

Association of serum IL-30 and soluble GP130 with the risk of psoriasis vulgaris

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Abstract

Cytokines play a major role in the pathogenesis and progression of psoriasis. Interleukin (IL)-30 is a multifunctional cytokine. It binds to glycoprotein 130 (GP130) and inhibits the GP130 signaling pathways of psoriasis associated cytokines such as IL-6, IL-11, and IL-27. The study intended to assess associations of IL-30 and GP130 with the risk of psoriasis and Psoriasis Area Severity Index (PASI) score. Therefore, we measured the serum levels of IL-30 and GP130 in psoriasis patients and in a control group. An enzyme linked immunosorbent assay (ELISA) technique was used to measure IL-30 and GP130 levels in the serum of 43 patients and 43 normal controls. Statistical analysis of IL-30 and GP130 serum levels among patients and control groups and their correlation with PASI scores were performed. IL-30 serum levels showed a significant increase in patients with psoriasis compared with controls ($p < 0.001$) and a positive correlation with PASI scores. While serum levels of GP130 were not different in psoriatic patients and in the control group. Furthermore, the receiver operating characteristic (ROC) curve showed that IL-30 had diagnostic ability for prediction of psoriasis in comparison to controls, at cut of point of >14.34 showed a sensitivity of 97.7%, 100% specificity. In conclusion, IL-30 was elevated in psoriasis patients than controls, therefore, it can be considered a sensitive biomarker for diagnosis of psoriasis.

Keywords: Psoriasis, IL30, GP130

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Introduction

Psoriasis is a common chronic inflammatory skin condition that has indurated, scaly, itchy, and often painful erythematous plaques, characterized by a strong demarcation and spread over the surface of the skin.¹ In Egypt, varying prevalence estimates ranging from 0.1%

to 2% based on the general populations in previous studies with debilitating social and economic impacts.¹ Psoriasis has an increased risk of co-morbidities, such as psoriatic arthritis, cardiovascular disease, diabetes mellitus, compared to the general population.²

Psoriasis is an autoimmune disorder because of the hyperproliferation of keratinocytes by T

cell.³ It is believed that type 1 helper T cells and T helper cells 17 (Th1 and Th17, respectively) play an important role in the occurrence and development of psoriasis. Blocking Th1 and Th17 cells hyperproliferation and hyperactivation may be helpful for curing psoriasis.⁴

Cytokines and cytokine receptors have a broad range of physiological functions and biological activities across multiple tissues and cell types.⁵ Elevated expression levels of several inflammatory cytokines in lesional psoriasis skin together with elevated of their serum concentrations correlate with psoriasis disease severity and explain most of the clinical features of psoriasis, such as the hyperproliferation of keratinocytes, increased neovascularization, and skin inflammation. So understanding what cytokines play as pivotal role in the disease process may suggest potential therapeutic targets.⁶

Interleukin (IL)-30 originally identified as IL-27p28 subunit is a new polypeptide related to IL-12p35. It interacts with the Epstein–Barr virus-induced gene 3 (EBI3) to form IL-27, which modulates the inflammatory responses in autoimmune and infectious diseases.⁷ IL-30, independent of EBI3 is able to modulates the immune response in autoimmune and infectious disease.⁸ IL-30 could antagonize Th1 and Th17 responses and might have therapeutic implications for controlling autoimmune diseases.⁹

Glycoprotein 130 (GP130) is a receptor subunit capable of intracellular signaling that is required for the cellular action of a wide range of cytokines. The most well-known of these is IL-6. IL-6 and GP130 family of cytokines has been implicated in inflammation and immune response.¹⁰

When IL-6 binds to its receptor (IL-6R), the IL-6 and IL-6R complex heterodimerizes with two molecules of GP130, leading to the phosphorylation of GP130 and subsequently activating Janus kinase (JAK) and the signal transducer and activator of transcription 3 (STAT3) factor, which promotes the expression of genes that accelerate proliferation and inhibit apoptosis of the cells.¹¹

Imbalanced T regulatory/T effector dynamics in psoriasis are mediated by IL-6 signaling events in the lesional skin, acting on T cell subsets which express the IL-6R and which respond functionally through phosphorylation of the transcription factor STAT3.

IL-30 acts as a natural antagonist of GP130 signaling by binding to GP130 and inhibiting the signaling of many cytokines such as IL-6, IL-11, and IL-27.¹² IL-30 also binds to soluble interleukin 6 receptor (IL-6-R), which inhibits the trans-signaling pathway of IL-6 and broadly inhibits inflammatory responses produced by immune cells expressing GP130. Because of the extensive existence of GP130, IL-30 may have extensive functions and may be used as therapeutic target in psoriasis and other autoimmune diseases.¹³

Therefore, the evaluation of serum IL-30 and GP130 levels in patients with psoriasis might be useful for monitoring the pathology and prognosis of psoriasis. Consequently, this study aimed to determine the IL-30 and GP130 levels in the serum of patients with psoriasis and evaluate its correlations with the severity of the disease.

Subjects and Methods

This cross-sectional study included 43 patients aged 18 years or more with clinically confirmed diagnosis of various degrees of plaque-type psoriasis admitted to the Department of Dermatology at Assiut University Hospital between January 2022 and June 2022. Patients on systemic immunosuppressive drugs or chemotherapy, patients with other autoimmune diseases, malignant diseases and pregnant women were excluded from the study. The control group included 43 age- and sex-matched normal participants without family history of psoriasis and free from any autoimmune or chronic diseases. The control group consisted of patients consecutively referred to the Dermatology Outpatient Clinic for cosmetic conditions such as nevi.

An initial evaluation of the enrolled participants was performed, included demographic data such as age, gender, and background information duration of psoriasis,

history of chronic disease and previous treatment. Psoriatic patients were divided according to the Psoriasis Area Severity Index (PASI) score into three groups: mild (PASI<10), moderate (PASI 10–29) and severe (PASI>30).¹⁴

Measurements of serum levels of IL-30 and GP130

A venous blood sample (3 ml) was aseptically withdrawn from each participant. Blood samples were collected into plain sterile tube, left to clot for 20-30 min at 37°C, centrifuged at 2000 g for 10 minutes then sera separated. Serum samples were stored at -20°C for later use for laboratory assay.

Determination of IL-30 and GP130 serum levels in both patients and controls were determined by commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits (Catalogue no. ELK9349 for GP130 and Catalogue no. ELK9351 for IL-30, ELK Biotechnology Co., Ltd, China), according to the manufacturer's instructions.

The optical density of the final ELISA product was read at an absorbance of 450 nm using an ELISA plate reader (Bio Tek Instruments, Inc, USA). The concentration of IL-30 and GP130 in the samples were then determined by comparing the optical density of the samples to the standard curve. The detection range of the used kits is 7.82 -500 pg/mL and 125-8000 pg/mL for IL-30 and GP130, respectively.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Science (SPSS), version 26.0 for

Windows. Quantitative data were tested for normality by Shapiro-Wilk test data, expressed as mean \pm SD or median and range according to normality of data. Qualitative data are expressed as frequencies and percentages. The Independent Sample T-test and the Mann Whitney U tests were used to compare mean/median difference of IL-30 and GP130 between two independent groups. While One way ANOVA/ Kruskal Wallis were used to compare mean/median difference between more than two groups. The Chi square test was used to compare proportions between groups. The Spearman correlation was used to explore the correlation between IL-30, GP130 and other variables. The receiver operating characteristic (ROC) curve analysis was done to identify diagnostic ability of IL-30 in prediction of psoriasis, area under curve, sensitivity, specificity, positive and negative predictive values were calculated. The level of significance was considered at $p < 0.05$.

Results

Measurement of IL-30 and GP130 Concentrations in serum of Patients with Psoriasis and Control Subjects

Tables 1 and 2 list the clinical features of the 43 psoriasis patients and 43 controls included in the study. There was a statistically significant higher median of IL-30 in patients with psoriasis compared to controls ($p < 0.001$) (Table 3, Figure 1). However, there was no statistically significant difference in the mean of GP130 between patients with psoriasis and controls ($p > 0.05$).

Table 1. Characteristics of the study participants.

Variables	Psoriasis (n=43)	Controls (n=43)	p-value
Age (years) [Mean \pm SD (range)]	41.79 \pm 12.82 (18-74)	37.19 \pm 9.42 (20-58)	NS
Gender			
Male	28 (65.1%)	32 (74.4%)	
Female	15 (34.9%)	11 (25.6%)	NS
Marital status			
Single	8 (18.6%)	13 (30.2%)	
Married	35 (81.4%)	30 (69.8%)	NS**

Table 1. Continued.

Variables	Psoriasis (n=43)	Controls (n=43)	p-value
Smoking			
Yes	19 (44.2%)	--	
No	24 (55.8%)	--	--
Hypertension	9 (20.9%)	--	--
Diabetes Mellitus	8 (18.6%)	--	--

Data were expressed as mean \pm SD or frequency and %. *Independent Sample T test compare mean difference between groups. ** Chi square test compare proportions between groups. $p > 0.05$ is not significant (NS).

Table 2. Clinical data of patients with psoriasis.

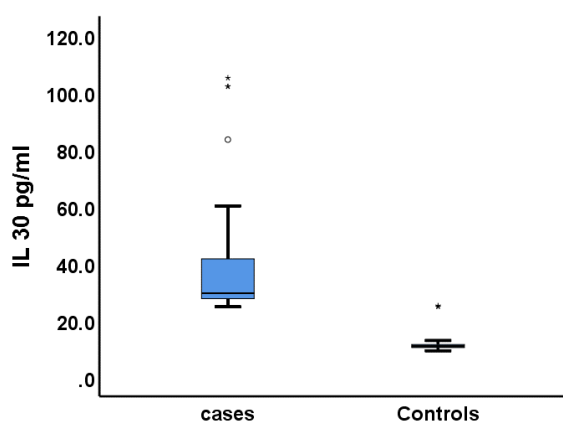
Variables	Psoriasis (n=43)
Family history	9 (20.9%)
Duration of disease (years)	
<10 years	30 (69.8%)
≥ 10 years	13 (30.2%)
Median (Range)	8.0 years (1 month-30.0 years)
Severity	
Mild	13 (30.2%)
Moderate	21 (48.8%)
Sever	9 (20.9%)
PASI score: Median (Range)	16.20 (1.4-40.5)
Lines of treatments	
Topical treatment	43 (100.0%)
Tablets	15 (34.9%)

Data were expressed as median (Range) or frequency and %.

Table 3. Comparison of interleukin (IL)-30 pg/ml and glycoprotein (GP)130 pg/ml between psoriasis cases and controls.

Variables	Psoriasis (n=43)	Controls (n=43)	p-value*
IL-30 pg/ml [Median (Range)]	29.49 (24.75-105.0)	10.87 (9.32-25.10)	<0.001
GP130 pg/ml (Mean \pm SD)	158.38 \pm 20.45	153.20 \pm 14.98	NS

Data were expressed as mean \pm SD. * Mann Whitney U test / Independent Sample T test. $p > 0.05$ is not significant (NS).

**Figure 1.** Box plot for interleukin (IL)-30 pg/ml in patients with psoriasis and controls.

There was a statistically significant difference in IL-30 level according to the severity of the psoriasis ($p=0.001$) (Table 4). There was no statistically significant difference between mild and moderate disease. However, there was a statistically significant difference between mild and severe and moderate to severe disease ($p<0.001$). There was no statistically significant difference in the level of IL-30 according to

disease duration, hypertension, diabetes mellitus, and family history of psoriasis, ($p>0.05$), (Figure 2).

There was no statistically significant difference in level of GP130 between psoriasis patients with different levels of disease severity (Figure 3), illness duration, hypertension, diabetes mellitus, and history of psoriasis in the family, ($p>0.05$).

Table 4. Factors affecting interleukin-30 (IL-30) pg/ml and glycoprotein (GP)130 pg/ml among cases with psoriasis.

Variables	IL-30 pg/ml		GP-130 pg/ml	
	Median (range)	<i>p</i> -value	Mean± SD	<i>p</i> -value
Severity of disease				
Mild	27.81 (25.38-30.70)	<0.001*	157.16±14.84	NS*
Moderate	29.34 (24.75-44.76)		157.36±20.74	
Sever	60.10 (39.09-105.0)		162.55±27.65	
Duration of diseases				
<10 years	30.04 (24.75-105.0)	NS**	158.49±20.55	NS**
≥10 years	28.86 (26.31-60.1)		158.14±21.03	
Hypertension				
Yes	44.31 (26.31-102.0)	NS**	168.20±27.14	NS**
No	29.10 (24.75-105.0)		155.79±17.90	
Diabetes Mellitus				
Yes	28.44 (26.31-60.10)	NS**	164.88±25.54	NS**
No	30.60 (24.75-105.0)		156.90±19.23	
Family history				
Yes	34.95 (24.75-83.37)	NS**	157.88±20.13	NS**
No	29.41 (25.53-105.0)		158.52±20.83	

Data were expressed as mean ± SD or median (range). $p > 0.05$ is not significant (NS).

* Kruskal Wallis/ANOVA test with pairwise comparison (p value in mild vs moderate = 0.466, mild vs sever <0.001, moderate vs sever<0.001). **Mann Whitney U test/Independent sample T test

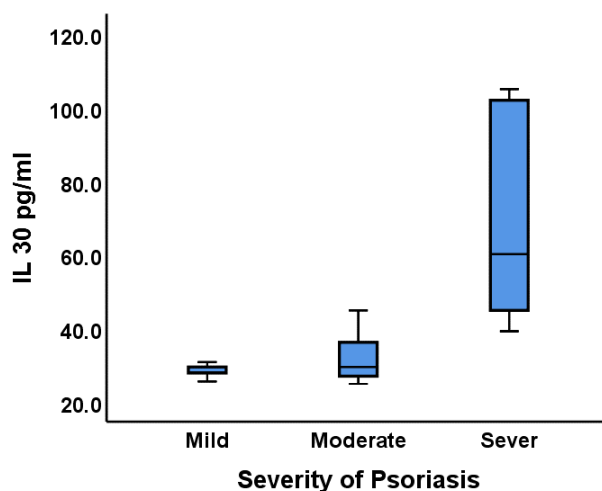


Figure 2. Box plot for interleukin (IL)-30 pg/ml in patients with psoriasis according to severity of disease.

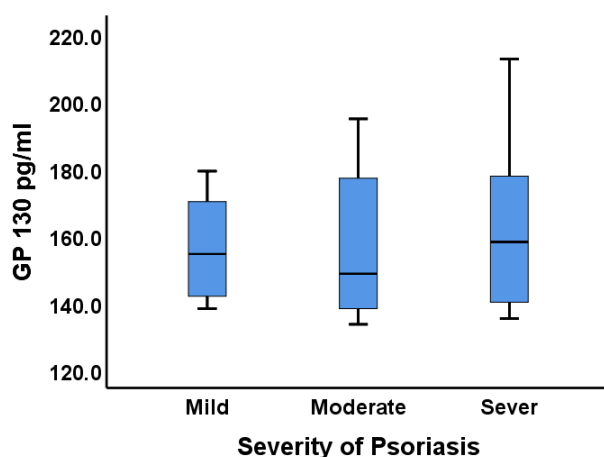


Figure 3. Box plot for glycoprotein (GP)130 pg/ml in patients with psoriasis according to severity of disease.

Correlations between serum Concentrations of IL-30 and GP130 and Clinical Parameters in Patients with Psoriasis

There was no statistically significant correlation between the level of IL-30 and age, disease duration, or level of GP130. However, as shown

in Figure 4 there was a moderate, statistically significant positive correlation between the level of IL-30 and PASI score ($r=0.498$, $p=0.001$). Moreover, there is no statistically significant correlation between the PASI score, age, or disease duration and GP130 level (Table 5).

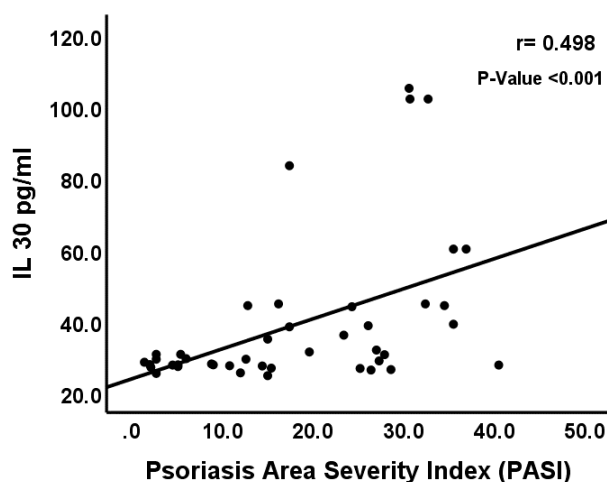


Figure 4. Scatter diagram for correlation between interleukin (IL)-30 pg/ml and Psoriasis Area Severity Index (PASI).

Table 5. Correlation between interleukin-30 (IL-30) pg/ml, glycoprotein (GP)130 pg/ml and other variables among patients with psoriasis.

Variables	IL-30 pg/ml		GP130 pg/ml	
	r	p-value	r	p-value
Age	-0.199	NS	0.103	NS
Duration of disease	-0.012	NS	-0.147	NS
PASI score	0.498	<0.001	0.10	NS
GP130	-0.237	NS	-----	

r (correlation coefficient) spearman correlation, PASI: Psoriasis Area Severity Index. $p > 0.05$ is not significant (NS).

Table 6 shows the diagnostic ability of IL-30 for prediction of psoriasis in comparison to controls. At a cut of point of >14.34, and area under the curve of 0.999 the IL-30 have a

sensitivity of 97.7%, 100% specificity, 100% positive predictive value and negative predictive value of 97.7% for prediction of psoriasis, $p < 0.001$ (Figure 5).

Table 6. Diagnostic ability of interleukin-30 (IL-30) pg/ml in prediction of psoriasis in comparison to controls._

Indices	Diagnostic criteria
Area under the curve (AUC)	0.999 (0.956-1.000)
Cut off	>25.1
Accuracy	99.0%
Sensitivity, %	97.7%
Specificity, %	100.0%
PPV, %	100.0%
NPP, %	97.7%
<i>p</i> value	<0.001

PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve. * $p \leq 0.05$ is significant.

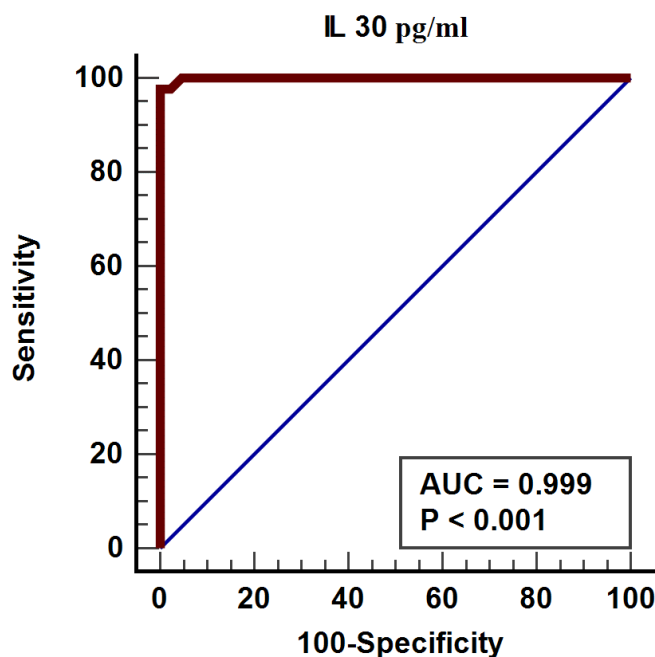


Figure 5. Receiver operating characteristic (ROC) curve for ability of interleukin (IL)-30 pg/ml in prediction of psoriasis in comparison to controls.

Discussion

The present study aimed at assessing IL-30 and GP 130 in Psoriasis. Psoriasis is an autoimmune T-cell mediated disease for which the etiology is uncertain.¹⁵ IL-30 has both pro-inflammatory and anti-inflammatory responses during autoimmune and infectious diseases. It also acts

as a natural GP130 antagonist, thereby dampening the signals of other cytokines associated with GP130 mainly IL-6.¹⁶ IL-6 and IL-27 bind to the GP130 subunit of cytokine receptors that inhibit macrophage activation, blocking their proinflammatory effects.¹⁰

In this study, serum IL-30 levels were significantly higher in psoriasis patients compared to controls. In addition, our results suggested a positive relationship between serum IL-30 levels and the severity of psoriasis. These results are consistent with the result reported by Omar, et al., 2021, that demonstrated a significant increase in IL-30 serum level in patients compared with the control group and found a positive correlation of the IL-30 level with PASI scores.¹⁷ This may indicate that downward regulation of IL-30 expression can reduce abnormal proliferation of keratinocyte and other pathological features of psoriasis.¹⁷ Another study reported that IL-30 attenuated the M5 cytokine-induced inflammatory response in the HaCaT keratinocyte cell lineage.¹⁸ IL-30 inhibited maturation and blocked the secretion of dendritic cell inflammatory cytokines, thereby inhibiting the dendritic cell mediated proliferation of T cells. These findings may contribute to the anti-inflammatory effect of IL-30 in psoriasis.

IL-30 can form complexes with varied subunits. In addition to the Ebi3 subunit, cytokine-like factor 1 (CLF1) can combine with IL-30. Crabé et al., 2009, demonstrated that the IL-30/CLF1 complex can be secreted by activated dendritic cells. The IL-30/CLF1 heterodimer promotes NK cell activity, suppresses T helper cell proliferation, and stimulates production of IL-17 and IL-10.¹⁹ Tormo et al., 2013, reported that heterodimer of IL-30/CLF1 also acts on B cells to enhance antibody production and plasma cell differentiation.²⁰ As IL-30 is able to compose complexes with diverse partnering subunits, the receptors utilized by such divergent complexes are also variable. The receptor for IL-27 is a heterodimeric transmembrane protein composed of WSX-1 (IL-27R α), an IL-6/IL-12 family receptor and GP130.²¹ GP130 is shared by receptors for IL-6, IL-35, ciliary neurotrophic factor, and cardiotrophin-like cytokine. GP130 is expressed throughout cells, including macrophages. A number of cytokines, including IL-6 and IL-27, bind to the GP130 subunit of cytokine receptors that inhibit macrophage

activation, blocking their proinflammatory effects.¹⁰

The receptors utilized by IL-30/CLF1 complexes are somewhat distinct from the IL-30/Ebi3 pair. Utilizing Ba/ F3 transfectants, Crabé et al., 2009, demonstrated that IL-30/CLF1 activates cells expressing IL-6R α in addition to WSX-1, utilizing a tripartite receptor (GP130/WSX-1/IL-6R α). Similar to IL-27, IL-30/CLF1 signaling utilizes the Jak/Stat and activates both the Stat1 and Stat3 pathways. IL-30 signaling via IL-6R α raises the possibility that IL-30 may associate with the soluble IL-6R α protein to 'trans-signal' in target cells through GP130-expressing target cells.¹⁹ Indeed, an IL-30/sIL-6R α fusion protein was able to stimulate STAT3 pathways and to induce the proliferation of GP130 transfectants. However, whether this "trans-signaling" mechanism occurs during immune responses remains to be investigated.²²

IL-30 is secreted in response to Toll like receptor agonists such as lipopolysaccharide (LPS) as well as interferon (IFN) γ treatment of both human and murine monocytic cells.²³ IFN- γ is one of the key cytokines in psoriasis. IFN- γ mRNA is elevated in skin lesions, with increased serum levels of IFN- γ .²⁴ Psoriasis individuals with metabolic syndrome showed a higher serum LPS concentration relative to controls. This may participate in increased production of IL-30.²⁴

Classically activated macrophages increase the inflammation and infiltration in psoriasis by production of proinflammatory molecules IL-23p19 and IL-12/23p40 as well as TNF and iNOS that increase epidermal proliferation and disease severity.²⁵ IL-30 decrease the production of tumor necrosis factor (TNF) and IL-6 in LPS-stimulated RAW 264.7 macrophages in a dose-dependent manner.¹⁰

In this study, serum levels of GP130 in psoriatic patients were comparable to their levels in the control group. This result was consistent with that obtained by another study.²⁶ There was no change in plasma levels of GP130 in patients with psoriasis compared to controls. The same study also reported a close correlation between IL-6 plasma concentrations and the severity of the disease, so increased plasma soluble IL-6R level did not correlate with

the altered expression of soluble GP130, which causes the enhanced IL-6 trans-signaling.²⁶

Soluble IL-6R and soluble GP130 collaboratively regulate the pathophysiology of many inflammatory diseases like rheumatoid arthritis and myocardial infarction. There is a correlation between high circulating soluble IL-6R and low soluble GP130 level with worse outcome in these diseases.²⁷ Soluble GP130FC competitively inhibits the binding of IL-6 to its membrane-bound receptor and has therefore been used as an IL-6 antagonist in the clinical treatment of some immunological diseases.²⁸ This may explain our results of unaltered levels of soluble GP130 in psoriasis patients in comparison to the control group. Accordingly, we supposed that unaltered GP130 levels leads to enhanced IL-30 trans-signaling via IL27R and/or IL-6Ra, if IL-30 /CLF1 heterodimer has been formed.¹⁹ However, this axis has to be investigated to establish its role in the immune mechanism.

In conclusion, IL-30 was elevated in psoriasis patients than controls, therefore, it can be considered a sensitive biomarker for diagnosis of psoriasis.

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Author Contributions

RRS; Conceptualization, Methodology, Formal analysis, Investigation, Validation, Funding acquisition. SAA; Conceptualization, Methodology, Formal analysis, Writing, review & editing, Visualization, Validation, supervision, Project administration. ASF; Writing original draft, Writing, review & editing, Visualization, Investigation, Validation. RAA; Investigation, Validation Writing, review & editing, Visualization. ASG; Methodology, Formal analysis, Investigation, Validation.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Assiut University (Dated: October 2021).

Informed consent

A written informed consent was obtained from each participant before being included in the study.

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