Journal of Population Therapeutics & Clinical Pharmacology

ORIGINAL ARTICLE
DOI: 10.15586/jptcp.2021.823

Serum level of cytokine IL-30 in psoriatic patients and correlation with disease severity

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Submitted: 8 May 2021; Accepted: 19 July 2021; Published: 31 August 2021

ABSTRACT

Psoriasis is a common chronic immune-mediated inflammatory skin disorder characterized by erythematous silvery scaling of the skin and associated severe itching. Reports indicate that psoriasis is affecting about 2% of the world population and life quality in a way that limits the patient activity and thereby productivity in a community. Therefore, determining appropriate therapeutics for psoriasis would make a difference in the lives of the patients and their communities. To address this, scientists have been working on different biological agents, such as interleukins and their antagonists, to regulate the common inflammatory process in psoriasis. For the current research project, serum was collected from 26 psoriatic patients and another 26 health controls, and the serums were examined for the level of IL-30 to determine differences among the tested groups and to investigate a possible correlation between IL-30 and psoriasis area severity index (PASI). The study delineated differences of the IL-30 among the groups and a positive correlation between IL-30 and PASI among the psoriatic cases, which insights a need for further studies that include a large scale of participants to fully elucidate the involvement of IL-30 in psoriasis.

Keywords: *psoriasis; interleukin-30; cytokines; psoriasis pathogenesis; PASI*

INTRODUCTION

Psoriasis is a common chronic autoimmune and skin inflammation expressed as erythematous-round lesions that occur due to rapid skin cell production and immature skin surface.[1,2] Typical psoriatic scales are whitish-silvery and develop in thick-red erythematous. In some instances, these patches get crack and bleed. Physiologically, the skin cell's typical life cycle is 1 month. However, in psoriasis patients, this process may only take place in a couple of days.[3] Because of this, skin cells do not have time to fall off, and thus the rapid overproduction leads to the buildup of skin cells.[4]

Psoriasis scales commonly observed on the big joints, such as elbows and knees. Also may develop on the back, hands, feet, neck, scalp, and face whereas rarely occur in the nails, the mouth, and the inguinal genitals.[1,5] It has generally associated with several other conditions that lead to reduced immunity, such as type 2 diabetes, inflammatory bowel, heart disease, psoriatic arthritis, anxiety, and depression.[6] Recent studies showed that there is a correlation between chronic skin inflammation and the immune disorders, emotional stress, trauma, infectious agents, and drugs for these activate a complex immunological cascade, leading to skin inflammation and accelerated epidermal and vascular growth.[7] Psoriasis is a replacing skin disorder that approximately represents 2% of the population globally, of which 6.7 million are Americans.[8]

Cytokines are small molecular weight proteins that function as immune system regulators via activating immune cells. Therefore, the cytokines evaluation has been of relevance for monitoring immune system responses to different infections or other body abnormalities, including chronic inflammation and autoimmune diseases such as psoriasis.[9–11] For that matter, several cytokines have been discovered, including interleukin-30 (IL-30) to IL-40.[12]

Interleukin-30 (IL-30) is a 28 kDa protein.[13] IL-30 belongs to the IL-6 cytokine family that appears in four-helix bundle cytokine which associates with Epstein–Barr virus-induced gene 3 (EBI3) to form the IL-27 cytokine.[14] Thus, IL-30 is sometimes called IL27-p28. Therein, IL-30 is mostly produced by immune cells of myeloid origin and malignant cells, such as prostate cancer cells that are mainly common in the prostate cancer microenvironment.[15] Of note, the IL-27-p28/IL-30 complex is thought to be capable of initiating both classic and trans-signaling by binding to either the membrane-bound or soluble forms of IL-6 R alpha, respectively. This capacity to activate both pathways suggests possible wide-range effects of IL-27-p28/IL-30 on different cell types. Additionally, the signaling of IL-27-p28/IL-30 has been reported along with the affinity for a homodimer signaling receptor subunit 130 kDa glycoprotein (gp 130).[15,16]

IL-30 independently plays a major role in the development and progression of autoimmune diseases, apparently psoriasis, via controlling both Th1 and Th17.[17] Moreover, another reported study remarked that the measurement of serum cytokines in psoriasis may allow for better understanding and prediction of the disease pathology.[18] These underlays for the possibility that the evaluation of psoriatic patients' serum IL-30 might be useful for monitoring the psoriasis pathological prognosis. This study, therefore, aimed to measure the IL-30 levels in psoriatic patient's serum and to correlate the parameter with the severity of the disease.

MATERIALS AND METHODS

Twenty-six patients with a previously confirmed diagnosis of various degrees of plaque-type psoriasis severity, were enrolled in this study. Besides, other 26 age- and sex-matched healthy, non-psoriatic volunteers with no family history of psoriasis were chosen as controls. For measuring serum interleukin-30, venous blood was drawn from patients admitted to the dermatology inpatient and outpatient departments of Nanfang Hospital, Guangzhou, China.

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Exclusion criteria were patients on systemic immunosuppressant, such as methotrexate, systemic steroids, and other drugs, besides patients of any kind of cancer or a systemic- or dermatological-disease which might compromise the immune system were not included in the study. The psoriatic patients of the study were divided into three groups according to their PASI score as mild (PASI <10), moderate (PASI 10–29), and severe (PASI >30). Signed informed consent was obtained from all participant patients and volunteers.

Whole venous blood was obtained from all participants of the study and their serum was separated by centrifugation, which was then frozen at –80°C until the time of examination. The serum IL-30 was examined by the enzyme-linked immunosorbent assay (ELISA) kit for human IL-30, which was purchased from Elabscience, Human IL-30 Elisa kit (Wuhan, China), and all steps were duplicated according to the manufacturer's manual.

Data were analyzed by statistical package for social sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) and Prism software (GraphPad 8 software, San Diego, CA, USA) and expressed as mean ± standard deviation. The comparison between two means was performed by student's T-test, more than two means were compared by one-way analysis of variance (ANOVA) test, and the not normally distributed data were analyzed by Mann–Whitney and Kruskal–Wallis tests. P-value < 0.05 was regarded as statistically significant.

RESULTS

Twenty-six patients having psoriasis alongside another 26 healthy controls were included in the study. The mean age ± SD of the cases was 45.5 ± 12.8 years, whereas that of the controls was 40.1 ± 16.2 years (P = 0.188) as presented in Table 1, which also shows that the highest proportion of the participants (44.2%) were aged less than 40 years. No significant difference was detected between the two groups regarding the age distribution (P = 0.656). More than two-third (69.2%) of the psoriasis cases were males compared with 46.2% of the control group (P = 0.092). The statistical analysis of IL-30 among cases (111.96) and controls (33.76), presented in Table 2 and Figure 1A, show significant differences in the mean of IL-30 among the groups. Moreover, data in Table 3, show that the mean rank of IL-30 in the serum of cases (890) was significantly (P < 0.001) higher than that of controls (488). However, no significant differences in the mean rank of IL-30 were determined among the age groups

TABLE 1. Age and gender distribution of the psoriatic patients and control groups.

	Psoriasis		Control		Total		P
	No.	(%)	No.	(%)	No.	(%)	
Age (years)							
<40	10	(38.5)	13	(50.0)	23	(44.2)	
40–49	6	(23.1)	4	(15.4)	10	(19.2)	
≥50	10	(38.5)	9	(34.6)	19	(36.5)	0.656*
Mean (±SD)	45.5	(±12.8)	40.1	(±16.2)			0.188†
Gender							
Male	18	(69.2)	12	(46.2)	30	(57.7)	
Female	8	(30.8)	14	(53.8)	22	(42.3)	0.092*
Total	26	(100.0)	26	(100.0)	52	(100.0)	

*†By T-test for two independent samples. *By Chi-square test.*

TABLE 2. Descriptive statistics of IL-30 in the psoriatic patients and control groups.

	Mean	(±SD)	Median	Minimum	Maximum
Psoriasis	111.96	(±149.66)	43.38	8.06	638.59
Control	33.76	(±56.48)	6.50	1.20	179.93

TABLE 3. Mann–Whitney test results comparing the mean rank of IL-30 of the psoriatic patients and control groups.

Group	N	Mean IL-30	(±SD)	Mean rank	P*
Psoriasis	26	111.96	(±149.66)	890.00	<0.001
Control	26	33.76	(±56.48)	488.00	

**By Mann–Whitney test.*

TABLE 4. IL-30 means by age and gender in the psoriatic patients and control groups.

	N	Mean IL-30	(±SD)	Mean rank	P*
Psoriasis					
Age (years)					
<40	10	72.94	(±97.41)	12.40	0.467
40–49	6	104.73	(±135.19)	11.50	
≥50	10	155.32	(±196.87)	15.80	
Gender					
Male	18	106.65	(±159.96)	12.72	0.437
Female	8	123.90	(±132.70)	15.25	
Control					
Age (years)					
<40	13	40.77	(±63.93)	14.54	0.720
40–49	4	6.06	(±3.72)	11.13	
≥ 50	9	35.95	(±57.99)	13.06	
Gender					
Male	12	29.30	(±51.95)	13.75	0.877
Female	14	37.59	(±61.78)	13.29	

**By Kruskal–Wallis test.*

(Table 4) of the cases (P = 0.467) and controls (P = 0.720). Additionally, a comparison of the mean rank of IL-30 among genders, presented in the same table (Table 4), also revealed no significant differences in both the case (P = 0.437) and control (P = 0.877) groups.

As for the IL-30 and PASI scores correlational statistics, a weak non-significant positive correlation was detected among psoriasis cases (rho = 0.174, P = 0.377) as presented in Figure 1B. Moreover, a comparison of the three categories of psoriasis (mild, moderate, and severe (Figure 1C)) concerning the mean rank of IL-30, shown in Table 5 and Figure S1, also revealed a non-significant difference (P = 0.993). Table 5 further demonstrates that there was no significant association between the psoriatic

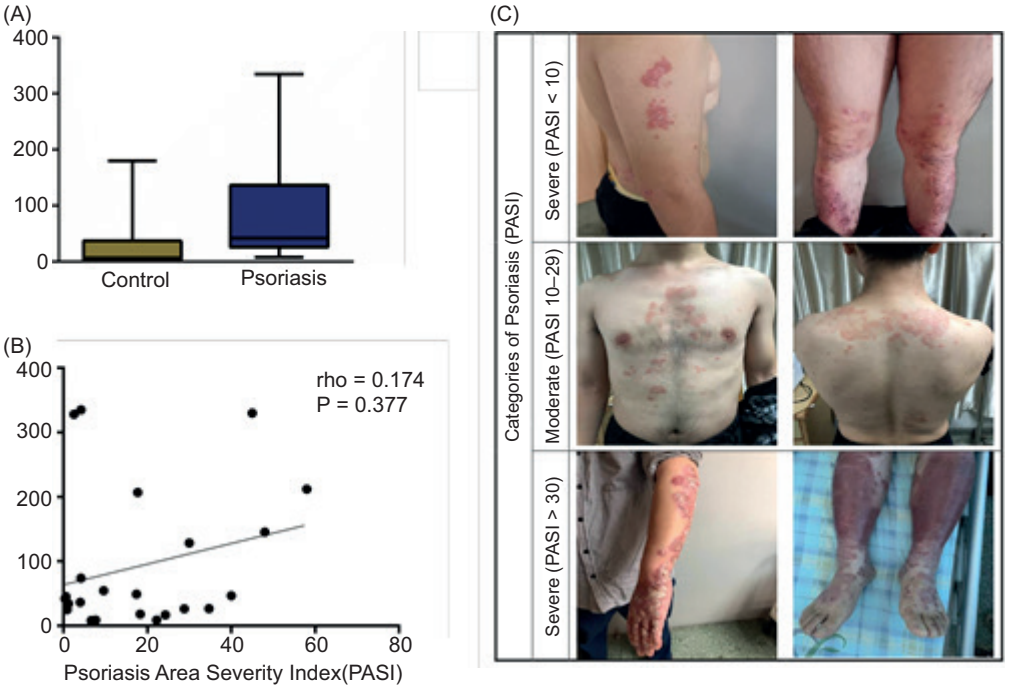

FIGURE 1. IL-30 attributes in psoriasis. (A) A comparison of the serum IL-30 levels of the psoriatic patients and control groups. (B) Correlation between IL-30 and PASI score among the psoriatic patients. (C) Representative images of the study participants that represent the three categories of psoriasis according to their PASI score as mild (PASI < 10), moderate (PASI 10–29), and severe (PASI > 30).

TABLE 5. Comparison of means and mean ranks of IL-30 with the severity-, duration-, and age-at diagnosis of psoriasis as assessed by PASI score.

Characteristics of psoriasis	N	Mean IL-30	(±SD)	Mean Rank	P
Severity					
Mild	14	121.23	(±183.87)	13.43	0.993*
Moderate	3	91.27	(±101.24)	14.00	
Severe	9	104.43	(±110.07)	13.44	
Duration (years)					
<10	14	86.96	(±113.82)	12.07	0.304†
≥10	12	141.12	(±184.03)	15.17	
Age at diagnosis					
<40	17	106.74	(±170.96)	12.00	0.169†
≥40	9	121.80	(±106.55)	16.33	
Total	26	111.96	(±149.66)		

**By Kruskal–Wallis test. †By Mann–Whitney test.*

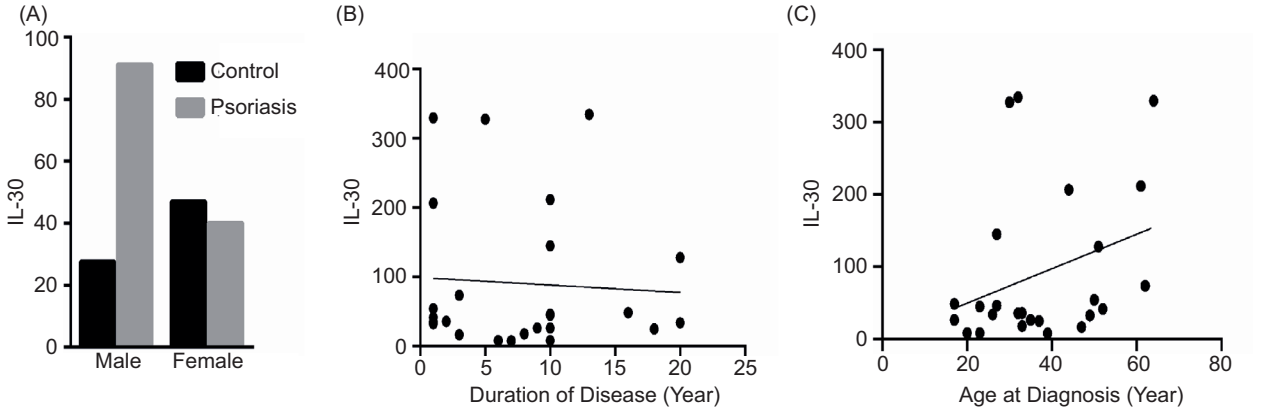

FIGURE 2. Contribution of gender, age at diagnosis, and duration of the disease to serum IL-30 in psoriasis. (A) The predominance of male psoriatic patients to females. No significant differences ($P > 0.05$) were observed in the psoriatic patients' mean rank of serum IL-30 to their age at diagnosis (B) and duration of disease (C).

patients' mean ranks of IL-30 and the duration of their psoriasis ($P = 0.304$, Figure 2B) or their age at diagnosis ($P = 0.169$, Figure 2C).

DISCUSSION

Psoriasis is a common chronic immune-mediated inflammatory skin disorder characterized by erythematous silvery scaling of the skin and associated severe itching. Reports indicate that psoriasis is affecting about 2% of the world population's life quality in a way that limits the patient activity and thereby productivity in a community.[8,19] With the advancement of knowledge in psoriasis, the study of the possible attribution of cytokines in the pathogenesis of psoriasis has been of relevant. To this end, several studies have reported on the association of psoriasis with overexpression of various serum cytokines levels, such as IL-6, IL-8, IL-12, IL-17, IL-18, and IL-23.[18,20–22]

However, as evidenced via a PubMed search engine, there is no reported study of the serum levels of IL-30 in psoriasis to-date. To address this knowledge gap, the current study was undertaken in psoriatic patients and controls demographic and clinical laboratory characteristics, which interestingly revealed the possible attributions of IL-30 in psoriasis. IL-30 has been reported as an independent cytokine produced by immune cells of myeloid origin that mediates antineoplastic effects in several tumor models,[23,24] presumably including psoriasis. The statistical analysis of the study determined that compared to those of controls, the psoriatic patient's serum IL-30 level was significantly higher. Moreover, findings of the study suggest that there exists a positive correlation of the serum levels of IL-30 with the severity of psoriasis, although not significant, as ascertained with PASI. Despite the PASI limitations, including having a non-linear scale[25,26] and a lack of sensitivity,[27] the PASI score has been the most commonly recommended clinical research measure of psoriasis clinical severity.[27] Of note, consistent with the results of previously reported studies on cytokines in psoriasis.[20,22] the present study data showed that the serum level of IL-30 has no association with age or gender ($P > 0.05$). As with their age and gender, the age at diagnosis and duration of the disease of the undertaken psoriatic patients of this study were determined not to have a significant association to the mean ranks of their serum IL-30. These non-significant associations of the mean rank of the psoriatic patient's

serum IL-30 to their age at diagnosis and duration of their psoriatic disease are coherent to the findings of reported studies on the association of related cytokines with psoriasis.[22,28]

In the literature, several studies have reported a uniform incidence of psoriasis in males and females.[29] However, the current study data shows a predominance of male psoriatic patients, consistent with the findings of Fernandez-Armenteros et al.,[30] while others reported the prevalence in females.[31] The reported studies of psoriasis with female predominance argue the possible contribution of gender to quality of life association for women are more concerned about their health and treatment than men.[32] Nevertheless, the limited available data and the population awareness of psoriasis may have contributed to selection bias. Additionally, unlike the findings of several reported studies that have reported age and sex as among the most contributing factors towards the severity of psoriasis,[33,34] the current study results suggest no significant differences in the psoriatic patients mean rank of serum IL-30 to their age or gender.

Recent insights into cytokines have enabled a better understanding of the psoriasis pathophysiology,[35] however, the pathogenesis mechanisms that lead to the disease are extremely complex.[36] Notably, the hyper-proliferation and abnormal differentiation of keratinocytes in psoriasis have been subjected to impaired T-lymphocytes.[37] Consistently, several inflammatory cytokines that elevate in serum concentrations during psoriasis have been shown to correlate with the disease severity. Thus, determining the specific or combined cytokine that plays the main role in the psoriasis pathogenesis can revolutionize the diagnosis and treatment of psoriasis. The effect of the IL-30 in psoriasis lesions is yet to be fully elucidated, following further in vitro and in vivo studies; however, the current study findings suggest a significantly increased difference in the cases where serum IL-30 level compared to the controls and a positive correlation of the IL-30 level with PASI. These findings insights that the downregulation of IL-30 expression may attenuate the abnormal keratinocyte proliferation and other related features that are common during the biological processes of psoriasis.

Overall, consistent with the theoretical features of psoriasis, the current study results demonstrate the involvement of IL-30 in the proliferation of epidermal cells during psoriasis, which further confirms that psoriasis represents an immune-mediated systemic disease. However, the origin of IL-30 in the serum and whether the changes in the serum IL-30 level in psoriatic patients are a cause or a consequence of the disease are still unclear.

CONCLUSIONS

The findings of the current study substantiate previously reported studies on the involvement of certain cytokines in the pathogenesis of psoriasis.[18,20–22] These cytokines involved in the interaction of keratinocytes with T-lymphocytes may contribute to the pathogenesis of psoriasis. However, the cytokines production process and their biological properties during psoriasis remain unknown. This study for the first time reports on the serum levels of IL-30 in psoriatic patients, that may enhance early diagnosis and comprehensive management of patients with the disease. Further in vitro and in vivo studies would be beneficial to fully elucidate the attributions of IL-30 in the pathogenesis of psoriasis.

REFERENCES

1. Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386(9997):983–94.
2. Xu X, Zhang HY. The immunogenetics of psoriasis and implications for drug repositioning. Int J Mol Sci. 2017;18(12):2650.
3. Hwang ST, Nijsten T, Elder JT. Recent highlights in psoriasis research. J Invest Dermatol. 2017;137(3): 550–6.
4. Takahashi H, et al., Serum cytokines and growth factor levels in Japanese patients with psoriasis. Clin Exp Dermatol. 2010;35(6):645–9.

5. Golinska J, Sar-Pomian M, Rudnicka L. Dermoscopic features of psoriasis of the skin, scalp and nails – A systematic review. J Eur Acad Dermatol Venereol. 2019;33(4):648–60.
6. Yeung H, et al. Psoriasis severity and the prevalence of major medical comorbidity: A population-based study. JAMA Dermatol. 2013;149(10):1173–9.
7. Ayala-Fontanez N, Soler DC, Mccormick TS. Current knowledge on psoriasis and autoimmune diseases. Psoriasis (Auckl). 2016;6:7–32.
8. Feldman SR, et al. The challenge of managing psoriasis: unmet medical needs and stakeholder perspectives. Am Health Drug Benefits. 2016;9(9):504–13.
9. Coondoo A. Cytokines in dermatology – A basic overview. Indian J Dermatol. 2011;56(4):368–74.
10. Kouris A, et al. Proinflammatory cytokine responses in patients with psoriasis. Eur Cytokine Netw. 2014;25(4):63–8.
11. Krause ML, et al. Assessing immune function by profiling cytokine release from stimulated blood leukocytes and the risk of infection in rheumatoid arthritis. Clin Immunol. 2011;141(1):67–72.
12. Catalan-Dibene J, Mcintyre LL, Zlotnik A. Interleukin 30 to interleukin 40. J Interferon Cytokine Res. 2018;38(10):423–39.
13. Di Carlo E. Decoding the role of interleukin-30 in the crosstalk between cancer and myeloid cells. Cells. 2020;9(3):615.
14. Petes C, et al. Interleukin (IL)-6 inhibits IL-27- and IL-30-mediated inflammatory responses in human monocytes. Front Immunol. 2018;9:256.
15. Stumhofer JS, et al. A Role for IL-27p28 as an antagonist of Gp130-mediated signaling. Nat Immunol. 2010;11(12):1119–26.
16. Baran P, et al. Minimal interleukin 6 (IL-6) receptor stalk composition for IL-6 receptor shedding and IL-6 classic signaling. J Biol Chem. 2013;288(21):14756–68.
17. Zhang J, et al. Soluble expression and purification of the functional interleukin-30 protein in Escherichia Coli. Prep Biochem Biotechnol. 2016;46(6):539–45.
18. Abdel-Hamid MF, et al. Serum levels of interleukin-8, tumor necrosis factor-alpha and gamma-interferon in Egyptian psoriatic patients and correlation with disease severity. J Dermatol. 2011;38(5):442–6.
19. Salman A, et al. Impact of psoriasis in the quality of life of children, adolescents and their families: A cross-sectional study. An Bras Dermatol. 2018;93(6):819–23.
20. Arican O, et al. Serum levels of TNF-Alpha, IFN-Gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005;2005(5):273–9.
21. Asadullah K, Sterry W, Volk HD. Analysis of cytokine expression in dermatology. Arch Dermatol. 2002;138(9):1189–96.
22. Kyriakou A, et al. Serum levels of TNF-Alpha, IL-12/23p40, and IL-17 in plaque psoriasis and their correlation with disease severity. J Immunol Res. 2014;2014:467541.
23. Garbers C, et al. Plasticity and cross-talk of interleukin 6-type cytokines. Cytokine Growth Factor Rev. 2012;23(3):85–97.
24. Liu X, et al. A protective role of IL-30 via stat and erk signaling pathways in macrophage-mediated inflammation. Biochem Biophys Res Commun. 2013;435(2):306–12.
25. Carlin CS, et al. A 50% reduction in the psoriasis area and severity index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004;50(6):859–66.
26. Spuls PI, et al. How good are clinical severity and outcome measures for psoriasis?: Quantitative Evaluation in a systematic review. J Invest Dermatol. 2010;130(4):933–43.
27. Puzenat E, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. J Eur Acad Dermatol Venereol. 2010;24 (Suppl 2):10–16.
28. Kyriakou A, et al. Serum levels of TNF-Alpha, IL-12/23 P40, and IL-17 in psoriatic patients with and without nail psoriasis: A cross-sectional study. Scientific World J. 2014;2014:508178.
29. Gudjonsson JE, Elder JT. Psoriasis: epidemiology. Clin Dermatol. 2007; 25(6):535–46.
30. Fernandez-Armenteros JM, et al. Epidemiology of psoriasis. A population-based study. Actas Dermosifiliogr. 2019;110(5):385–92.

31. Kyriakou A, Patsatsi A, Sotiriadis D. Detailed analysis of specific nail psoriasis features and their correlations with clinical parameters: A cross-sectional study. Dermatology. 2011;223(3):222–9.
32. Gottlieb AB, Ryan C, Murase JE. Clinical considerations for the management of psoriasis in women. Int J Womens Dermatol. 2019;5(3):141–50.
33. Hagg D, et al. Severity of psoriasis differs between men and women: A study of the clinical outcome measure psoriasis area and severity index (PASI) in 5438 Swedish register patients. Am J Clin Dermatol. 2017;18(4):583–90.
34. Lopez-Estebaranz JL, Sanchez-Carazo JL, Sulleiro S. Effect of a family history of psoriasis and age on comorbidities and quality of life in patients with moderate to severe psoriasis: Results from the Arizona study. J Dermatol. 2016;43(4):395–401.
35. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. Cytokine. 2015;73(2):342–50.
36. Kim J, Krueger JG. The immunopathogenesis of psoriasis. Dermatol Clin. 2015;33(1):13–23.
37. Schon MP, Boehncke WH. Psoriasis. N Engl J Med. 2005;352(18):1899–912.

SUPPLEMENTARY MATERIALS

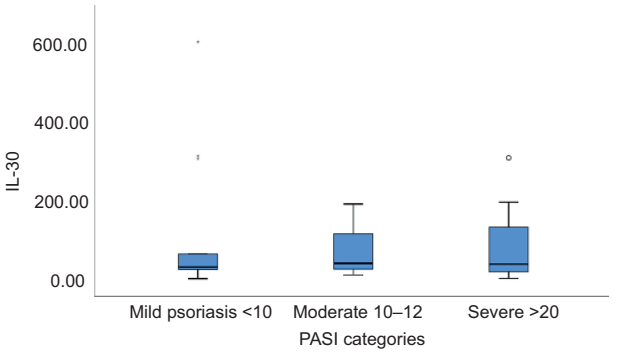

FIGURE S1. Box plot showing the relation between IL-30 and severity of psoriasis according to PASI. P = 0.959 (By Mann–Whitney test).

Table S1. Correlation between IL-30 with age at diagnosis and duration of the psoriasis disease.

	Correlation with IL-30	
	rho	**P**
Age at diagnosis	0.232	0.253
Duration of the disease	0.082	0.690