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# Serum interleukin-31 level and pruritus in atopic dermatitis: A Meta-analysis

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**ABSTRACT**

**Objective:** To investigate associations of interleukin-31 (IL-31) and pruritus in atopic dermatitis (AD) with Meta-analysis.

**Methods:** Materials were extracted from the citations listed in the following databases: PubMed, Science Direct, Web of Science and Cochrane. Key search terms included: atopic dermatitis, pruritus, and IL-31. The Meta-analysis was used to analyze the correlation between pruritws in AD and IL-31 expression level.

**Results:** The Meta-analysis showed that serum IL-31 levels were higher in AD patients than those in the healthy controls. The levels of IL-31 were higher in severe AD patients than those in the mild and moderate AD patients. Moreover, a positive correlation between serum IL-31 levels and severity of pruritus was identified.

**Conclusion:** Increased serum levels of IL-31 generally exist in the AD patients, and it may accelerate the pruritus in the AD patients.

**KEY WORDS** interleukin-31; dermatitis; atopic; pruritus; Meta-analysis

# 血清白介素-31水平与特应性皮炎瘙痒相关性的Meta分析

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**[摘要] 目的：**采用Meta分析的方法分析特应性皮炎(atopic dermatitis，AD)与血清白介素-31(interleukin-31，IL-31)水平的变化关系。**方法：**以“atopic dermatitis”“pruritus”及“IL-31”为关键词，在PubMed，Science Direct，Web of Science，Cochrane等数据库中检索相关文献，并使用Meta分析对AD与IL-31表达水平的相关性进行分析。**结果：**Meta分析结果显示相对于健康人群，AD患者血清IL-31表达水平更高，且重度AD患者的IL-31水平高于轻度AD患者；AD患

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者病情严重程度与IL-31表达水平呈正相关。**结论**：IL-31在AD患者中表达升高，且IL-31水平与AD患者瘙痒程度呈正相关。

**[关键词]** IL-31；特应性皮炎；瘙痒；Meta分析

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by intense and severe pruritus. It mainly affects children under 5 years old and less frequently occurs in adults, with a predilection for skin flexures[1]. The pathogenesis of AD involves impaired skin barrier function associated with an aberrant cutaneous immune response, which makes pruritus the major and disrupting symptom. The degree of severity of AD is related to the trans-epidermal water loss levels and decreased skin hydration. Thus, when the affected skin is poorly hydrated, pruritus becomes a major and disturbing symptom that disrupts the patient's quality of life and causes high levels of distress[2]. It is therefore an important symptom to be focused on. Pruritus is a hallmark in the course of AD. It is often referred as "the itch that rashes", resulting in a negative cycle referred as the "itch-scratch cycle" when itching leads to further scratching and damage to skin barrier function[3]. Pathogenesis of pruritus in AD is a complex interaction that involves central and peripheral mechanisms. Biomarkers also play an important role in the pathogenesis of pruritus, and targeting specific biomarkers can help develop novel medications to treat this symptom. One of these biomarkers is interleukin-31 (IL-31), a recently discovered cytokine that belongs to the Th2 cell mediated immune response[4]. It is a four-helix bundle cytokine activated by $CD4^+$ T cells and has 2 receptors: IL-31 receptor alpha (IL31RA) and oncostatin M receptor (OSMRB), which are expressed on epithelial cells and keratinocytes. Recent study[5] has shown that this cytokine is highly expressed in patients with AD, and the blockade of its receptor can inhibit the sensation of pruritus in mice[5]. Thus, the aim of this Meta-analysis is to determine the association between serum IL-31 levels in patients with AD-related pruritus and severity of the disease.

# 1 Materials and methods

## 1.1 Search strategy

A systematic search was performed using the databases, including PubMed, ScienceDirect, Web of Science, and Cochrane, to identify all the studies regarding the relationship between IL-31 and pruritus in AD. The search strategy was based on combinations of the words: atopic dermatitis, pruritus, and interleukin-31. There was no limit on time period, sample size, population or language of the studies reviewed.

## 1.2 Selection criteria

The studies with the following criteria were included: 1) Patients with diagnosis of atopic dermatitis, 2) data to extract risk difference (RD) and their corresponding 95% confidence interval (95% CI). Studies with the following criteria were excluded: Incomplete data, reviews and abstracts.

## 1.3 Data extraction

For each eligible study the following information was extracted: First author's name, year of publication, country, number of cases and controls with high levels of IL-31 and IL-31 measured at pg/mL level, mean, standard deviation, and journal.

## 1.4 Statistical analysis

Data and analysis of the articles included in this Meta-analysis were obtained using Review Manager Software 5.0. The mean ± standard deviation difference ($\bar{x}\pm s$) and risk difference (RD) with 95% confidence interval (CI) were calculated. Heterogeneity among studies was examined using the inconsistency index ($I^2$) test. A fixed model was adopted as the pooling method. Possible publication bias was determined using the Funnel plot obtained from Review Manager. $P<0.05$ was considered significantly different.

# 2 Results

## 2.1 Characteristics of the eligible studies

As shown in Figure 1, a total of 79 articles were identified from PubMed, ScienceDirect, Web of Science, and Cochrane databases using the key terms previously described. After reading their titles and abstracts 42 articles were excluded due to the types of studies (review articles, incomplete data, no availability) that either didn't match

our criteria or had no relationship with the aim of this study. Seven out of remaining articles were excluded due to inability to extract data. After reading full-text of remaining ones ($n$=30), 12 articles were included in this study. The studies included in this Meta-analysis were clinical trials, which detected blood levels of IL-31 or number of patients with higher levels of IL-31 compared to healthy controls. Their general characteristics are summarized in Table 1.

## 2.2 Quantitative analysis

A summary of the studies regarding the association between IL-31 levels in patients with AD and healthy conrtols is shown in Figure 2. A total of 147 patients with AD and 62 healthy controls were included in this study. There was a significant association between higher levels of IL-31 in patients with AD and healthy controls (RR=0.85,

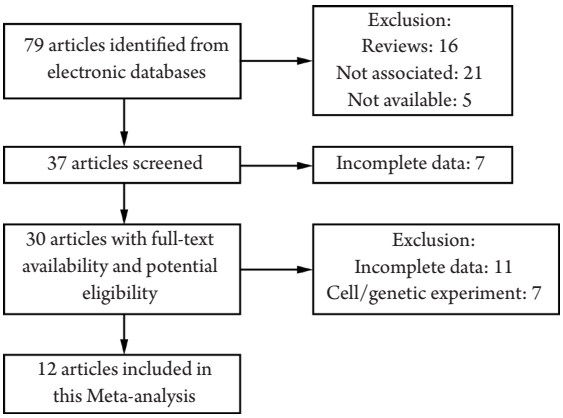


**Figure 1 Flow diagram of studies included and excluded in this Meta-analysis**

**Table 1 General characteristics of the studies included in this Meta-analysis**

| Author | Year | Type of study | Type of intervention |
|---|---|---|---|
| Cheon et al[6] | 2015 | Clinical trial | Measured mean and standard deviation in groups divided into mild, moderate and severe AD |
| Sokołowska et al[7] | 2013 | Clinical trial | Measurement of IL-31 associated with SCORAD |
| Kato et al[8] | 2014 | Clinical trial | Number of cases and controls with higher IL-31 levels |
| Siniewicz et al[9] | 2013 | Clinical trial | IL-31 levels between AD cases and controls |
| Cevikbas et al[10] | 2014 | Clinical trial | Tested cases and controls positive for higher IL-31 levels |
| Raap et al[11] | 2012 | Clinical trial | IL-31 levels between AD cases and controls |
| Nobbe et al[12] | 2012 | Clinical trial | Tested cases and controls positive for higher IL-31 levels |
| Song et al[13] | 2011 | Clinical trial | IL-31 levels between AD cases and controls |
| Hong et al[14] | 2012 | Clinical trial | IL-31 levels between AD cases and controls |
| Ezzat et al[15] | 2011 | Clinical trial | IL-31 levels between AD cases and controls, and evaluated according to severity of the disease |
| Grimstad et al[16] | 2009 | Clinical trial | Tested cases and controls positive for higher IL-31 levels |
| Dillon et al[17] | 2004 | Clinical trial | Tested cases and controls positive for higher IL-31 levels |

SCORAD: Scoring of atopic dermatitis

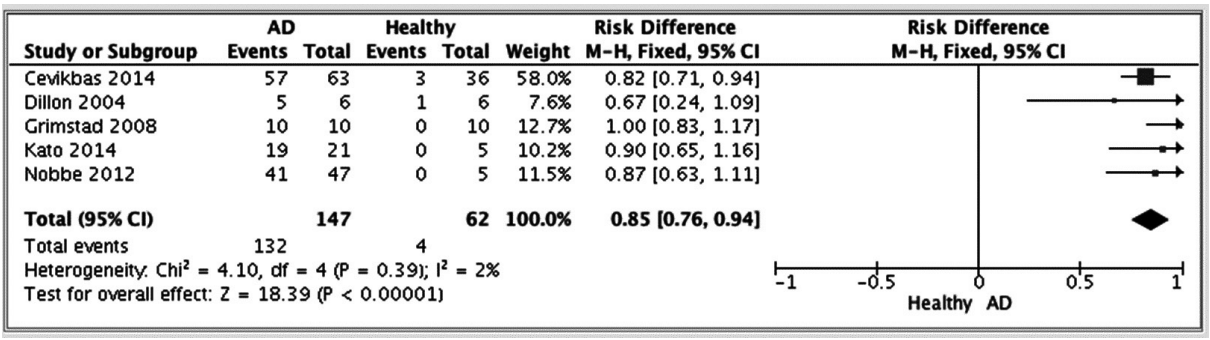


**Figure 2 Comparison of higher IL-31 levels between the AD patients and the healthy controls**

95% CI 0.76 to 0.94, $P$<0.00001).

2.2.1 IL-31 levels in AD patients compared with healthy controls

When comparing mean and standard deviation of studies with IL-31 levels in AD patients and healthy controls, a significant difference in IL-31 level was found in AD patients. Three studies were included in this analysis (95% CI 0.59 to 4.31, $P$<0.00001). Results are shown in Figure 3.

2.2.2 IL-31 levels in patients with different severity of AD

Three studies were included in this Meta-analysis to determine the relationship between pruritus and severity of AD. It was found that patients with severe AD had higher levels of IL-31 compared with patients with mild AD as shown in Figure 4. There was a significant association between severe AD and higher IL-31 levels (95% CI –2.12 to –0.17, $P$<0.00001).

2.2.3 Comparison of IL-31 at the pg/mL level between patients with AD and healthy controls

Three studies reported IL-31 at the pg/mL level, with data neither on mean nor standard deviation. The results showed that there were higher levels of IL-31 in patients with AD than those in healthy controls (Figure 5).

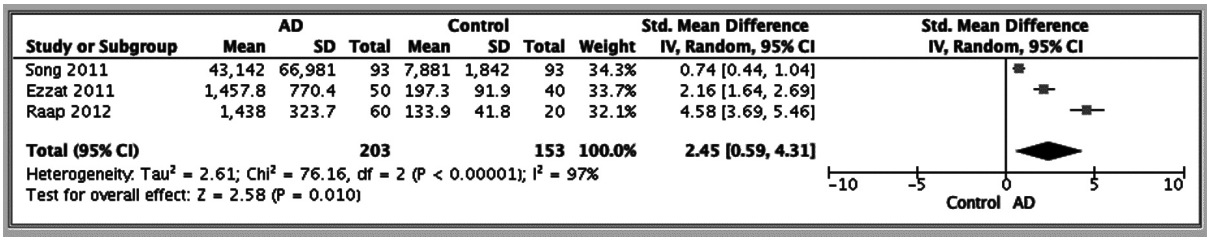


**Figure 3 Comparison of IL-31 levels between the AD patients and the healthy controls**

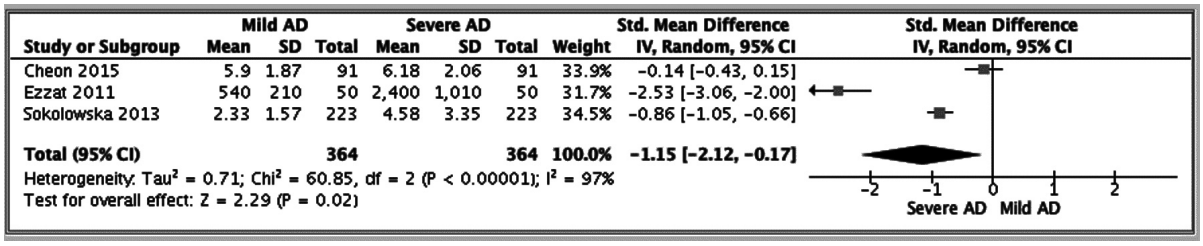


**Figure 4 Comparison of IL-31 levels between patients with severe and mild AD**

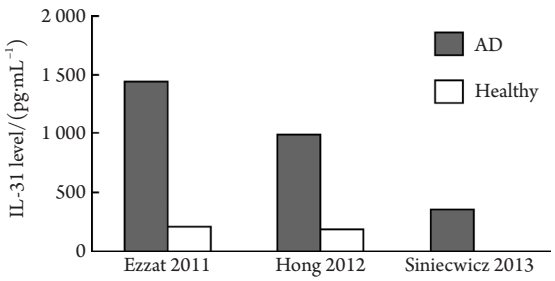


**Figure 5 IL-31 levels in AD patients and healthy controls**

## 2.3 Sensitivity analysis

To assess the reliability of the present study, a sensitivity analysis was carried on by excluding studies individually, therefore ensuring that each study was eligible for the aim of this study. No individual study was found having excessive influence on the pooled effect.

## 2.4 Publication bias

Potential publication bias in this Meta-analysis was estimated using funnel plot. The shape of the funnel plot revealed symmetry, which identified the absence of publication bias.

## 3 Discussion

In this Meta-analysis, 12 studies were screened to determine the association between IL-31 and pruritus in patients with AD compared with healthy controls. We found that IL-31 serum levels were higher in AD patients than those in healthy controls. And higher levels of IL-31 were found in severe AD patients compared with mild AD patients. Those results suggest that IL-31 may be involved in the AD pathogenesis.

IL-31 is a recently discovered cytokine involved in the pathogenesis of pruritus[14, 18-19]. Pruritus is a crucial symptom in AD, therefore IL-31 may affect AD by prompting pruritus. Pruritus has become a major health problem affecting 100% of patients with AD. Various cells (such as eosinophils, keratinocytes, mast cells, etc.) play a role in the pathogenesis of pruritus. Besides, inflammatory cell, genetic, environmental, and mechanical factors will contribute to the diagnosis of AD. The recent investigation[20-21] has concluded that AD results from the activation of Th2 cell lineage with the subsequent secretion of Th2 cytokines, especially IL-4 and IL-13, but recent study[22] has also shown IL-31to be a key cytokine in the generation of itch.

Role of IL-31 in pruritus has been studied by many researchers. Nobbe et al[12] measured IL-31, IL-31RA, CD68, OSMRB, and CD45RO levels in different skin diseases including AD, psoriasis, Sezary syndrome, alopecia areata, and micosisfungoides, and found that IL-31 immunoreactivity stimulated by inflammatory cells predominate in 87% of AD samples when compared with other itching diseases. The authors concluded that during the acute stage of AD there is a predominance of Th2 cytokines, while there is a predominance of Th1 cytokines during the chronic stages. Injecting IL-31-antibody in mouse models showed an initial reduction of scratching behavior over time, suggesting that IL-31 might play a role unique to AD, as it is elevated in peripheral sensory neurons in AD samples. Grimstad et al[16] also tested the mechanism by injection of monoclonal IL-31 antibody and found that it helps in reduction of scratching, making it a potential therapeutic approach in AD and pruritic diseases. However, higher IL-31 is found in severe AD but does not have a positive correlation between IL-31 and severity of pruritus[7].

IL-31 is demonstrated to promote the release of pro-inflammatory cytokines IL-1b, IL-6 from eosinophils by binding to its receptors, IL-31RA[23]. Recent study[8] has suggested that neurons express a small population of receptor IL31RA, transient receptor potential cation channel vanilloid subtype 1 (TRPV1), and transient receptor potential cation channel ankyrin subtype 1 (TRPA1), which are critical in the immune link between Th2 cells and sensory nerves that generate itching. They also concluded that IL-31 level is highly increased in pruritic AD skin and induces severe pruritus in mouse models. Moreover, neutralization of IL-31 reduces scratching and improves skin inflammation. There is a co-expression of IL-31RA and TRPV1 in dorsal root ganglia neurons, making an important contributor to scratching behavior[9]. IL-31 level is significantly reduced after the deletion of TRPA1. At the end of the study, they concluded that different pathways contribute to the generation of pruritus like the activation of IL-31RA on TRPV1 and TRPA1 sensory nerves in the skin, and that the receptor is exclusively expressed by a sub-population of TRPV1 and TRPA1 dorsal root ganglia neurons, evoking intense scratching in mouse models activated by IL-31 injection. Therefore, the inhibition of IL-31RA can block the sensation of AD itch[24].

Keratinocytes play an important role in the pathogenesis of pruritus. They express neural mediators and receptors related to the sensation of pruritus[14]. These neural mediators and receptors include opioids, proteases, substance P, nerve growth factor, endocannabinoids, interleukins, etc. Among interleukins, special attention has been paid to receptors of IL-31 and their ability to induce itching in mouse models with AD. IL-31 is highly expressed in keratinocytes in AD, suggesting a key role in the pathogenesis of pruritus. Special attention should be paid to develop new pruritus treatment alternatives.

It is very interesting that AD is a disease with a defective sweating mechanism. Dai et al[25] found that IL-31 is a part of the sweat components and directly activates epidermal keratinocytes. Once the keratinocytes are activated, keratinocytes are more prone to stimulate and secrete inflammatory cytokines, thereby to promote the itching cycle.

Evidence is now heading towards this recently discovered cytokine that still needs further evaluation. Major findings show that IL-31 plays a key role in the development of pruritus and is a strong biomarker for the

severity of AD[23]. It is therefore important to focus on this cytokine to understand its role in the pathogenesis of pruritus in AD. Due to pruritus the main disrupting symptom referred by AD patients which alters their quality of life, it is crucial to conduct more studies and experiments to determine the exact mechanism and develop new therapies.

In conclusion, this Meta-analysis showed that IL-31 serum levels are higher in AD patients than those in the healthy controls and levels of IL-31 are higher in severe AD patients than those in the mild AD patients. Recent clinical trials have demonstrated that treatment with IL-31 receptor inhibitors decreases pruritus and improves skin condition. Based on the results of the current study and understanding of the immunological basis of the disease, experiments can now be conducted to determine new treatments for pruritus and therefore, novel target should be developed for the future treatment of AD.

**Conflict of interest:** The authors declare that they have no conflicts of interest to disclose.

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