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Increased serum interleukin-31 levels correlate with pruritus in psoriatic patients: a cross-sectional study in Vietnam

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Abstract

Psoriasis is recognized not only as a skin disease but also as a systemic disorder. Interleukin-31 (IL-31) may be associated with psoriasis and systemic inflammation. We aimed to quantify serum IL-31 levels in patients with psoriasis and explore their associations with specific clinical manifestations.

30 patients with psoriasis and 30 healthy controls were included in this study. Demographic information and clinical characteristics were obtained through physical examination and medical history review. Serum IL-31 levels were measured using an enzyme-linked immunosorbent assay. IL-31 concentration was significantly higher in patients with psoriasis than in the control group ($p<0.001$). Patients with psoriasis vulgaris, psoriasis erythroderma, and pustular psoriasis had significantly higher serum IL-31 levels than healthy controls. Additionally, serum IL-31 levels were associated with itch numerical rating scale (NRS) scores and body mass index (BMI) but not with disease severity as measured by the Psoriasis Area and Severity Index (PASI).

In patients with psoriasis, increased serum IL-31 levels correlated with itch severity but not with PASI. This suggests that IL-31 may play a critical role in the pathogenesis of psoriasis and could be a valuable target for further studies and therapeutic interventions.

Introduction

Psoriasis is a prevalent immune-mediated disease that affects approximately 2–3% of the population. It primarily manifests in the skin and joints, increasing susceptibility to comorbidities that frequently lead to various mental health issues.[1] Itch, which is often underestimated in psoriasis, significantly impairs the quality of life of patients.[2] The role of IL-31 in psoriasis pathogenesis remains poorly understood. Recent research has indicated that IL-31 plays a pivotal role in itching mechanisms and the development of inflammatory skin diseases. IL-31 is predominantly secreted by activated $CD4^+$ (Th2) T cells and binds to its receptors, IL-31RA and OSMR. Numerous studies have reported elevated serum IL-31 levels in patients with psoriasis.[3-5] IL-31 also indirectly induces the secretion of other pro-inflammatory factors, such as IL-6, IL-32, and MMP, prompting further investigation into its role in psoriatic inflammation. Studies comparing serum IL-31 levels between patients with psoriasis and healthy controls have yielded inconsistent results. Previous studies have reported increased serum IL-31 levels, specifically in psoriasis vulgaris; however, its variations across different psoriasis types, such as psoriatic arthritis, psoriatic erythroderma, and pustular psoriasis, remain unexplored. Diverse conceptual frameworks are essential for comprehending psoriasis pathogenesis, necessitating tailored investigative approaches.[6]

This study aimed to quantitatively analyze variations in serum IL-31 levels among different psoriasis subtypes and assess the relationship between IL-31 concentration, itch severity, and clinical psoriasis severity. This enhances the understanding of the role of IL-31 in psoriasis pathogenesis, laying the groundwork for further exploration of the immune pathophysiology of psoriasis and providing a scientific basis for the development of novel, more effective treatment methods.

Materials and Methods

Study population

This study was conducted at Ho Chi Minh City Hospital of Dermatology-Venereology, Vietnam, between January 2022 and August 2022. 30 patients diagnosed with psoriasis and 30 healthy volunteers without a personal or family history of psoriasis or inflammatory disorders were enrolled in the study. We also excluded patients with psoriasis who had been treated with systemic anti-inflammatory or immunosuppressive agents (such as methotrexate, cyclosporin, corticosteroids, or omalizumab) within 6 months or with antihistamine H1 agents within 2 weeks before the study. All patients refrained from using topical psoriasis medications or emollients for at least 2 weeks before evaluation. Additionally, pregnant or lactating patients and those with other acute and chronic diseases associated with elevated serum IL-31 levels (such as atopic dermatitis, urticaria, and contact dermatitis) were excluded.[3,4] All participants signed an informed consent form after fully understanding the benefits and risks of the study.

After qualified physicians conducted a physical examination to confirm the diagnosis of psoriasis, each patient underwent a comprehensive medical history review, including general health, age, sex, occupation at presentation, disease course and duration, and family history. Clinical examinations and laboratory tests were also performed. Patients with symptoms that met the classification criteria for psoriatic arthritis (CASPAR) were classified as having psoriatic arthritis. Skin disease severity was determined using the Psoriasis Area Severity Index (PASI) and body surface area (BSA). Itch was evaluated using the itch numeric rating scale (Itch NRS; a 0- to 10-point numeric rating scale).[7-10]

Blood sample preparation

Up to 3 mL of peripheral blood was collected from both patients and healthy subjects and stored in plasma separator tubes containing ethylenediaminetetraacetic acid (EDTA). Blood samples were analyzed at the Medical Center (Ho Chi Minh City, Vietnam) within 2h of collection, and serum IL-31 levels were quantitatively detected using a human IL-31 enzyme-linked immunosorbent assay kit (Abcam). Blood samples were collected from the patients and paired with routine analyses at the first visit.

Statistical analyses

All collected data were coded and analyzed using standard software (R version 3.6.3, Mac OS). Qualitative data are presented as frequencies and percentages (%). Quantitative data with normal distributions were described using the mean and standard error of the mean (SEM), whereas those with non-normal distributions were described as median and interquartile range. The Chi-square test was used to compare non-numerical data. For normally distributed data, Student's *t-test* and ANOVA were used to determine the statistical significance of the difference between two or more study group means. Mann–Whitney and Kruskal–Wallis tests were used to compare two or more groups with non-normal distributions. Spearman's correlation test was used to study the correlation between quantitative parameters. All statistical tests were two-sided, and a p-value<0.05 was considered significant in all statistical tests.

Results

Serum IL-31 concentrations in psoriatic patients

The selected demographic, clinical, and laboratory characteristics of the patients with psoriasis and healthy controls are summarized in Table 1. There were no statistically significant differences between the two groups in terms of sex, age, or BMI. The mean serum IL-31 level in patients was

243.6±63.4 ng/mL (Min 135.7, Max 373.3). This level was significantly higher than that in controls, which averaged 42.6±9.1 ng/mL (Min 25.09, Max 65.89; $p<0.001$) (Figure 1).

Serum IL-31 concentrations in different psoriatic subtypes

All subgroups of psoriasis also exhibited significantly elevated IL-31 levels compared to the control groups. However, there were no significant differences in IL-31 levels among patients with different psoriasis subtypes, although the levels were slightly elevated in patients with psoriatic arthritis (Table 2).

Serum IL-31 levels in correlation with itch severity and BMI

In this study, serum IL-31 levels were not correlated with demographic characteristics, including age, age at onset, and disease duration in patients with psoriasis (Table 3). We did not detect any relationship between serum IL-31 levels and psoriasis severity, as assessed by PASI ($r=0.037$, $p=0.85$); however, there was a correlation between serum IL-31 levels and Itch NRS ($r=0.57$; $p=0.001$) and BMI ($r=0.402$, $p=0.028$) (Figure 2 A,B).

Discussion

In this study, we assessed the serum levels of IL-31 in 30 patients with psoriasis to investigate its relationship with clinical manifestations. We found that increased serum IL-31 levels correlated with itch severity but not with PASI, suggesting that IL-31 may play an important role in determining the pathogenesis of psoriasis and may serve as a valuable target for further studies and targeted treatment. We propose two points of discussion that emphasize the importance of our findings.

Serum IL-31 levels were significantly higher in patients with psoriasis than in the control group.

The pathophysiology of itching in psoriasis has been studied; however, the specific itch mediators responsible remain unclear.[11] IL-31 is an itch-mediating cytokine produced by abundant cells, including Th2 cells, $CD4^+$ $CD45RO^+$ CLA^+ skin helper T cells, $CD4^+$ $CD45RO^+$ CLA^+ skin helper cells, mast cells, keratinocytes, and fibroblasts.[12,13] The release of IL-31 by human mast cells provides a novel mechanism for inflammatory reactions.[14] IL-31 signals through IL-31R, which comprises IL-31RA and oncostatin M receptor β (OSMRβ). OSMRβ is ubiquitously expressed, whereas IL-31RA expression is stimulated mainly by IFNγ and TGFβ.[12,15] The binding of IL-31 to its receptors promotes cell signaling through the activation of three pathways: STAT3/5, PI3K/Akt, and mitogen-activated protein kinase (MAPK).[16,17]

Recently, IL-31 has been implicated in dermatitis by activating dendritic cells in the skin and increasing the levels of inflammatory mediators that regulate cell proliferation and tissue regeneration.[13,15] A review of the literature on the role of IL-31 in psoriasis is presented in Table 3. Previous studies have demonstrated that IL-31 levels are elevated in patients with plaque psoriasis[3,18] and that serum IL-31 levels in patients with psoriasis and itching are significantly higher than those in healthy subjects.[5,18] Experimental studies on irradiation have demonstrated a decrease in IL-31 levels and a reduction in itching, suggesting that IL-31 may contribute to the pathogenesis of itching in psoriasis.[3,19,20,21] Recent studies have highlighted the pathophysiology of IL-31 as a pro-inflammatory cytokine closely associated with the Th17 cytokine profile, suggesting that IL-31 may directly or indirectly induce a Th17 response in patients with psoriatic arthritis.[4] In 2024, Wongjirattikarn *et al.*[22] found that tissue expression of IL-31 in patients with psoriasis, assessed via immunohistochemistry, was significantly higher than that in healthy skin. The prevalence and intensity of itch symptoms experienced by patients with different clinical types of psoriasis were investigated, and itching was significantly more severe in erythroderma and

inverse psoriasis and tended to increase with clinical severity.[23] These findings are consistent with those of previous studies but particularly indicate that patients with other subtypes of psoriasis, including psoriatic erythroderma and pustular psoriasis, have significantly higher serum IL-31 levels than healthy controls. This finding indicates that serum IL-31 may act as an "itchy cytokine" in the complex pathogenesis of this disease as an inflammatory protein.

Serum IL-31 levels correlate with itch severity and BMI but not the severity of psoriasis

Psoriasis significantly diminishes the quality of life, primarily due to itching, which is the predominant symptom affecting patients with psoriasis.[24] The prevalence of itching among patients with psoriasis was 88.3%,[18] 84%,[20] 80%,[19] and 67%[25] in various studies. Most patients with psoriasis in our study (28/30, 93.3%) reported itching, which is consistent with the study by Purzycka-Bohdan *et al.*[26] There were two cases of moderate-to-severe psoriasis vulgaris without pruritus; however, their serum IL-31 levels were still higher than those of healthy participants. Our study showed no differences in serum IL-31 levels across different severity categories based on the PASI score. Similarly, in 2021, Purzycka-Bohdan *et al.* reported that serum IL-31 levels did not correlate with psoriasis severity, itch intensity, disease onset, or psoriatic arthritis.[26] Chaowattanapanit *et al.* found that serum IL-31 levels in patients with pruritic psoriasis were significantly higher than those in healthy subjects. However, no significant difference was observed in the lesional expression of IL-31 according to the disease severity or itch intensity.[5] Wongjirattikarn *et al.* found increased tissue expression of IL-31 in patients with psoriasis compared to healthy skin; however, there was no significant difference in the lesional expression of IL-31 according to disease severity or itch intensity.[22] Our findings are reasonable because there was no correlation between pruritus and psoriasis severity in a previous study (Table 3). In contrast to prior research indicating that serum IL-31 levels may not serve as reliable markers of psoriatic

pruritus,[26,5,22] our study identified, for the first time to the best of our knowledge, a positive correlation between serum IL-31 levels and itch severity. Although there are disparities in the literature, these findings suggest that IL-31 may not play a direct pathological role in psoriasis but acts as an effector cytokine that induces a downstream inflammatory cascade, especially itching in psoriasis.

Additionally, we observed an inverse correlation between serum IL-31 levels and BMI. To the best of our knowledge, this relationship has not been previously reported. IL-31 may potentially induce a Th17 response directly or indirectly in patients with psoriatic arthritis[4], while pro-inflammatory cytokines have been noted for their dual role in adipogenesis, exerting both inhibitory and stimulatory effects.[27] IL-17 inhibits the expression of several pro-adipogenic transcription factors, such as PPARγ and C/EBPα.[28] Therefore, adipogenesis is suppressed by IL-17 due to the combined action of transcription factors that govern adipocyte differentiation.[28-30] Reports have also suggested that IL-17 acts as a negative regulator of adipogenesis and glucose metabolism and delays the onset of obesity.[29] Therefore, we assumed that IL-31 may act as an effector via IL-17 signaling during the anti-adipogenesis process. Further research is needed to clarify the exact role of IL-31 in the anti-adipogenic properties of metabolic syndrome.

While this study offers valuable insights into the role of IL-31 in psoriasis, it has some limitations that are important to acknowledge. First, scalp psoriasis is associated with more intense itching than other types of psoriasis, leading to considerable impairment in quality of life.[31] In our study, all 30 recruited psoriatic patients had scalp lesions; therefore, we could not compare patients with and without scalp psoriasis. Assessing itch severity in scalp psoriasis is a valuable focus for future research. Second, a significant limitation is that we used circulating serum IL-31 levels as a proxy

for its expression within the affected psoriatic tissue. Ideally, future studies with larger patient populations should directly measure IL-31 expression in tissues to confirm its contribution and explore the underlying mechanisms of different immunological pathways in psoriasis pathogenesis.

Conclusions

Increased serum IL-31 levels in patients with psoriasis are correlated with itch severity and BMI. In this study, we hypothesized that serum IL-31 levels play a role in psoriasis pathogenesis and serve as valuable clinical biomarkers of itch severity. Further investigation is needed to provide insights into the role of IL-31 in itching and metabolic syndrome, which may contribute to the development of more effective psoriasis treatments.

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Table 1. Clinical manifestation of studied groups.

Characteristics	Patients with psoriasis (n=30)	Control subjects (n=30)	P value
Sex, n (%)			0.796 †
Male	14 (43,3)	16 (56.7)	
Female	16 (56,7)	14 (43.3)	
Age, years	52.2 (34.0 – 59.0)	42.0 (31.0 – 53.0)	0.068 §
Age of onset, n (%)			
< 40 yrs old	15 (50.0%)		
≥ 40 yrs old	15 (50.0%)		
Duration of disease, n (%)			
≤ 10 years	20 (66.7%)		
>10 years	10 (33.3%)		
BMI (kg/m^2)	22.5 ± 3.6	22.0 ± 3.5	0.624§
BMI Categories, n (%)			0.624¶
Underweight	1 (3.3%)	2 (6.7%)	
Normal weight	17 (56.7%)	17 (56.7%)	
Overweight	5 (16.7%)	9 (30.0%)	
Obese	7 (23.3%)	2 (6.6%)	
Subgroups of psoriasis, n (%)			
Psoriasis vulgaris	23 (76.7%)		
Pustular psoriasis	2 (6.7%)		

Psoriatic erythroderma	5 (16.7%)
PASI	
Psoriasis vulgaris	16.7 ± 8.24
Psoriatic erythroderma	41.4 ± 4.4
Psoriasis arthritis, n (%)	
Yes	5 (16.7%)
No	25 (72.3%)

Data were described using mean (±standard deviation) for normal distribution and median (interquartile range) for non-normal distribution. Differences between patients and controls were analyzed by using †Chi-square, ‡Mann–Whitney, §T-Test, and ¶Fisher's Exact Test.
*Statistically significance ($p<0.05$).
BMI: Body Mass Index, BSA: Body Surface Area, GPP: Generalized Pustular, PASI: Psoriasis Area Severity Index

Table 2. Serum IL-31 levels in subgroups of psoriasis.

	Controls n = 30	Psoriasis vulgaris n = 23	Psoriatic erythroderma n = 5	Pustular psoriasis n = 2
Serum IL-31 levels (pg/mL)	40.8±9.1	248.2 ±65.3	221.2±69.5	249.6±17.1
p (vs. controls)		< 0.0001*	< 0.0001*	< 0.0001*

Data were presented as mean±SD. Statistical analysis is done using the Independent *t-test*. *Statistically significance ($p<0.05$).

Table 3. Literature review of IL-31 in psoriasis.

Study	Year	Subjects	Aim and Method	Result	
Wongjirattikarn et al. [22]	2024	Twenty-six biopsy specimens of psoriasis patients and 10 tissue samples of healthy subjects	Tissue expression of IL-31 in patients with psoriasis was measured by immunohistochemistry	Epidermal and dermal psoriasis lesions had significantly higher IL-31 expression than healthy skin lesions.	No significant difference in lesional expression of IL-31 by disease severity or itch intensity.
D. Purzycka-Bohdan et al. [26]	2021	Three hundred psoriasis patients and 186 healthy volunteers	• Analyze IL-31 -1066G/A and -2057G/A promoter gene polymorphisms and serum IL-31 level and their correlation with the severity of psoriasis and pruritus. • The polymorphisms were analyzed using the ARMS-PCR method. • Serum levels of IL-31 were measured using ELISA.	Significance of IL-31 gene polymorphisms and IL-31 serum level in psoriasis in correlation with pruritus.	Serum levels of IL-31 did not correlate with the studied polymorphic variants of the IL-31 gene, severity of psoriasis, disease onset, presence of psoriatic arthritis, and pruritus intensity.

S. Chaowattanapanit et al. [5]	2020	30 psoriasis patients with pruritus and 31 healthy subjects	Serum IL-31 levels were measured by ELISA.	Psoriasis patients with pruritus had significantly higher mean serum IL-31 when compared with the healthy subjects.	Serum IL-31 levels of psoriasis patients did not differ significantly according to disease or itching severity.
L. A. Bautista-Herrera et al. [4]	2020	50 patients with PsA and 30 control subjects matched by age and gender	The cytokine serum levels were quantified by a magnetic bead-based assay using the Bio-Plex MAGPIX system, and RORC mRNA expression was determined by qPCR.	Significant higher serum IL-31 and Th17 cytokine profiles (IL-17A, IL-17F, IL-17E) were observed between the PsA and control groups.	Positive correlations between IL-31 and Th17 cytokine profile serum levels were found.
J. Bilsborough et al. [3]	2013	Fifty-nine psoriatic patients treated with NB-UVB (20 exposures), and 50 healthy, age and sex-matched participants.	IL-31 substance P was analyzed by ELISA before the treatment, and in the psoriatic group, the analysis was also done after 10 and 20 irradiations.	A significantly higher concentration of IL-31in psoriatic psoriasis compared to the control group.	Twenty NB-UVB exposures caused a significant decrease in IL-31 level (748.6 vs. 631.7 ng/ml; $p < 0.0001$).

IL-31: Interleukine-31; ELISA: Enzyme-linked immunosorbent assay; ARMS-PCR: Amplified refractory mutation system - polymerase chain reaction; NB-UVB: Narrow-band ultraviolet B; qPCR: quantitative polymerase chain reaction; PsA: Psoriatic arthritis

Figure 1. Patients with psoriasis show significantly elevated serum IL-31 levels.

Serum IL-31 levels of 30 patients with psoriasis (right) and 30 healthy controls (left) were given. The horizontal bars show the mean values.
P values < 0.05 are statistically significant. The significance of the difference between groups was tested by the Mann–Whitney U test (**** p<0.0001).

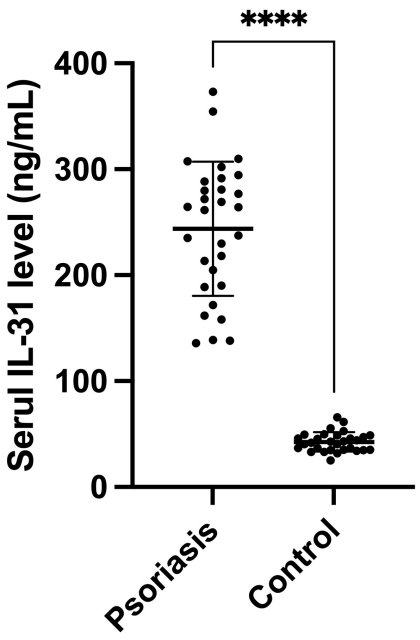
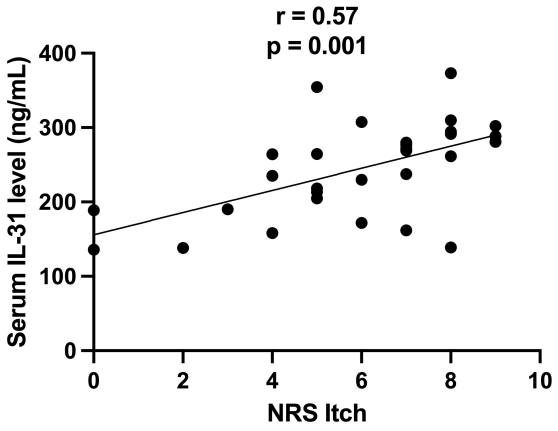
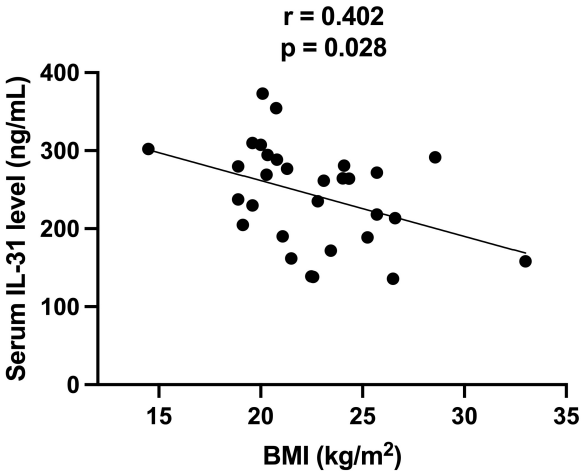


Figure 2. Correlation between serum IL-31 levels and Itch severity.

There was a correlation between serum IL-31 levels and Itch NRS (r=0.57; p=0.001) **(A)** and BMI (r=0.402, p=0.028) **(B)**.
BMI: Body Mass Index, PASI: Psoriasis Area Severity Index.
*Statistically significance (p<0.05).



(A)



(B)