallah et al. observed a clear increase in IL-31 levels with rising AD severity, as measured by SCORAD. Mild AD had the lowest IL-31 levels, while moderate and severe AD showed significantly higher levels ($p < 0.001$), with significant differences between all severity categories [8]. This result aligns with Ezzat et al.'s findings of a positive correlation between IL-31 levels and disease severity indices, as well as Raap et al.'s significant association between IL-31 and SCORAD scores ($p < 0.01$), especially in children with extrinsic AD [9,10]. Duca et al. found that interleukin-31 (IL-31) is positively correlated with disease intensity and activity in AD, which underscores its crucial role as an inflammatory mediator [11].

Research findings have been inconsistent. A study by Ozceker et al. revealed no significant disparity in interleukin-31 (IL-31) levels among individuals with different skin disease severities. Although average IL-31 concentrations fluctuated within each group, there was no significant variation between groups as a whole [7]. Siniewicz-Luzeńczyk et al. even reported an inverse correlation, although it was not statistically significant ($p = 0.1$)[5]. Similarly, Cheon et al. found no significant differences in IL-31 levels across levels of disease severity [12]. The inconsistencies in results might be explained by several factors. These include small sample sizes, diverse patient groups, varying measurement techniques, and the existence of different subtypes of AD (intrinsic versus extrinsic), which can influence cytokine profiles.

IL-31 levels are higher in severe AD, driving cutaneous inflammation. Together with IL-33, it acts as an alarmin, activating immune cells like eosinophils, fibroblasts, and dendritic cells. This leads to the production of pro-inflammatory chemokines (CCL17, CCL22, CXCL1, CXCL10) that reinforce Th2 immune cell recruitment. In addition, IL-31 also causes pruritus, leading to scratching that disrupts the skin barrier, increases inflammatory mediators, and promotes bacterial colonization by Staphylococcus aureus. This exacerbates inflammation and further stimulates IL-31 production. The itch-scratch cycle, along with genetic predispositions such as IL-31 haplotype polymorphisms and environmental influences like vitamin D insufficiency or excessive UV exposure, intensify the Th2 immune response. This leads to elevated IL-31 levels, which serve as both an indicator of disease activity and a pivotal factor in the progression of AD [18].

This study has limitations. The limited number of included studies may affect the strength of evidence and generalizability. Most studies had small sample sizes and heterogeneous designs, contributing to high meta-analysis heterogeneity. Despite these limitations, the study significantly contributes to understanding IL-31's role as a potential inflammatory biomarker in pediatric atopic dermatitis, which provides a robust scientific basis for further research on its use as an objective disease severity indicator.

To conclude, Interleukin-31 has been found to play a crucial role in the development and severity of atopic dermatitis in children. Higher concentrations of IL-31 were strongly linked to more severe disease, indicating its potential as an inflammatory marker for assessing disease activity and severity. Accordingly, IL-31 may serve as a more sensitive biological marker of atopic dermatitis severity.

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Nothing to declare

Conflicts of interest
The authors declare no potential conflict of interest

Authors' contributions
AEOBP: Study conception and planning; data collection, analysis and interpretation; statistical analysis; preparation and writing of the manuscript; approval of the final version of the manuscript. MI: Study conception and planning; data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. WW: Study conception and planning; data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. DK: Data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Data availability
Study data is available on request from the corresponding author according to institutional policies.

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