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Evaluation of Serum Interleukin-33 and Tumor Necrosis Factor-α Levels in Patients with Psoriasis: Correlation with Disease Severity

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Abstract: Psoriasis is an immune-mediated dermatological disorder marked by accelerated skin cell proliferation, leading to thickened, rough, scaly lesions capable of causing itching, discomfort, and inflammation. This study investigates Interleukin-33 (IL-33) in psoriasis pathogenesis and evaluates its therapeutic potential. By understanding its mechanisms, the research aims to create effective treatment strategies for use in clinical practice, improving the well-being of individuals with the disease. Serum concentrations of Interleukin-33 and tumor necrosis factor-α (TNF-α) were assessed using the ELISA test in 44 subjects with psoriasis and 44 matched healthy controls. The severity of psoriasis was evaluated using Psoriasis Area and Severity Index (PASI scores), which enabled stratification into mild, moderate, and severe forms. Data were statistically analyzed to compare cytokine levels in patients and controls and to examine the relationship between cytokine concentrations and disease severity. Compared to their matched controls, psoriasis patients exhibited significantly increased median concentrations of Interleukin-33 [(268: 235–316) and tumor necrosis factor-α (294: 241–435). Also, the serum TNF-α levels exhibited a notable correlation with PASI scores (r= 0.389, p value= 0.009), while IL-33 levels did not exhibit a statistically significant association with PASI scores (r= 0.251, p value= 0.100). This study demonstrated a significant elevation in serum TNF-α and IL-33 concentrations in individuals with the disease, suggesting their involvement in disease pathogenesis. Moreover, TNF-α levels showed a proportional correlation with disease severity, as reflected by PASI scores, indicating its potential role as a biomarker for monitoring psoriasis progression. This positive association suggests a possible interplay in disease progression.

1. Introduction

Psoriasis is an immune-driven condition that impacts around 2-3% of people worldwide [1]. It is most commonly observed in men between the ages of 30-39 years and 60-69 years, but it typically appears 10 years earlier in women [2]. Although psoriasis is primarily a skin disorder, it is often associated with comorbidities like metabolic syndrome, arthritis, and cardiovascular complications [3, 4].

Among all types of psoriasis, plaque psoriasis occurs most frequently [5]. These plaques occur as red, round, or oval, well-defined spots and come in various sizes [6]. They can appear alone or merge, and they are usually covered with white-silver scales [7]. Guttate psoriasis is identified by many tiny, erythematous, and scaly nodules [8]. Pustular psoriasis shows sterile pustules on a red background and is classified into acrodermatitis continua of Hallopeau which represents severe and often refractory

forms of psoriasis, generalized pustular psoriasis, and palmoplantar pustulosis, based on where it appears [9, 10]. Erythrodermic psoriasis, a severe type, can be seen as a complication of the condition, affecting about 3% of people with psoriasis [11].

Genetic factors, autoimmunity, and chronic inflammation are crucial in the development of the disease; both hormonal influences and oxidative stress also play a role in the progression of the disease [12, 13]. Dendritic cells, T lymphocytes, cells of innate immunity, and keratinocytes release cytokines that contribute to the overgrowth of keratinocytes, which in turn causes psoriatic skin lesions [14, 15].

As a cytokine of the interleukin (IL)-1 family, IL-33 is largely localized in the lungs, skin, and gastrointestinal tract [16]. IL-33 functions as an "alarmin"—a molecular alert secreted during cellular damage, triggering the mobilization and activation of numerous components of the immune system [17, 18]. Elevated IL-33 levels in psoriatic skin lesions originate from blood vessels, keratinocytes, immune-cell infiltrates, and sweat glands. Tumor necrosis factor-α (TNF-α), also elevated in these lesions, triggers Interleukin-33 synthesis by keratinocytes, dermal fibroblasts, and activated macrophages [19, 20]. This highlights the crucial interplay between the cytokines in the patients, emphasizing the complexities of the inflammatory mechanisms involved. The interaction between these molecules impacts the disease state and worsening symptoms and offers insights into potential therapeutic targets for treatment, crucial for addressing the pathophysiology of psoriasis [21].

Few studies have examined Interleukin-33 serum concentrations in psoriasis individuals, highlighting a gap in understanding this cytokine's role. Gaining insight into these inflammatory mediators may contribute to improved clinical approaches and support the advancement of targeted therapies for managing this persistent skin condition. Thus, this study aims to measure serum concentrations of TNF-α and IL-33 in patients, exploring their roles in disease progression. Additionally, this research investigates how IL-33 and TNF-α concentrations relate to psoriasis severity using the Psoriasis Area and Severity Index (PASI) score as a clinical metric, by measuring these interleukins in patients with psoriasis, to better understand their involvement in disease dynamics.

2. Materials and Methods

2.1. Target Population

Participants involved in this comparative cross-sectional research were confirmed to have psoriasis by expert dermatologists at the Dermatology teaching center in Sulaymaniyah City in Iraqi Kurdistan Region from September 2024 to March 2025, allowing for a thorough assessment of the condition and its impact on the patients involved.

2.2 *Ethical Approval and Consent*

The College of Health and Medical Technology's Research Ethics Board at Sulaimani Polytechnic University, along with the Directorate of Dermatology teaching center in Sulaymaniyah City, granted ethical approval for this study. All participants provided written informed consent before they participated in the research, having received a thorough explanation of the study's protocols.

2.3. *Study Criteria*

Psoriasis patients, along with age- and gender-matched healthy control participants, were carefully selected to ensure the absence of any concurrent dermatological conditions that might influence study outcomes. All individuals included in the study had not used any topical treatments for a minimum of two weeks prior to sample collection and had discontinued systemic treatments for a minimum period of six weeks. These criteria were established to eliminate residual drug effects and to obtain accurate and unbiased measurements of cytokine levels in both study groups.

Individuals diagnosed with metabolic syndrome, obesity, or diabetes mellitus were excluded from participation in the study to minimize potential confounding variables and ensure a more homogeneous study population. This exclusion criterion was applied to both psoriasis patients and healthy control subjects to maintain the integrity and accuracy of the comparative analysis.

2.4 *Demographic Information of Psoriasis Patients and Healthy Controls*

The comprehensive questionnaire features multiple sections for both psoriasis patients and healthy controls. It gathers essential demographic details such as age, gender, duration of the disease, marital status, and a thorough family medical history. The types of psoriasis documented among participants included plaque psoriasis, guttate psoriasis, scalp psoriasis, psoriatic arthritis, and erythrodermic psoriasis. The PASI score was also employed to quantify the degree of cutaneous psoriasis [22, 23].

2.5. *Blood Collection and Cytokine Levels Analysis*

Whole blood samples were obtained from 44 individuals with psoriasis and 44 control group without psoriasis for comparison. These samples were kept at room temperature for 20 minutes to enable clotting. Afterwards, the serum was obtained by spinning the samples at 10,000 rpm for 10 minutes using a centrifuge. The collected serum was aliquoted and frozen at -80°C for storage to maintain its integrity for future assays. Serum concentrations of TNF-α and IL-33 were analyzed in psoriasis individuals and healthy controls using sensitive ELISA kits from "BT Lab Company, UK". The tests were performed according to the manufacturer's protocols to ensure accuracy, with results reported in picograms per milliliter (pg/mL).

2.6. *Statistical Analysis*

All data were analyzed using IBM SPSS Statistics, version 26.0, supplemented by Microsoft Excel for data organization and graphical representation. Categorical variables, such as demographic and clinical characteristics, were expressed in terms of frequencies and percentages. Chi-square and Fisher's exact tests were used to compare different variables. Due to the lack of normal distribution in the quantitative data, the data were analyzed using Mann–Whitney U tests and Kruskal–Wallis tests. Additionally, Spearman's rank correlation assessed the relationship between IL-33 and TNF-α concentrations.

3. Results

3.1. *Types of Psoriasis Detected in the Present Study*

The psoriasis group consisted of 44 patients in total. The types of psoriasis observed among them included plaque psoriasis, scalp psoriasis, guttate psoriasis, psoriatic arthritis, and erythrodermic psoriasis. Plaque psoriasis was the most common form, observed in 29 patients. Scalp psoriasis were identified in five patients, whereas, guttate psoriasis, pustular psoriasis and erythrodermic psoriasis were found in three patients each followed by psoriatic arthritis in one patient (Figures 1 and 2).

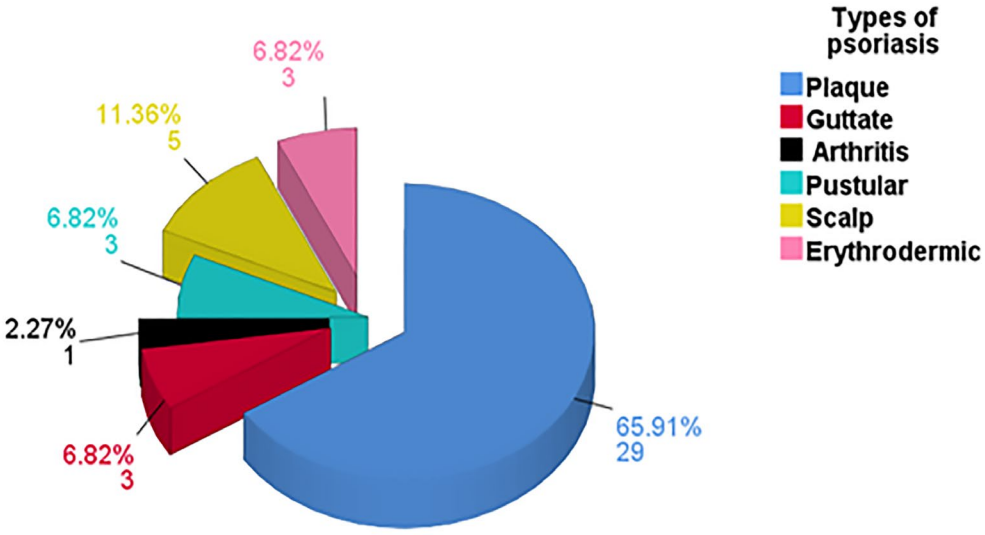

Figure 1: Types of psoriasis and their frequencies among the participants in the present research.

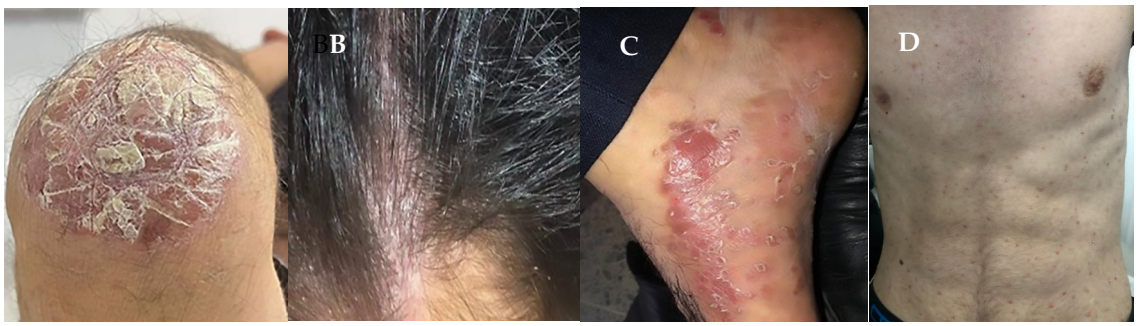

Figure 2: Psoriasis lesions of participants in this study. (A) Plaque psoriasis. (B) Scalp psoriasis. (C) Erythrodermic psoriasis. (D) Guttate psoriasis.

With the exception of the erythrodermic psoriasis which was found in three male patients and psoriatic arthritis which was found in one female patient, no statistically significant differences were found between numbers of male and female patients affected by the other types of psoriasis (p-value= 0.342, Figure 3). In addition, there is no significant differences between patients with positive family history and those with negative family history affected by the different types of psoriasis (Figure 4).

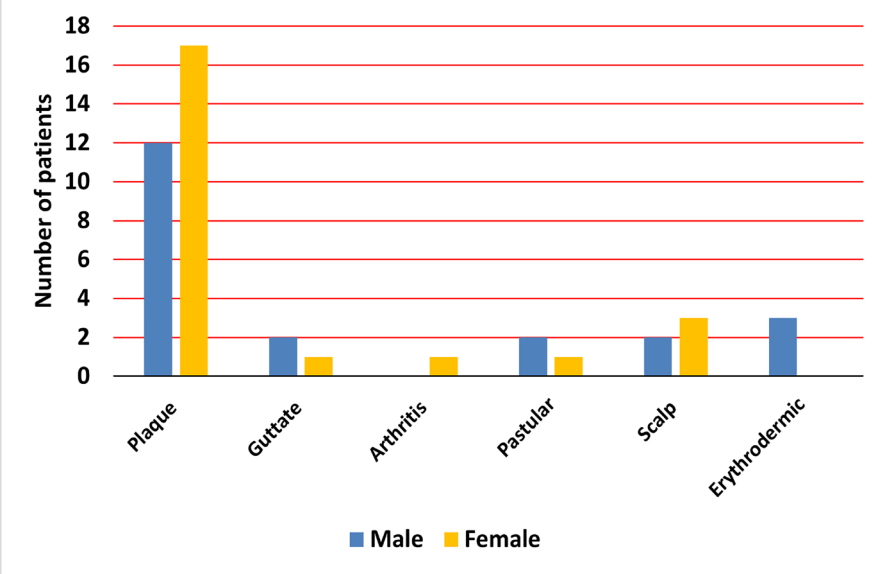

Figure 1: The number of male and female individuals suffering from different forms of psoriasis encountered in this study.

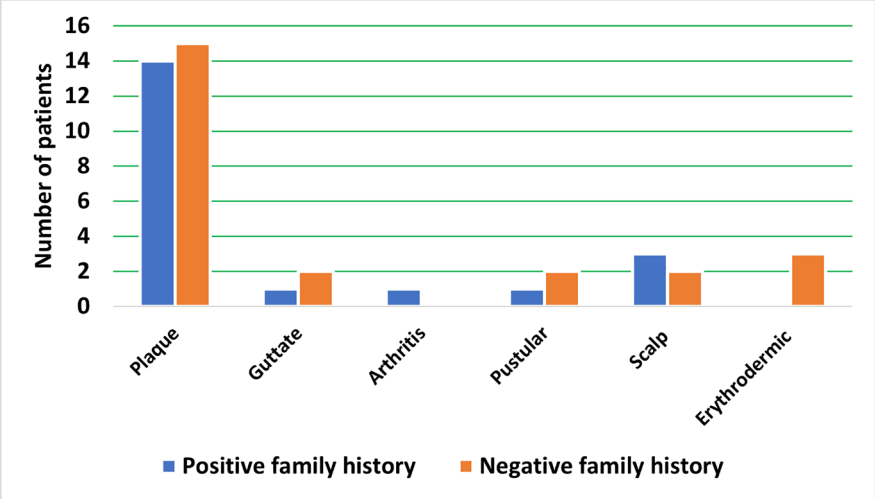

Figure 2: The count of patients diagnosed with various forms of psoriasis in relation to family history.

3.2. Demographic and Clinical Features of Patients with Psoriasis

As shown in table 1, among the 44 patients with psoriasis examined, 21 were male and 23 were female while 44 healthy controls (19 males and 25 females) were also involved in the present study; patients had a median age of 42 and 30 years for controls. Twenty out of the 44 patients reported a positive family history of psoriasis compared to a negative history in all of the 44 healthy control individuals.

Table 1: Number of individuals with patients and controls concerning their gender, age, and family history.

Properties	Psoriasis individuals (n=44)	Healthy controls (n=44)
Gender (Male, Female)	21, 23 (%47.7, %52.3)	19, 25 (%43.2, %56.8)
Age in years Median, (Range)	42 (12-80)	30 (12-80)
Family history of psoriasis:		
Positive	20	0
Negative	24	44

As shown in table 2, most patients were aged between 35 and 56 years (19 out of the total 44 patients), followed by those between 12 and 34 years old (15 patients), and those between 57 and 80 years old (10 patients). The duration of psoriasis lesions in patients extended from 1-13 years in 27 patients (12 males and 15 females), 14-26 years in 10 patients (4 males and 6 females), and 27-40 years in seven patients (5 males and 2 females). The PASI scores were < 7 in 23 cases (10 males and 13 females), 7-15 in 15 patients (8 males and 7 females), and > 15 in six patients (3 males and 3 females).

Table 2: Characteristics (demographic and clinical) and PASI index of patients with psoriasis.

Age group	Male	Female	Numbers and %
12-34	7 (15.9%)	8 (18.2%)	15 (34.1%)
35-56	9 (20.5%)	10 (22.7%)	19 (43.2%)
57-80	5 (11.4%)	5 (11.4%)	10 (22.7%)
Duration			
1-13	12 (27.3%)	15 (34.1%)	27 (61.4%)
14-26	4 (9.1%)	6 (13.6%)	10 (22.7%)
27-40	5 (11.4%)	2 (4.5%)	7 (15.9%)
PASE score			
< 7	10 (22.7%)	13 (29.5%)	23 (52.3%)
7-15	8 (18.2%)	7 (15.9%)	15 (34.1%)
> 15	3 (6.8%)	3 (6.8%)	6 (13.6%)
Total	21 (47.7%)	23 (52.3%)	100%)

3.3. Serum Concentrations of TNF-A and IL-33 in Individuals with Psoriasis Versus Controls

Serum levels of IL-33 were found to be statistically significantly higher in patients with psoriasis, with a p- value of 0.002, when compared to the control individuals (Table 3). Similarly, the serum levels of TNF-αwere significantly elevated in the psoriasis patient group, with a p-value of 0.038, in comparison to the control group.

Table 3: Serum concentrations of IL-33 and TNF-α were compared between psoriasis individuals and non-affected individuals.

Study groups	Sample size	IL-33 (pg\ml) Median (25%-75% IQR*)	TNF-alpha (pg\ml) Median (25%-75% IQR)	Mann-Whitney U (P- value)
Patients	44	268 (235-316)	294 (241-435)	< 0.05
Controls	44	238 (206-258)	283 (217-320)	

* IQR: Interquartile range.

3.4. Serum Concentrations of TNF-A and IL-33 in Psoriasis Cases Concerning their Age, Gender, Family History, PASI, and Disease Duration

There were no statistically significant differences in TNF-α and IL-33 concentrations detected among patients grouped by varying age ranges (specifically 12-34 years old, 35-56 years old, and 57-80 years old) or when comparing male and female patients (p-values > 0.05). Furthermore, serum concentrations of TNF-α and IL-33 did not show any significant increase in patients who had a positive family history when evaluated against those with a negative family history (p > 0.05).

To further assess the relationship between psoriasis severity and serum cytokine levels, patients were stratified into three groups: mild (PASI < 7), moderate (PASI 7–12), and severe (PASI > 12). When analyzed using this stratified approach with the Kruskal-Wallis test, serum levels of IL-33 and TNF-α were significantly higher in the severe PASI group compared to the mild and moderate groups (p < 0.05), as shown in table 4.

Table 4: TNF-α and IL-33 serum levels concerning demographic characteristics of psoriasis patients.

Variables	Groups	IL-33 (pg\ml) Median (25%-75% IQR*)	TNF-α (pg\ml) Median (25%-75% IQR)	Kruskal-Wallis test (P-value)
Age	12-34	278 (224-316)	364 (219-453)	> 0.05
	35-56	248 (237-307)	289 (242-417)	
	57-80	264 (231-602)	308 (240-899)	
Gender	Male	264 (225-323)	290 (267-417)	> 0.05
	Female	272 (237-303)	303 (231-453)	
Duration (year)	0-13	258 (224-316)	285 (231-405)	> 0.05
	14-26	278 (242-307)	350 (256-517)	
	27-40	256 (242-511)	314 (270-807)	
Family history	Yes	271 (238-1041)	326 (242-1099)	> 0.05
	No	264 (234-305)	294 (241-392)	
PASI score	(Mild < 7)	258 (225-312)	280 (230-364)	< 0.05
	(Moderate 7-12)	256 (233-307)	298 (239-417)	
	(Severe >12)	1250 (272-2006)	1145 (453-3682)	

* IQR: Interquartile range.

3.5. Association Between PASI Scores and Serum Concentrations Of IL-33 and TNF-A

The observed correlation between serum IL-33 concentrations and 'PASI scores' showed a slight positive correlation (correlation coefficient = 0.251); however, the results did not show statistical significance (p-value= 0.100), indicating weak evidence for this relationship, as shown in figure 5.

The examination showed a significant moderate positive association between tumor necrosis factor-α levels and PASI scores with a correlation coefficient = 0.389 (p = 0.009). Further, as TNF-α levels rise, psoriatic symptoms tend to intensify (Figure 6).

Serum concentrations of IL-33 levels and TNF-α showed a strong, statistically significant correlation, with a correlation coefficient of 0.716 (p-value < 0.001). Higher IL-33 levels were significantly linked to increased TNF-α in the samples, suggesting a joint upregulation of these inflammatory markers in patients with psoriasis, (Figure 7).

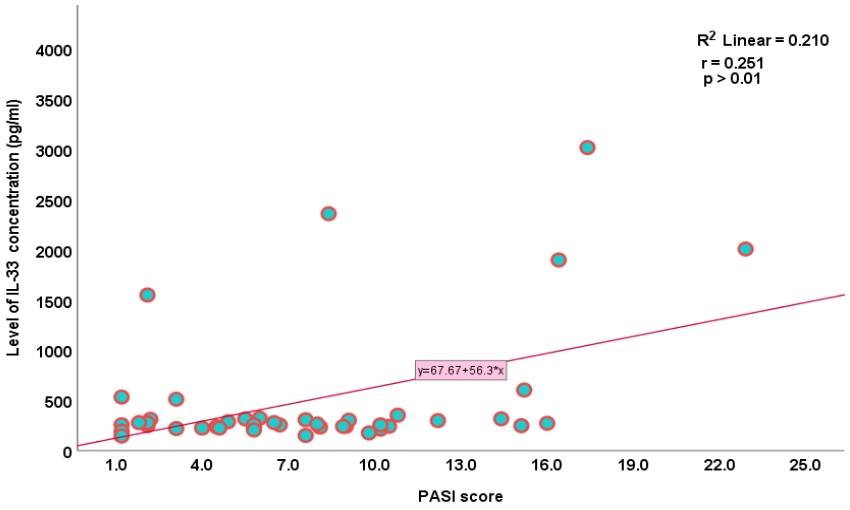

Figure 3: The correlation coefficient between IL-33 and PASI scores was tested by Spearman's rank correlation analysis. Serum IL-33 concentrations showed a trend of increasing in parallel with PASI scores; however, the relationship was not statistically significant.

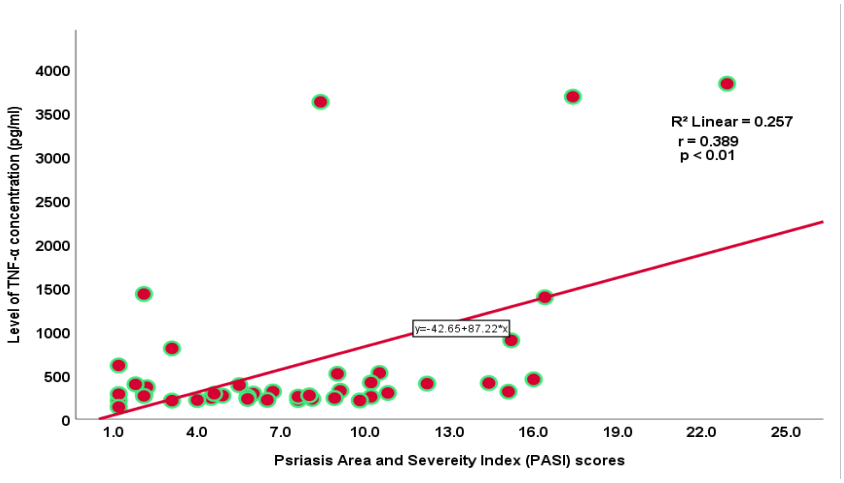

Figure 6: The correlation coefficient between TNF-α and PASI scores was tested by Spearman's rank correlation analysis.

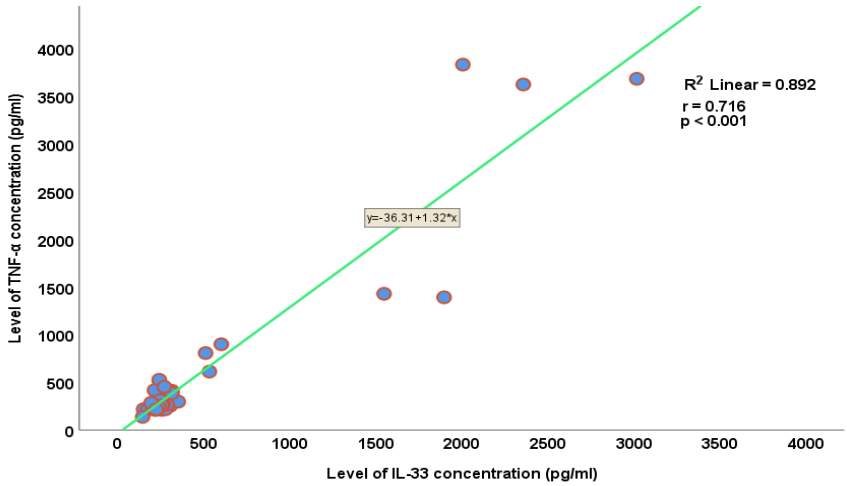

Figure 4: A strong positive association between TNF-α and IL-33 concentrations in psoriasis individuals was revealed by Pearson correlation analysis.

4. Discussion

Psoriasis is a long-term, immune-mediated skin condition managed with systemic anti-inflammatory treatments and anti-cytokine therapies [24, 25]. Elucidation of the function of psoriasis's cytokines in its disease progression will be important for developing future therapeutic approaches [26]. This highlights the important functions of TNF-α and Interleukin-33 in the disease and their potential relations with disease progression.

The findings of this study showed that the median age of patients was 42 years old. This finding, which reflects that psoriasis mainly occurs in middle-aged people, is in line with previous studies [25, 27].The comparison between patients based on family history of psoriasis revealed no significant differences. However, the majority of psoriasis patients (54.5%) reported a negative family history, while the remaining 45.5% had a positive family history. This is in contrast to the observations of Sehat *et al*, [27], who found the family history of psoriasis was positive for only 14 patients and negative for 33 patients. This difference suggests that genetic make-up may play a role in psoriasis susceptibility, consistent with several reports describing multiple genetic loci, including HLA-Cw6, which has been strongly associated with early-onset psoriasis [28]. The varying prevalence of these genetic markers across different populations might partially explain the observed discrepancies in family history patterns.

The outcomes of the current research showed that serum IL-33 concentrations were markedly increased in individuals with the disease compared to matched control subjects, highlighting IL-33 as a potential player in psoriasis pathogenesis. These results are consistent with findings by other studies reporting elevated cutaneous expression of IL-33 in psoriasis [29-32] and elevated serum IL-33 concentrations of individuals with the disease. Their data suggest IL-33 is a common inflammatory marker in various psoriasis subtypes, such as psoriatic arthritis, pustular psoriasis, and psoriasis vulgaris [21, 33]. IL-33 enhances inflammation via several mechanisms, including the stimulation of keratinocytes, neutrophils, and mast cells, thus aggravating the symptoms. Though the p-value did not indicate significance, this study observed a positive correlation between IL-33 concentrations and psoriasis disease severity, indicating the involvement of IL-33 in promoting inflammation in psoriasis. More extensive research is required to facilitate our understanding of this association and its clinical significance.

TNF-α is involved in the progression of psoriasis by stimulating keratinocyte growth and encouraging the release of pro-inflammatory substances like IL-1 and IL-6. A range of skin cell types, including T cells, keratinocytes, and mast cells, contribute to its production [34].

In this research, the increased concentrations of TNF-α in psoriasis individuals' serum indicate its involvement in disease progression. This was consistent with other authors' results [33, 35, 36] which importantly showed relevant serum TNF-α concentrations in individuals diagnosed with the disease, with ongoing lesion development observed.

Additionally, TNF-α concentrations in serum were significantly associated with PASI scores, and higher levels of TNF-α were associated with more severe disease and a greater PASI score, which supports the idea that TNF-α is a potential biomarker of psoriasis severity with possible implications for monitoring of the disease and therapeutic intervention points. These findings are consistent with those reported in earlier studies by Pietrzak *et al*., Takahashi *et al*., and Rodriguez-Cerdeira *et al*. [12, 36, 37].Their findings indicate that tumor necrosis factor-α is a primary mechanism in the psoriasis pathogenesis and may be an important marker of psoriasis severity in clinical practice-based assessment measures. On the contrary, other studies, including Pirowska *et al*. and Abdel-Hamid *et al*. [38, 39] demonstrated a weak association of serum concentrations of tumor necrosis factor-α with the intensity of the disease, which was statistically non-significant. Such a discrepancy may be attributed to differences in subject selection, as demonstrated in the study by Pirowska *et al*. [38] which involved individuals with psoriasis who also presented with a cluster of metabolic risk factors, while the current investigation focused exclusively on patients with psoriasis without any associated comorbidities.

TNF-α-induced production of IL-33 among the main cell types is responsible for IL-33 production in macrophages, dermal fibroblasts, and keratinocytes [31, 40]. Outcomes observed in this research demonstrated a significant link between serum concentrations of IL-33 and TNF-α. This observation,

which implies a possible involvement of these inflammatory mediators in the disease pathology, is in line with the conclusions of Mitsui *et al*. [21], who noted the involvement of TNF-α and IL-33 in the progression of psoriasis.

A key strength of this study is the evaluation of IL-33 and TNF-α levels in psoriatic patients, which has not been previously reported in our region and may contribute to the regional understanding of disease pathogenesis. However, the main limitation is the small sample size, as the study was conducted as part of a thesis project with time constraints.

5. Conclusions

Most psoriasis patients involved in the present study were middle-aged, with plaque psoriasis being the most frequently observed type. There was no significant difference in the distribution of the disease between male and female patients. A positive family history of psoriasis was reported among several patients; however, the difference in familial occurrence among patients did not reach statistical significance. Serum levels of IL-33 and TNF-α were significantly elevated in psoriasis patients compared to the control group. While TNF-α levels showed a positive correlation with PASI scores, indicating its potential role in disease severity, IL-33 levels did not demonstrate any significant correlation with PASI. These findings highlight the potential involvement of TNF-α in the pathogenesis and severity of psoriasis, whereas the role of IL-33 remains uncertain.

It is recommended that future research explore therapeutic strategies targeting TNF-α as a potential means to control disease severity, while also investigating the precise immunological role of IL-33 to determine whether it may serve as a biomarker or a secondary therapeutic target in psoriasis. Further large-scale studies are necessary to validate these observations and to better understand the specific contributions of these cytokines to disease development and progression.

Author contributions: Tanya Kamil Mohammed Gharib: Conceptualization, Investigation, Methodology, Project administration, **Ali Hussein Hassan:** Writing – original draft, Writing – review & editing.

Data availability: Data will be available upon reasonable request.

Conflicts of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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