Serum Interlukin-22 in Psoriasis Vulgaris

Doaa A. Elshibly[1*], Sherif R. Ismail[1], Yousra I. Sadeq[2], Manar E. Sallam[1]
Departments of [1]Dermatology, Andrology & STDs and
[2]Clinical Pathology, Faculty of Medicine, Mansoura University, Egypt
*Corresponding Author: Doaa Abdelfattah Elshibly, Mobile: (+20)0106 931 9738, Email: doaahady24@gmail.com

ABSTRACT
Background: Psoriasis vulgaris (PV) has been considered as a frequent immune-mediated chronic, inflammatory dermal disease representing approximately 2% globally. Interleukin-22 (IL-22) is a recently described IL-10 family cytokine produced by a lot of cellular sources, which include Th17 and Th22 cells, and it plays an essential role in several autoimmune diseases (AIDs) such as rheumatoid arthritis (RA), and PV.
Objective: To determine the diagnostic value of serum IL-22 level for PV; and to examine the possible correlation between serum IL-22 and disease severity and activity.
Patients and Methods: This was a case control study conducted on 60 patients complaining from psoriasis; 30 patients complaining from active psoriasis, 30 patients with stable psoriasis, and 30 age- and sex-matched healthy controls (HC). Psoriasis area and severity index was used to assess both involved body area and clinical appearance of psoriatic lesions.
Results: IL-22 was significantly increased among cases with active than stable disease and among progressive disease than intermittent disease. There was a statistically significant higher IL-22 among patients compared to HC. Area under curve (AUC) of IL-22 in differentiating patients from HC was excellent with sensitivity of 93.3%, specificity of 83.3% and accuracy of 90%.
Conclusion: Interlukin-22 (IL-22) produces inflammatory signals which induce dermal and systemic manifestations in PV. IL-22 serum concentration may be an accurate marker of detecting severity of disease progression.
Keywords: Interlukin-22, Psoriasis vulgaris, Psoriasis area and severity index.

INTRODUCTION

Psoriasis vulgaris (PV) has been considered as a common immune-mediated chronic, inflammatory dermal disease. The etiology and pathogenetic mechanisms of PV are still unclear. The cellular innate and adaptive immune responses, in particular the simulation of T cells and production of cytokines by T cells, have an essential role in the context of PV pathogenesis [1].

Interlukin-22 (IL-22) is a cytokine formed by a lot of cellular sources, which include Th17 and Th22 cells [2]. IL-22 can suppress keratinocyte differentiation and could induce PV-like epidermal changes. IL-22 mRNA was significantly increased among cases with PV. Additionally, IL-22 has the ability to synergize with the different pro-inflammatory cytokines to elicit several pathogenic phenotypes from keratinocytes with a subsequent exaggeration of PV progression [3].

All such results propose that IL-22 has essential roles in terms of PV pathogenesis. We hypothesized that IL-22 released by keratinocytes could have a main role in this AID; as a result, suppressing IL-22 activity could be a breaking novel therapeutic plan as regards PV management.
Aim of the work was to determine the diagnostic value of serum IL-22 level for PV; and to examine the possible correlation between serum IL-22 and disease severity and activity.

SUBJECTS AND METHODS

This was a case control study conducted on 60 cases complaining from psoriasis; 30 cases suffering from active psoriasis, 30 cases with stable psoriasis, and 30 age- and sex-matched HC presented to the outpatient clinic of Dermatology, Andrology and STDs, Mansoura University Hospitals.

Inclusion criteria: the included patients were either patients with active disease presented with the development of new lesions throughout the preceding one month or with stable disease with stationary existent lesions for more than 3 months, and patients had no treatment for psoriasis in the past month. We included patients of both genders with active and stable psoriasis, with age ranged from 18 to 60 years, with body mass index (BMI) between 18.5 to 24.9 kg/m^2, before inclusion in the study.

Exclusion criteria: patients who refused to contribute to the study, pregnant or lactating females, cases treated with narrowband UVB, irradiations, or systemic treatment in the past month, and subjects with any concomitant dermatological diseases, or immune-mediated comorbidities.

Methods

Entire cases were subjected to history taking that included personal history (name, age, gender, occupation, residence), analysis of complain (age at onset, disease duration, progressive, regressive, stable over the last 3 months), family history of psoriasis, medical history (type and duration of previous treatments) and other diseases and their treatments.

Clinical Examination

The examination included full general examination to exclude systemic or autoimmune diseases, full body

skin examination in adequately illuminated examining room, diagnosis of psoriasis vulgaris by clinical picture, dermoscopy or biopsy for suspected cases and psoriasis area and severity index (PASI) was used to evaluate both involved body area and clinical appearance of psoriatic lesions [4].

Measurement of serum IL-22 levels
The serum IL-22 values were calculated by an ELISA, as the instruction of the user manufacturer. Five ml of peripheral venous blood was withdrawn from cases and controls; left to clot and centrifuged at 2000 r.p.m for fifteen min. Clear serum was separated and stored at -20ºC until assayed.

Assay principle
This ELISA kit used the Sandwich-ELISA principle. The micro-ELISA plate provided in this kit is pre-coated with an antibody (AB) distinctive to Human IL-22. Specimens (or Standards) were added and combined with the specialized AB. After that, a biotinylated determination AB specialized for Human IL-22 and Avidin-HRP conjugate were added efficiently to all micro plate wells followed by incubation. The substrate solution was added to all wells. The wells that comprised IL-22, biotinylated detection AB and Avidin-HRP conjugate were the only ones that revealed bluish colour. The enzyme-substrate reaction was ended by adding the stop solution in which the color changes into yellow. The OD was evaluated by using spectrophotometric method at a wavelength of 450 nm±2 nm. The OD value had a proportionate relationship with IL-22 concentration.

Ethical Considerations
Approval was obtained from the Ethical Committees at Faculty of Medicine, Mansoura University (MS.21.03.1425). Informed written consent was obtained from all the included subjects. Confidentiality and privacy were respected and all data were used in scientific purpose only. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis
The collected data were coded, tabulated and inserted using SPSS Version 25.0. Data were presented and suitable analysis was done based on the data type acquired for all parameters. Kolmogorov-Smirnov test was performed to properly assess the normality of data distribution. Mean±SD was utilized for parametric numerical data, on the other hand median and range were utilized for nonparametric numerical ones. Qualitative data were presented as frequency and percentage. Student t-test, Mann-Whitney U test and Chi-Square test were utilized. When the p-value was equal to or less than 0.05, it was deemed significant.

RESULTS
Table (1) reveals that there was no statistically significant difference between studied groups regarding sociodemographic characteristics; namely age, sex, occupation, marital status, and smoking.

Table (1): Sociodemographic characteristics of the studied groups

	Patients group n=60	Control group n=30	Test of significance
Age/years mean±SD	40.28±11.64	36.20±10.63	t=1.61 p=0.110
Sex n (%) Female Male	27(45.0) 33(55.0)	14(46.7) 16(53.3)	X²=0.022 p=0.881
Occupation n (%) House wife Manual worker Professional worker	24(40) 33(55) 3(5)	8(26.7) 17(56.7) 5(16.7)	X²=4.07 p=0.131
Marital status n (%) Single Married	8(13.3) 52(86.7)	6(20.0) 24(80.0)	X²=0.677 p=0.411
Smoker n (%) Non smoker Smoker	40(66.7) 20(33.3)	14(46.7) 16(53.3)	X²=3.33 p=0.068

t: Student t test, X²=Chi-Square test

Table **(2)** shows the median PASI score in the studied patients.

Table (2): Median PASI score among studied cases

	n=60
PASI score median (Min-Max)	1.3(0-16.7)

Figure (1) illustrates statistically significant strong positive correlation between serum IL-22 and PASI score.
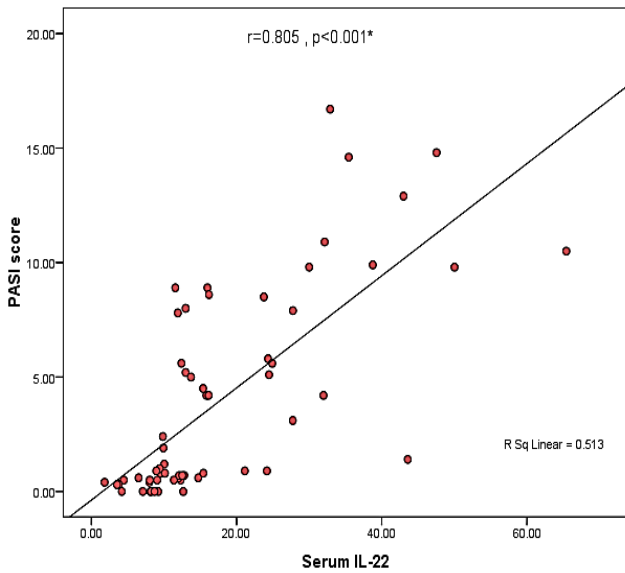
Figure (1): Scatter diagram showing correlation between serum IL-22 and PASI score among studied cases.

Table (3) demonstrates no statistically significant relation between disease onset and serum IL-22 among studied cases. Also, no statistically significant correlation is detected between serum IL-22 and age of onset or disease duration among studied cases. A statistically significant higher median IL-22 among cases with active than stable disease. Also; statistically significant higher median IL-22 was detected among progressive disease than intermittent disease.

Table (3): Relation between serum IL-22 and disease onset, duration, disease course and activity

	Serum IL-22	Test of significance
Onset Acute Gradual	13.35(3.51-50.03) 12.41(1.82-65.43)	z=0.736 p=0.462
Age of onset/years	r=0.126, p=0.336	
Duration	r=0.17, p=0.172	
Activity Active Stable	24.40(9.85-65.34) 9.31(1.82-24.18)	z=5.52 p<0.001*
Course Progressive Intermittent	19.96(9.92-50.03) 10.75(1.82-65.43)	z=3.31 p=0.001*

Z: Mann Whitney U test, r: Spearman correlation coefficient, IL-22 was described as median (min-max), *Statistically significant.

Table (4) demonstrates non statistically significant relation between serum IL-22 and presence of systemic disease, surgical history, drug history, previous systematic therapy, previous phototherapy and positive family history.

Table (4): Relation between serum IL-22 and associated comorbidities among studied cases

	Serum IL-22	Test of significance
Systemic disease -ve +ve	12.59 (1.82-65.43) 31.26 (23.76-38.76)	z=1.52 p=0.128
Surgical history -ve +ve	12.66 (1.82-65.43) 38.76 (38.76-38.76)	z=1.42 p=0.157
Drug history -ve +ve	12.59(1.82-65.43) 31.26(23.76-38.76)	z=1.52 p=0.128
Previous systematic therapy -ve +ve	12.89 (3.51-65.43) 12.25 (1.82-43.58)	z=0.591 p=0.554
Previous phototherapy -ve +ve	12.73 (1.82-43) 12.75 (3.51-65.43)	z=1.06 p=0.290
Family history -ve +ve	12.97 (1.82-50.03) 12.52 (7.08-65.43)	z=0.386 p=0.700

Z: Mann Whitney U test, IL-22 is described as median (min-max).

Table (5) demonstrates that at cut off 4.43, IL-22 could differentiate between patients and control group with marked sensitivity.

Table (5): Validity of IL-22 in differentiating patients from control

	AUC (95%CI)	P-Value	Cut off point	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
IL-22	0.952 (0.911-0.994)	<0.001*	4.43	93.3	83.3	91.8	86.2	90.0

IL: Interleukin, AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value, *Statistically significant.

Table **(6)** demonstrates that AUC of IL-22 in differentiating active from stable disease was excellent with the best detected cut off point was 12.35.

Table (6): Validity of IL-22 in differentiating active from stable psoriasis

	AUC (95%CI)	P-Value	Cut off point	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
IL-22	0.914 (0.847-0.982)	<0.001*	12.35	86.7	76.7	78.8	85.2	81.7

IL: Interleukin, AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value, *Statistically significant.

DISCUSSION

Psoriasis vulgaris (PV) represents ninety percent of all cases with PV, some presenting with different systemic co-morbidities such as psoriatic arthritis, cardiac disorders, diabetes, malignant tumors, and depressive manifestations, as a result inducing critical affection of life quality [5].

It is a complicated inflammatory process, which involves several adaptive immune processes. Extensive stimulation of myeloid dendritic cells (DCs) develops owing to the cytokines formed by plasmacytoid DCs (pDC), keratinocytes, macrophages, and T cells, which ultimately ends in IL-12 and IL-23 release [6]. IL-12 triggers naive T cells for differentiation into Th1 cells that discharge INF-γ and TNF-α. Of note, IL-23 has a main role for Th17- and Th22-mediated cytokine formation, in other words, Th17 discharges IL-17, IL-22, and TNF-α, and in contrast Th22 forms IL-22. In general, such inflammatory signals have been demonstrated to be accompanied by the dermal and systemic manifestations in PV, such as keratinocyte proliferations, dermal infiltration by immune cells, vasodilation, and angiogenesis (formation of new blood vessels) [7].

Additionally, IL-22 controls host defense and mainly targets nonhematopoietic epithelial and stromal cells, in which it could encourage tissue regeneration and proliferation. On the other hand, IL-22 is associated with a lot of situations comprising pathological inflammation of tissues [8]. As a result, we aimed to explore the blood levels of IL-22 in chronic plaque psoriasis; and to investigate whether it can be a biomarker in monitoring disease activity or correlates with disease severity.

The current study was a case-control study carried out on 3 groups: 30 patients with active psoriasis, 30 patients with stable psoriasis, and matched age and sex 30 HC. The present study revealed that, the mean age of patients group was 40.28 years with median age of onset was 31 years and the mean age of control group was 36.2 (10.63) years with male predominance in both groups. While **Alamri et al**. [9] had revealed that out of total of 139 cases with PV, 79 (56.8%) were male and 60 (43.2%) were female, with a mean age of 45.53 years, which agreed with our results. Preceding researches revealed no fixed gender differences among cases with PV. Certain researches revealed a greater percentage of male cases that ranged from 56% to 77% [10]. The present study was in the same line with **Parisi et al**. [11] who displayed that mean age of onset of PV is at 33 years. On the other hand, it presents at a younger age in males compared to females. In the context of females, PV often manifests at a mean age of 19 or 57 years.

Our study displayed that, out of the studied patients; 55% were manual workers, 40% were housewives and 5% were professional workers versus 56.7% were manual workers, 26.7% were housewives and 16.7% were professional workers for control group. Of the studied cases; 86.7% are married versus 80% of control group. In addition, **Bayomy et al**. [12] had examined 109 cases with PV whose ages were ranging from 18 to 66 years. The percentage of male to female ratio was 41.28/58.72%. About 34% of their studied cases were employed, 26.6% of them were students and 65.14 % of them were married. The present study revealed that smokers represented 33.3% of patients and 53.3% of control group. While **Nstantin et al.** [13] noticed that the percentage of smoking patients was 46.8%. Former smokers represented 7.3% and nonsmokers represented 45.9%, that reveals that smoker group comprised 54% of PV cases, while non-smokers group comprised 45.9% of PV cases, which agreed with our results.

Our study showed that, 63.3% of the studied cases have gradual disease with median PV duration was 5 years. Progressive disease course was detected among 33.3% of the studied cases, while **Przepiórka-Kosińska et al**. [14] revealed that PV duration was from months up to forty-eight years, 19 years on average. The current study found that 50% of the studied cases were active disease and 50% had stable disease. In the present study, 3.3% of cases had positive history of systemic disease, 1.7% had positive surgical history, 3.3% had positive drug history, all cases received topical therapy, 20% had received previous systemic therapy, the current study showed that 88.3% of cases had skin lesion, 35% of cases had hair lesion and 18.3% had nail lesion. The present study found that, 56.7% had received previous phototherapy and 21.7% had positive

family history. While from 1847 patients with psoriasis, 199 having a family history of PV. Cases with a previous family history of PV were associated with a significantly earlier disease onset compared to cases with no family history. In addition, cases with a family history of PV had significantly longer disease duration [15]. While **Cordoro et al.** [16] who examined pediatric psoriasis revealed that the majority had mild psoriasis at onset of biopsies, however moderate-to-severe disease was recorded by all. In the past, the most commonly utilized therapies comprised local steroids (in one hundred percent), calcipotriene, and systemic therapy such as acitretin and phototherapy (four cases).

The current study reported a significant greater median IL-22 among patients compared to HC; 12.73 ranging from 1.82 to 65.43 versus 2.88 ranging from 0 to 11.01. In the same line, **Wawrzycki et al**, [17] recorded that serum values of IL-22 were increased in cases with PV in comparison with HC, which came in accordance with preceding records [18,19]. Moreover, **Michalak-Stoma et al.** [20] revealed a significant increase in IL-22 values among cases with PV compared to HC. This acme in disagreement with **Sobhan et al.** [21] who had displayed that mean serum value of IL-22 was 284.1±49.7 pg/ml in cases versus 425.4±82.8 pg/ml in HC that was in disagreement with our results.

The present study found a significant increase in IL-22 values among cases with active compared to cases with stable disease, in addition there was a statistically significant higher IL-22 values among progressive disease than intermittent disease. Our study revealed no statistically significant relation between disease onset, age of onset, disease duration and serum IL-22 among studied cases. On the other hand, **Nikamo et al**. [22] recorded that a genetic IL-22 variant that encourages epithelial barrier defense is specially enriched in and might trigger PV onset at an early age. The present study revealed non-statistically significant relation between serum IL-22 and presence of systemic disease, surgical history, drug history, previous systematic therapy, previous phototherapy and positive family history. Our study demonstrated a statistically significant strong positive relationship between serum IL-22 and PASI score. The present results agreed with other reports who revealed that, the IL-22 values had a significant relationship with PV severity (as revealed by PASI) [23].

Michalak-Stoma et al. [20] found a significant positive association with PV severity evaluated by PASI. Also, **Sobhan et al.** [21] had revealed that the severity of PV was significantly associated with high IL-22 values. While **Fotiadou et al.** [24] displayed that IL-22 values in the serum of PV cases didn't demonstrate positive correlation with PV severity (based on PASI score). The current study revealed that IL-22 was excellent in differentiating patients from control group; (cutoff=4.43) with a sensitivity of 93.3%,

specificity of 83.3% and total accuracy of 90%. Moreover, IL22 was excellent for differentiating active from stable disease; with the best detected cutoff point was 12.35 yielding sensitivity of 86.7%, specificity of 76.7% and total accuracy 81.7%. This is in agreement with other study who reported that the cases with active disease revealed a significant increase in IL-22 levels, compared with controls. Cases with stable PV, in contrast, revealed no significant difference of IL-22 values compared to HC. Of note, the active group was associated with a significant increase in IL-22 values in comparison with the stable group [24].

LIMITATIONS

The small sample size has been considered the main limitation. Also, effects of various psoriasis treatment on level of IL-22 should be studied in further multicenter reports.

CONCLUSION

In conclusion, IL-22 produces inflammatory signals, which induce dermal and systemic manifestations in PV, and according to obtained results, IL-22 serum concentration was higher in psoriatic cases and thus may be an accurate marker of detecting severity of disease progression.

- **Limitation:** This case series was limited to drawing any definite conclusion.
- **funding:** none
- **Conflict of Interest:** The authors had nothing to declare.

REFERENCES

1. **Ayala-Fontánez N, Soler D, McCormick T (2016):** Current knowledge on psoriasis and autoimmune diseases. Psoriasis: Targets and Therapy, 6: 7-32.
2. **Shabgah A, Navashenaq J, Shabgah O et al. (2017):** Interleukin-22 in human inflammatory diseases and viral infections. Autoimmunity Reviews, 16(12): 1209-1218.
3. **Hao J (2014):** Targeting interleukin-22 in psoriasis. Inflammation, 37(1): 94-99.
4. **Fredriksson T, Petterson V (1978):** Índice de área e severidade da psoríase (PASI). Dermatologic, 157: 238-44.
5. **Rendon A, Schäkel K (2019):** Psoriasis pathogenesis and treatment. Int J Mol Sci., 20(6): 20(6): 1475. doi: 10.3390/ijms20061475
6. **Armstrong A, Read C (2020):** Pathophysiology, clinical presentation, and treatment of psoriasis: A review. JAMA., 323(19): 1945-60.
7. **Cruz C, Yang C (2023):** Clinical application of serum biomarkers for detecting and monitoring of chronic plaque psoriasis. Front Mol Biosci., 10:1196323. doi: 10.3389/fmolb.2023.1196323.
8. **Dudakov J, Hanash A, van den Brink M (2015):** Interleukin-22: immunobiology and pathology. Annu Rev Immunol., 33: 747-85.
9. **Alamri A, Alqahtani R, Alshareef I et al. (2022):** Psoriasis in Saudi population: Gender differences in

clinical characteristics and quality of life. Cureus, 14(3): e22892. doi: 10.7759/cureus.22892

10. **Soliman M (2020):** Patient-reported disease severity and quality of life among Arabic psoriatic patients: a cross-sectional survey. Clin Cosmet Investig Dermatol., 13: 601–609.

11. **Parisi R, Iskandar I, Kontopantelis E *et al.* (2020):** Global psoriasis atlas. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. BMJ., 369: 1590. DOI:10.1136/bmj.m1590

12. **Bayomy H, Albedaiwi Y, Alabdulatif S *et al.* (2022):** Psoriasis in Northern Saudi Arabia: Clinical features and implications for quality of life. J Public Health Res., 11(4): 22799036221123961. doi: 10.1177/22799036221123961

13. **Nstantin M, Bucur S, Mutu C *et al.* (2021):** The Impact of smoking on psoriasis patients with biological therapies in a Bucharest Hospital. J Pers Med., 11(8):752-56.

14. **Przepiórka-Kosińska J, Bartosińska J, Raczkiewicz D *et al.* (2020):** Serum concentration of osteopontin and interleukin 17 in psoriatic patients. Adv Clin Exp Med., 29(2):203-208.

15. **Ohata C, Anezaki H, Kaneko S *et al.* (2023):** Clinical characteristics of patients with psoriasis with family history: A multicenter observational study. J Dermatol., 50(6):746-752.

16. **Cordoro K, Hitraya-Low M, Taravati K *et al.* (2017):** Skin-infiltrating, interleukin-22-producing T cells differentiate pediatric psoriasis from adult psoriasis. J Am Acad Dermatol., 77(3):417-424.

17. **Wawrzycki B, Pietrzak A, Grywalska E *et al.* (2019):** Interleukin-22 and its correlation with disease activity in plaque psoriasis. Arch Immunol Ther Exp., 67(2):103-108.

18. **Lo Y, Torii K, Saito C *et al.* (2010):** Serum IL-22 correlates with psoriatic severity and serum IL-6 correlates with susceptibility to phototherapy. J Dermatol Sci., 58(3):225-7.

19. **Shimauchi T, Hirakawa S, Suzuki T (2013):** Serum interleukin-22 and vascular endothelial growth factor serve as sensitive biomarkers but not as predictors of therapeutic response to biologics in patients with psoriasis. J Dermatol., 40:805–812.

20. **Michalak-Stoma A, Bartosińska J, Kowal M *et al.* (2013):** Serum levels of selected th17 and TH22 cytokines in psoriatic patients. Disease Markers, 35:625–631.

21. **Sobhan M, Farshchian M, Hoseinzadeh A *et al.* (2016):** Serum levels of IL-10 and IL-22 cytokines in patients with psoriasis. Iran J Immunol., 13(4):317-323.

22. **Nikamo P, Cheuk S, Lysell J *et al.* (2014):** Genetic variants of the IL22 promoter associate to onset of psoriasis before puberty and increased IL-22 production in T cells. J Invest Dermatol., 134(6):1535-1541.

23. **Boniface K, Guignouard E, Pedretti N *et al.* (2007):** A role for T cell-derived interleukin 22 in psoriatic skin inflammation. Clin Exp Immunol., 150(3):407-15.
    Fotiadou C, Lazaridou E, Sotiriou E *et al.* (2015): IL-17A, IL-22, and IL-23 as markers of psoriasis activity: A cross-sectional, hospital-based study. J Cutan Med Surg., 19(6):555-60.