

The Clinical Relevance of Serum Interleukin-21 in Grading Acne Vulgaris

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ABSTRACT

Acne vulgaris (AV) is an inflammatory skin disorder with multifactorial pathogenesis involving genetics, hormones, and immune dysregulation. Interleukin-21 (IL-21), a pleiotropic cytokine mainly secreted by T follicular helper and Th17 cells, has been implicated in various inflammatory skin diseases. However, its role in AV remains unclear. This cross-sectional study included 46 patients with AV, classified into mild (n=19), moderate (n=16), and severe (n=11) groups. Serum IL-21 levels were measured using an enzyme-linked immunosorbent assay (ELISA). Baseline characteristics were compared across groups, and interobserver reliability of AV severity grading was evaluated using Cohen's kappa test. One-way ANOVA was applied to assess differences in IL-21 levels among severity groups, with a significance level set at $p < 0.05$. The mean serum IL-21 level was highest in the severe AV group (303.53 pg/mL), followed by the moderate (223.7 pg/mL) and mild (213.2 pg/mL) groups. Although there was a trend toward increasing IL-21 levels with higher AV severity, statistical analysis revealed no significant difference among the three groups ($p = 0.130$). Serum IL-21 levels were elevated in AV patients compared with previously reported healthy controls but did not differ significantly across severity levels. These findings suggest that IL-21 may play a role in the pathophysiology of AV, though it is not a reliable marker of clinical severity. Further case-control and tissue-based studies are needed to clarify its role.

Keywords: *Interleukin-21, Severity, Acne vulgaris*

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INTRODUCTION

Acne vulgaris (AV) is a chronic, multifactorial disorder of the pilosebaceous unit that most commonly manifests during adolescence. Its global prevalence is estimated at 9.4% and affects up to 85% of individuals between 12 and 25 years of age (Wang et al., 2022). The pathogenesis of AV is closely related to increased sebum production, hyperproliferation of follicular keratinocytes, proliferation of *Cutibacterium acnes* (*C. acnes*), and subsequent inflammatory responses (Goh et al., 2019). Several risk factors have been implicated in the development of AV, including the use of certain medications such as steroids and lithium, ultraviolet exposure, occlusive accessories such as headbands or shoulder pads, cosmetic use, hormonal disturbances, genetic predisposition, and dietary intake of processed foods (Hazarika, 2019).

Acne vulgaris lesions most frequently develop in areas rich in sebaceous glands, particularly the face and back (Leung et al., 2021). Clinically, AV presents as comedones, papules, pustules, or nodules (Legiawati et al., 2023). Lesions located on the face often raise cosmetic concerns and may result in substantial psychosocial burden, including low self-esteem and impaired self-image. These psychological effects can further interfere with occupational performance, social interactions, and interpersonal relationships (Hazarika & Archana, 2016). This impact becomes more profound with increasing disease severity (Tasneem et al., 2023). Given its broad clinical and psychosocial consequences, AV continues to be a major focus of research, particularly regarding its pathophysiology and the role of

cytokines in disease progression, in pursuit of more effective therapeutic strategies (Elattar et al., 2022).

Cytokines are small protein molecules that play essential roles in cell signaling and in the pathophysiology of immune-mediated skin diseases (Gadina, Gazaniga, Vian, & Furumoto, 2017). They serve as major determinants of T cell lineage differentiation within the CD4⁺ T cell population (Turchin & Bourcier, 2022). *C. acnes* can induce inflammation by stimulating immune cells and follicular keratinocytes to secrete proinflammatory cytokines through toll-like receptor (TLR)-2 and TLR-4 activation. This leads to the production of cytokines such as interleukin (IL)-1 β , IL-6, and IL-12, which drive naïve T cells to differentiate into five main subtypes: T helper (Th)1, Th2, Th17, T follicular helper (Tfh), and regulatory T (Treg) cells (Kim et al., 2018). Each subset has a distinct role: Th1 cells mediate intracellular immunity via interferon (IFN)- γ secretion; Th2 cells regulate mucocutaneous immunity through IL-4 and IL-5 release; Th17 cells produce IL-17, IL-21, and IL-22 to recruit neutrophils and activate stromal and epithelial cells; Tfh cells support B cell differentiation and antibody production; and Treg cells exert immunosuppressive functions (Ruterbusch et al., 2020; Shilovskiy et al., 2023; Nalbant, 2018; Mesas-Fernández et al., 2023).

Interleukin-21 (IL-21) has recently gained considerable attention due to its role in the pathogenesis of several inflammatory skin diseases, including psoriasis, lichen planus, atopic dermatitis, and pemphigus. Elevated IL-21 levels have been reported to induce keratinocyte hyperproliferation and hyperplasia, promote the migration of inflammatory cells into the dermis and epidermis, and enhance the expression of other cytokines such as IFN- γ , IL-17, and IL-22. Furthermore, serum IL-21 levels have been shown to correlate with disease severity across multiple dermatologic conditions (Mesas-Fernández et al., 2023). IL-21 is a member of the common γ -chain cytokine family and is primarily secreted by Th17 cells, Tfh cells, and dendritic cells (Koh et al., 2024). Its effects are mediated through IL-21 receptor binding, leading to activation of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling pathway (Mizutani et al., 2017). IL-21 receptors are expressed on multiple cell types, including keratinocytes (Long et al., 2019). The immunologic and keratinocyte-related effects of IL-21 closely align with key pathogenic features of AV, such as keratinocyte hyperproliferation, inflammatory responses, and Th17 regulation (Sardana & Verma, 2017).

While IL-21 has been extensively investigated in psoriasis and atopic dermatitis, where its role in disease pathogenesis and severity correlation is well established, systematic examination of IL-21 in acne vulgaris remains limited. In psoriasis, IL-21 levels correlate significantly with disease severity as measured by PASI scores (Wang et al., 2016), and in atopic dermatitis, serum IL-21 shows strong associations with disease activity indices (Mizutani et al., 2017). However, whether similar relationships exist in AV has not been comprehensively explored. The few existing studies on cytokine profiles in AV have primarily focused on IL-17 and IL-22 (Singh et al., 2023; Kelh  l   et al., 2014), with minimal attention to IL-21 despite its critical role in Th17 cell differentiation and keratinocyte proliferation—both central to acne pathogenesis.

Furthermore, most cytokine research in AV has examined tissue-level expression rather than serum biomarkers, creating a knowledge gap regarding whether systemic IL-21 measurements can serve as clinically useful indicators of disease severity. Given that serum biomarkers offer practical advantages for non-invasive assessment and therapeutic monitoring,

establishing whether IL-21 correlates with AV severity would have significant clinical implications.

This study represents the first systematic investigation of serum IL-21 levels across different acne severity grades in an Indonesian population, addressing a critical gap in understanding AV immunopathogenesis. The novelty of this research lies in: (1) providing baseline data on IL-21 levels in AV patients from Southeast Asia, where genetic and environmental factors may differ from previously studied populations; (2) evaluating whether serum IL-21 can serve as a practical biomarker for severity assessment; and (3) generating evidence to inform potential IL-21–targeted therapeutic approaches for AV management.

Given its central role in immune regulation and keratinocyte activity, IL-21 represents a promising target for investigation in acne vulgaris. This study therefore aimed to evaluate the clinical relevance of IL-21 by assessing differences in serum IL-21 levels across varying degrees of acne severity. Specifically, we hypothesized that serum IL-21 levels would demonstrate a significant positive correlation with AV severity, potentially establishing IL-21 as a useful biomarker for disease assessment and therapeutic monitoring. Findings from this work may provide further insight into the immunopathogenesis of AV and inform the potential development of IL-21–targeted therapeutic strategies.

METHOD

This study was designed as an analytical observational study with a cross-sectional approach. The severity of AV was assessed using the Lehmann score, while serum IL-21 levels were measured in all participants. Subject recruitment, clinical diagnosis, and acne severity assessment were carried out at the Dermatology, Venereology, and Aesthetic Outpatient Clinic of Dr. Moewardi General Hospital, Surakarta. Serum IL-21 analysis was performed at the Biomedical Laboratory, Faculty of Medicine, Universitas Sebelas Maret. The study was conducted over a 3-month period, from April to June 2025. Ethical approval was obtained from the Health Research Ethics Committee of Dr. Moewardi Hospital, Surakarta (No. 2.257/IX/HREC/2024).

The sample size of 46 participants was determined using a comparative analytical formula for three independent groups with continuous outcomes. Based on preliminary data and previous cytokine studies in inflammatory dermatoses, we anticipated a mean difference of 50 pg/mL in IL-21 levels between groups, with an estimated standard deviation of 60 pg/mL. Using a significance level (α) of 0.05, power ($1-\beta$) of 80%, and accounting for potential 10% dropout, the minimum required sample size was calculated as 42 participants. The final enrollment of 46 subjects exceeded this minimum requirement, providing adequate statistical power for the primary analysis. The distribution across severity groups (mild: $n=19$; moderate: $n=16$; severe: $n=11$) reflected the natural prevalence pattern observed in our clinical setting, with mild cases being most common.

Eligible participants were patients with mild, moderate, or severe AV, classified according to the Lehmann score. Subjects who had not received topical or systemic AV therapy, or those who had received therapy but underwent a 1-month washout period, were included. Additional inclusion criteria were: age between 18 – 39 years and willingness to participate by providing written informed consent. Exclusion criteria included: obesity with

body mass index (BMI) ≥ 30 kg/m²; active smoking; current or recent (within the past month) use of medications known to influence acne (including isotretinoin, benzodiazepines, lithium, cyclosporine, ramipril, isoniazid, iodides, bromides, selective serotonin reuptake inhibitors, epidermal growth factor receptor inhibitors, progestin-only contraceptives, and corticosteroids); presence of other inflammatory skin diseases such as atopic dermatitis, lichen planus, systemic lupus erythematosus, pemphigus, psoriasis, or Sjögren's syndrome; abnormal vital signs; and female participants undergoing menstruation at the time of recruitment.

Each participant underwent medical history taking, physical examination, and standardized clinical photography. Physical examination included measurement of vital signs, body weight, height, and evaluation of acne lesions. Acne severity was graded using the Lehmann scoring system, independently assessed by three examiners. This scoring system quantifies three types of lesions, comedones, papules, and pustules, by assigning weights (comedones = 1, papules = 2, pustules = 3). The weighted lesion counts are summed to obtain a total score, which categorizes AV severity into mild (0–30), moderate (31–60), or severe (>60).

Venous blood samples (3 mL) were collected from the median cubital vein of each subject between 08:00 and 10:00 a.m. Blood sampling was performed on the same day as acne severity assessment. Samples were immediately stored in appropriate containers and processed according to laboratory protocols. Serum IL-21 concentrations were determined using a quantitative sandwich ELISA method with a standard commercial kit (Human IL-21 Immunoassay, Bioassay Technology Laboratory®, Shanghai, China).

This study aimed to evaluate the association between serum IL-21 levels and acne severity. Comparative statistical tests were used, depending on data distribution. One-way ANOVA was applied for normally distributed data, while the Kruskal–Wallis test was used for non-normally distributed data. A *p*-value <0.05 was considered statistically significant. Inter-rater agreement among the three examiners for acne severity assessment was evaluated using Cohen's kappa test. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 25.0 (IBM Corp., Chicago, IL, USA).

RESULTS AND DISCUSSION

Baseline Characteristics of Study Subjects

A total of 46 subjects with AV were included in this study. Of these, 19 subjects had mild AV, 16 had moderate AV, and 11 had severe AV. The highest mean age was observed in the severe group (25.73 years), followed by the moderate group (22.75 years) and the mild group (22.74 years). All groups were predominantly female, with the highest proportion observed in the moderate group (68.75%). The mean body mass index (BMI) was 22.46 kg/m² in the severe group, 22.27 kg/m² in the moderate group, and 21.88 kg/m² in the mild group. Across all groups, the majority of participants were college students, and most had completed high school education. Statistical analysis revealed no significant differences in baseline characteristics between the three groups (*p* > 0.05), indicating that potential bias from these factors was minimized (Table 1).

Table 1. Baseline Characteristics

Characteristics	Mild (n = 19)	Moderate (n = 16)	Severe (n = 11)	p
Age	22.74±3.45	22.75±3.92	25.73±6.18	0.104
Sex				0.714
Male	8 (42.11%)	5 (31.25%)	5 (45.45%)	
Female	11 (57.89%)	11 (68.75%)	6 (54.55%)	
Body mass index	21.88 ± 2.38	22.27 ± 1.78	22.46 ± 2.01	0.744
Occupation				0.459
Students	1 (5.26%)	0 (0%)	1 (9.09%)	
College students	14 (73.68%)	10 (62.5%)	3 (27.27%)	
Cleaning service	2 (10.53%)	1 (6.25%)	1 (9.09%)	
Private employees	1 (5.26%)	3 (18.75%)	3 (27.27%)	
Medical doctor	1 (5.26%)	2 (12.5%)	1 (9.09%)	
Teacher	0 (0%)	0 (0%)	1 (9.09%)	
Nurse	0 (0%)	0 (0%)	1 (9.09%)	
Education				0.224
Middle school	0 (0%)	0 (0%)	1 (9.09%)	
High school	14 (73.68%)	12 (75%)	6 (54.55%)	
Diploma	0 (0%)	0 (0%)	1 (9.09%)	
Undergraduate	5 (26.32%)	4 (25%)	3 (27.27%)	

Inter-rater Reliability of Acne Severity Assessment

Acne severity was independently assessed by three examiners. To ensure consistency, Cohen's kappa test was applied. A kappa value <0.2 indicates poor agreement, 0.2–0.4 fair, 0.4–0.6 moderate, 0.6–0.8 substantial, and >0.8 almost perfect agreement. The results showed perfect agreement between examiner pairs: examiner 1 vs. 2 ($\kappa = 1$), examiner 2 vs. 3 ($\kappa = 1$), and examiner 1 vs. 3 ($\kappa = 1$). Thus, the overall inter-rater reliability for acne severity grading was almost perfect ($\kappa > 0.8$) (Table 2).

Table 2. Inter-rater Reliability of AV Severity

Observer	κ
Observer 1 and observer 2	1.000
Observer 2 and observer 3	1.000
Observer 1 and observer 3	1.000

Serum IL-21 Levels Across Different Acne Severity Groups

Differences in serum IL-21 levels across acne severity groups were analyzed using one-way ANOVA. A p-value <0.05 was considered statistically significant (Figure 1). The highest mean IL-21 concentration was observed in the severe group (303.53 pg/mL), followed by the moderate group (223.7 pg/mL) and the mild group (213.2 pg/mL). However, statistical analysis yielded a p-value of 0.130, indicating no significant difference in serum IL-21 levels among the three severity groups. Therefore, the study hypothesis, that serum IL-21 levels differ significantly according to acne severity, was not supported.

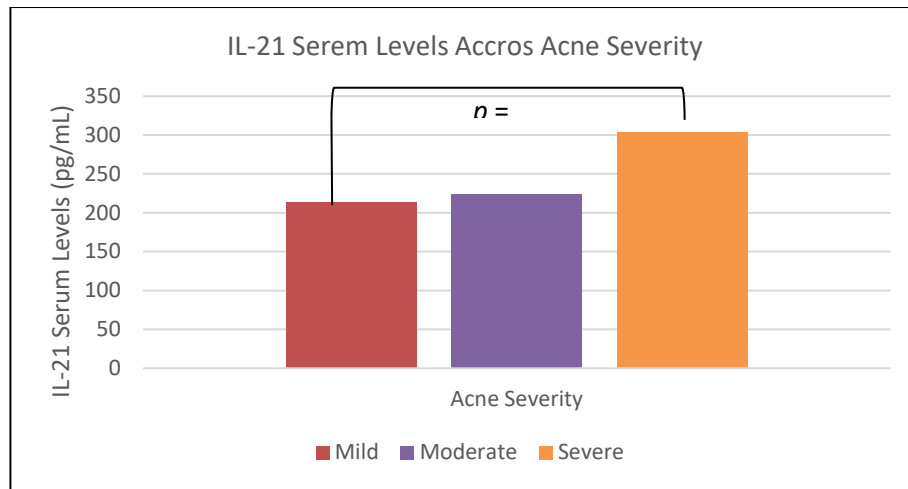


Figure 1. IL-21 Serum Levels Across Acne vulgaris Severity

Discussion

In this study, the mean serum IL-21 levels were 303.53 pg/mL in the severe AV group, 223.7 pg/mL in the moderate group, and 213.2 pg/mL in the mild group. These values are markedly higher than previously reported levels in healthy individuals, which average around 20 pg/mL (Mootha et al., 2021) and 28 pg/mL in another study from Taiwan (Chao et al., 2015). This suggests an approximate tenfold increase in IL-21 levels in patients with AV compared with healthy controls. Elevated IL-21 levels have also been consistently observed in other inflammatory skin diseases. For instance, patients with psoriasis exhibit average IL-21 concentrations of approximately 80 pg/mL, which positively correlate with disease severity (Wang et al., 2016), while in atopic dermatitis, median levels have been reported as high as 454 pg/mL, also showing a strong association with disease activity (Mizutani et al., 2017).

The elevated IL-21 levels observed in AV patients reinforce its potential role in the disease's pathophysiology. IL-21 is a pleiotropic cytokine with key immunoregulatory functions (Wang et al., 2018). It promotes the activation of follicular helper T (T_{fh}) cells and B cells (Quast et al., 2022), and is mainly secreted by Th17 and T_{fh} cells (Tangye & Ma, 2020). In inflammatory settings, IL-21 can stimulate IL-17 production and contribute to chronic immune activation. Its role has been documented in atopic dermatitis and psoriasis (Mesas-Fernández et al., 2023). Although less extensively studied in AV, the findings from this study highlight IL-21 as a potential player, possibly through its effects on follicular hyperkeratinization and sebaceous gland hyperplasia (Koh et al., 2024). Supporting this, a Korean study reported that IL-21 promotes keratinocyte hyperproliferation, resulting in epidermal thickening, and further amplifies its own production by favoring differentiation toward Th17 cells rather than other CD4⁺ T subsets (Um et al., 2024).

Despite the observed trend of increasing IL-21 levels with greater acne severity, statistical analysis revealed no significant differences across severity groups. This contrasts with the initial hypothesis that higher IL-21 levels would correlate with more severe AV. These results suggest that while IL-21 may be involved in the pathophysiology of AV, serum IL-21 levels may not be sensitive markers of clinical severity. Similar findings were reported by Li and Chi (2023), who observed that photodynamic therapy with 5-aminolevulinic acid reduced the severity of moderate-to-severe AV without significantly altering serum IL-21 levels. In

addition, Singh et al. (2023) found no differences in IL-17 and IL-22 levels across different severity grades of AV, despite these cytokines being co-secreted with IL-21 by Th17 cells.

Several factors explain the lack of statistical significance in this study. First, the sample distribution was uneven, with only 11 participants in the severe group compared to 16 in the moderate and 19 in the mild groups. Unequal group sizes can reduce statistical power and limit the ability to detect true differences (Biau et al., 2008). Second, serum IL-21 levels were measured only once due to the cross-sectional design, which captures a single time point. This reflects the dynamic fluctuations of IL-21 during different stages of AV activity. Since AV is characterized by variable inflammatory processes, cytokine levels change over time (Kistowska et al., 2014). Third, cytokine assessment was limited to serum samples, which do not fully represent local cytokine activity within the pilosebaceous unit. Previous studies have demonstrated discrepancies between cytokine profiles in serum and lesional skin in AV (Agak et al., 2014; Kelh  la et al., 2016). Therefore, relying solely on serum measurements obscures IL-21's role in localized inflammation and lesion severity. Finally, inter-individual variability, influenced by genetic polymorphisms, immune regulation, and microbiome composition, could also contribute. Variants in IL-21 or IL-21R genes have been associated with differential cytokine expression in inflammatory conditions (Hao et al., 2021).

Although serum IL-21 levels were not significantly different among severity groups in this study, the overall trend toward higher concentrations with increasing severity supports its potential role in AV pathogenesis. This aligns with evidence suggesting that IL-21 contributes to keratinocyte hyperproliferation through the JAK/STAT signaling pathway (Costanzo et al., 2010). Further studies with larger, more balanced sample sizes, longitudinal designs, and combined serum and tissue-based analyses are warranted to clarify the clinical relevance of IL-21 in AV.

CONCLUSION

This study demonstrated that there was no significant difference in serum IL-21 levels across various degrees of AV. Several limitations should be noted. First, routine blood tests and additional blood biomarkers were not included for initial screening of systemic infections or other conditions that influence IL-21 levels. Future studies are encouraged to incorporate these assessments. Second, this study did not employ a case-control design with a healthy control group for comparison, which would provide stronger evidence regarding the role of IL-21 in AV. Future research should therefore consider a case-control approach. Third, IL-21 expression in skin tissue with AV lesions was not examined, which has provided a more comprehensive understanding of its local role in the disease process. Further investigations should explore IL-21 expression directly in lesional skin.

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