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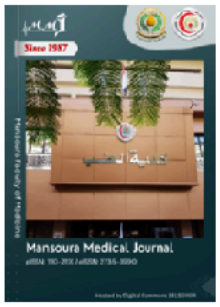

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Serum Interleukin-22 in non-segmental Vitiligo

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ORIGINAL STUDY

Serum Interleukin-22 in Nonsegmental Vitiligo

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Abstract

Background: **A depigmenting skin condition called vitiligo affects 0.5−2% of people globally. It seems to be caused by an interaction between neurological, immunological, and genetic factors. Vitiligo is mediated by cell-mediated reactions, as Th1/Th17 and Tc1 cells. It is thought that the Th17 cell's most specialized cytokine is interleukin-22 (IL-22).**

Aim: **To explore the blood levels of IL-22 in nonsegmental vitiligo and to investigate whether it can be a biomarker in monitoring disease activity and it is correlation with disease severity.**

Patient and methods: **This study included 30 healthy individuals and 60 nonsegmental vitiligo cases (30 with stable vitiligo and 30 with active vitiligo). Vitiligo extent score (1) was needed for the estimation of the affected body surface area. IL-22 serum levels were estimated using ELISA.**

Results: **When comparing cases with active vitiligo to those with stable vitiligo, the IL-22 median serum level in the former group was statistically significantly elevated ($P < 0.001$). Additionally, in comparison to the control, IL-22 serum level was statistically significantly raised in cases with both active and stable vitiligo ($P < 0.001$). With a sensitivity and specificity of 96.7% and 90%, respectively, the optimal cutoff point of serum IL-22 level to distinguish cases with active vitiligo from those with stable vitiligo was 11.64. With a statistically significant value of P less than 0.001, the area under curve was 0.970.**

Conclusion: **There is promising evidence that IL-22 could be used as a biomarker for vitiligo activity. Since IL-22 is involved in immune modulation, it may be a promising new target for manipulating the immune system to treat vitiligo.**

Keywords: Interleukin-22, Vitiligo, Vitiligo extent score (VES)

1. Introduction

The most prevalent depigmentation condition, vitiligo, is thought to affect 0.5−2% of people worldwide. However, in countries like India, reports of a prevalence rate as high as 8.8% have been made (Li et al., 2019).

Segmental and nonsegmental vitiligo (NSV) are the two primary alternatives to the disease. The differences in prognosis and treatment response between these two primary types form part of the basis for this classification (Kumar Jha et al., 2018).

The progression of many autoimmune diseases including vitiligo is associated with shifting from Th2 and T regulatory cells toward (Th)1 and Th17 (Gibson et al., 2017). The Th17 cells secrete cytokines such as interleukin-17 (IL-17), IL-6, IL-22, and tumor necrosis factor (TNF), that enhance IL-1a, IL-6, and TNF release from keratinocytes. Th17 also acts with these inflammatory mediators to inhibit the proliferation of melanocytes (Habeb et al., 2013).

Numerous innate and adaptive immune cells produce IL-22. Th17 and Th22 are primary sources of IL-22 among the latter. IL-22 serum levels are markedly elevated in generalized vitiligo in comparison to localized disease, and more in vitiligo cases than in controls (Custurone et al., 2021).

The role of IL-22 in the proinflammatory process is confirmed by the upregulation of matrix metalloproteinase 3, platelet-derived growth factor A, and the chemokine CXCL5. Additionally, it induces keratinocyte migration and downregulates the expression of seven genes essential for keratinocyte

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differentiation in an *in vitro* injury model (Boniface et al., 2005).

To ascertain whether IL-22 could be utilized as a marker to monitor the course or severity of non-segmental/generalized vitiligo (NSV), this research set out to measure IL-22 serum levels in NSV cases.

2. Patients and methods

This research was done at the dermatology outpatient clinic of Mansoura University Hospital in Mansoura, Egypt, using a case-control design. Thirty cases with stable vitiligo and 30 with active vitiligo, comprising 60 cases with NSV, were involved in the research along with thirty seemingly healthy age and sex matched controls.

2.1. Inclusion criteria

The study involved cases of both sexes with active and stable NSV, with ages between 18 and 60 years. All patients were new cases or medication-free for at least 1 month before the study.

Active vitiligo is defined as patients with an appearance of new lesions or a progression of old lesions within the last 12 months. Lesions that did not progress within 12 months were considered stable vitiligo (Ezzedine et al., 2012).

2.2. Exclusion criteria

Cases with segmental or unclassified vitiligo, refusal to participate, pregnant or lactating women, patients who received any treatment for vitiligo in the last 1 month, and patients with any concomitant dermatological diseases, or immune-mediated comorbidities.

Detailed history was taken from the cases, a general examination to rule out any systemic or autoimmune diseases, and a dermatological examination that included skin, hair, nails, and oral mucosa in an adequately illuminated examining room. Examination of vitiligo using wood lamp considering the following characteristics: size, color, symmetry, extent, and clinical types. The vitiligo extent score (VES) (Abdelmaksoud et al., 2019) was used to determine the severity of the disease (van Geel et al., 2016).

Quantitative evaluation of human IL-22 by enzyme-linked immunosorbent assay kit (Catalog No: E-EL-H0106; Elabscience, Wuhan, China) was made according to the manufacturer's instructions.

2.3. Statistical analysis of data

Utilizing the Statistical Package for Social Sciences (SPSS) version 27 for Windows (SPSS Inc, Chicago, IBM, IL, USA), the data was coded, processed, and examined. Both a percentage and a number (frequency) were used to represent categorical data. The Fisher's exact or Monte–Carlo test, commonly referred to as the χ^2 test, was used to compare the independent groups with categorical data. The normalcy of quantitative data was checked using the Kolmogorov–Smirnov test. Parametric data were shown as mean ± SD, while nonparametric data were shown as a median (range). Two independent groups were compared using parametric and nonparametric data, respectively, using the independent samples *t*-test and the Mann–Whitney *U*-test. Plotting sensitivity (Beyzaee et al., 2022) against 1-specificity (FP) at different cut-off values yields the receiver operating characteristic curve. The diagnostic performance of the test is indicated by the area of the receiver operating characteristic curve. Numerical data was correlated using either Pearson's or Spearman's correlation (r). Significant *P* values are those that fall below 0.05.

3. Results

Our study revealed that the mean age was 31.37 ± 13.14 years and 35.0 ± 11.02 years in the cases and control groups respectively, with a nonstatistically significant difference between the two groups ($P = 0.196$). Female patients represented 63.3% of the case group and 50% of the control group. There was no statistically significant difference between the two groups regarding sex ($P = 0.226$).

Table 1 reveals that, in comparison to cases of inactive vitiligo, the percentage of cases with an

Table 1. Comparison of disease characteristics and Vitiligo extent score between active and stable vitiligo cases.

Variables	Stable vitiligo $N = 30$ [n (%)]	Active vitiligo $N = 30$ [n (%)]	Test of significance
Onset			
Acute	12 (40)	22 (73.3)	0.009[a]
Gradual	18 (60)	8 (26.7)	
Age of onset/years			
Median (min–max)	18.5 (10–47)	31 (8–59)	0.029[a]
Course			
Intermittent	12 (40)	9 (30.0)	<0.001[a]
Progressive	8 (26.7)	21 (70)	
Regressive	10 (33.3)	0	
Duration/years			
Median (min–max)	4 (0.5–20)	3 (0.5–22.0)	0.562
Family history			
No	23 (76.7)	17 (56.7)	0.1
Yes	7 (23.3)	13 (43.3)	
Vitiligo extent score			
Median (min–max)	1.194 (0.08–6.16)	0.66 (0.02–17.72)	0.193

[a] Statistically significant ($P < 0.05$).

acute onset of the disease was statistically significantly higher in active cases (73.3% and 40%, respectively) ($P = 0.009$). In the cases with active vitiligo, the median age of onset was statistically significantly higher; (31 in active vitiligo versus 18.5 in stable vitiligo). However, there was a non-statistically significant difference ($P > 0.05$) in the medication history, length of disease, topical therapy, systemic therapy, family history, and VES between the two groups.

Table 2 reveals that IL-22 median serum level in active vitiligo cases was 18.08 (ranged 10.93–32.85) which was statistically significantly higher compared with the stable vitiligo cases with its IL-22 median serum level was 9.51 ranged (5.5–19.62) ($P1 < 0.001$). Additionally, in relation to the control, the serum level of IL-22 was statistically significantly higher in cases with both active and stable vitiligo ($P2$, $P3 < 0.001$).

According to Table 3, there was no statistically significant relationship found between the serum level of IL-22 and the patient's age, the age at which vitiligo first appeared, the length of the disease, or the vitiligo extent score.

Table 4 reveals that the best cut-off point of serum IL-22 level to identify active vitiligo cases from that with stable vitiligo was 11.64 with 96.7% sensitivity and 90% specificity. The area under the curve was 0.970 with a statistically significant value ($P < 0.001$), (Fig. 1). Moreover, 7.06 had the highest cut-off point for serum IL-22 levels with 96.7% sensitivity and 96.7% specificity to distinguish vitiligo cases from the control group. The area under the curve was 0.993 with a statistically significant value ($P < 0.001$), (Fig. 2).

4. Discussion

IL-22 level of active vitiligo cases differed statistically significantly ($P < 0.001$) from those with stable vitiligo in our study. Furthermore, in both cases of active and stable vitiligo, IL-22 serum level was statistically significantly elevated than in the control ($P < 0.001$).

This agreed with Yasmin and colleagues case-control study, which included 35 vitiligo cases and 35 age and sex matched healthy volunteers. The researchers demonstrated that, in comparison to individuals in good health, vitiligo cases had significantly elevated average serum levels of IL-22 ($P \leq 0.001$). Additionally, a significant difference was discovered in means of serum IL-22 levels between generalized and nongeneralized types of vitiligo (focal and segmental), as well as between active vitiligo (VIDA score equal to 1, 2, 3, or 4) and stable vitiligo (VIDA score equal to 0 or −1) ($P \leq 0.001$) (Yasmin et al., 2021).

Sushama and colleagues reported similar findings, showing that cases with vitiligo had elevated levels of Th17 cell-secreted cytokines (IL-2, TNF-a, IL-6, IL-17, and IL-22) than age and sex matched healthy controls did, as well as significantly elevated IL-17 and IL-22 serum levels in generalized cases in comparison to localized cases. They claimed that those cytokines are significant because they rise in proportion to the degree of vitiligo (Sushama et al., 2019).

In keeping with this, a study by Nieradko-Iwanicka and colleagues included 50 vitiligo patients and 38 controls. The findings revealed that patients in the study group had blood serum concentrations of IL-22 that were statistically significantly raised than those in control. The study group with body surface area (BSA) less than or equal to 10 exhibited significantly higher IL-22 concentrations compared with the control, with the BSA greater than or equal to 10 groups exhibiting the elevated concentrations ($P < 0.05$) (Nieradko-Iwanicka et al., 2022).

Similarly, Ratsep and colleagues found that IL-22 was significantly raised in cases with vitiligo, both by the mRNA expression and protein level in sera. It was two to four folds higher than the controls. They also stated that IL-22 was elevated in active compared with stable vitiligo and reported that IL-

Table 3. Comparison between serum interleukin-22 and patient age, age of vitiligo onset, duration, and vitiligo extent score among studied cases.

Variables	Serum IL-22	
	R	*P*
Age/years	0.243	0.062
Age of onset/years	0.236	0.07
Duration/years	−0.045	0.733
Vitiligo extent score	−0.071	0.587

Table 2. Comparison of serum interleukin-22 between active, stable vitiligo cases and control groups.

	Stable Vitiligo	Active Vitiligo	Control	General *P* value	Within group significance
Serum IL-22	9.51 (5.5–19.62)	18.08 (10.93–32.85)	3.95 (1.14–7.73)	KW = 75.75 $P < 0.001$[a]	$P1 < 0.001$[a] $P2 < 0.001$[a] $P3 < 0.001$[a]

*P*1: difference between stable and active cases.
*P*2: difference between stable and control group and *P*3: between active and control group.
[a] Statistically significant ($P < 0.05$).

Table 4. Validity of serum interleukin-22 between active and stable vitiligo cases and between cases and controls.

	AUC (95%CI)	*P* value	cut off point	Sensitivity%	Specificity%	PPV%	NPV%	Accuracy%
IL-22 (between active and stable vitiligo cases)	0.970 (0.927–1.0)	<0.001[a]	11.64	96.7	90.0	90.6	96.4	93.3
IL-22 (between cases and cobtrol)	0.993 (0.983–1.0)	<0.001[a]	7.06	96.7	96.7	93.5	98.3	96.7

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.
[a] Statistically significant ($P < 0.05$).

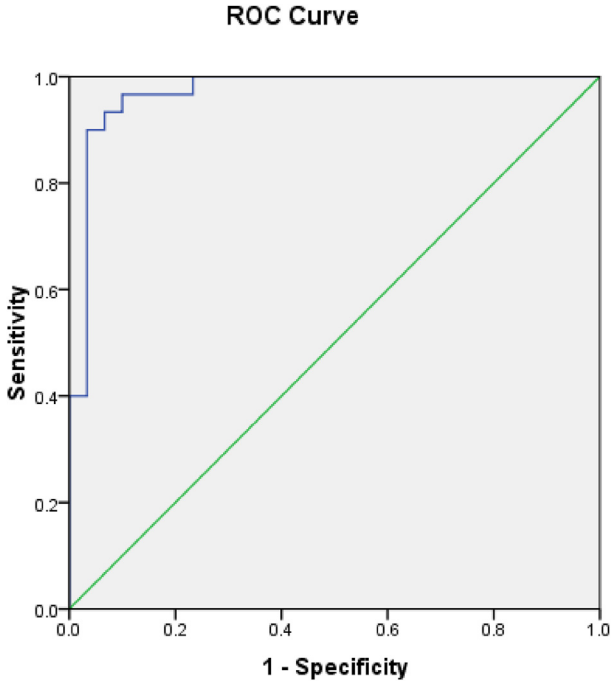

Fig. 1. Receiver operating characteristic curve of serum interleukin-22 level differentiating active from stable vitiligo groups.

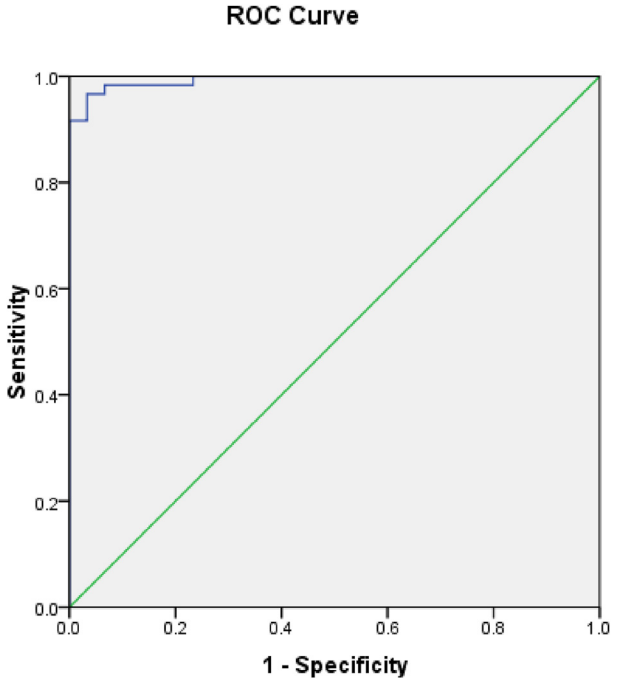

Fig. 2. Receiver operating characteristic curve of serum interleukin-22 level differentiating cases from control group.

22 provokes inflammatory pathways causing destruction of melanocytes (Rätsep et al., 2008).

When 84 NSV cases and 80 controls were studied, Abou Elela *et al.* found the same outcomes. The findings demonstrated a significant increase in serum IL-22 between the patient group (43.53 ± 11.95 pg/mL) and the control group (9.92 ± 4.7 pg/ml) (Abou Elela et al., 2013).

Also, in an *in-vitro* study by Dong *et al.*, According to reports, the IL-22 tissue level in lesional skin was significantly elevated than in controls, and it was even higher in perilesional skin. IL-22 raised IL-1β level via reactive oxygen species production (Dragoni et al., 2017) which led to NOD-like receptor family, pyrin domain containing 3 (NLRP3) activation in HaCaT cells (Dong et al., 2017).

However, in a study by Cengiz *et al.*, They did not discover any appreciable variations in the expression of epidermal IL-22R between the vitiligo and control groups (Cengiz et al., 2015). The disparity in IL-22R expression levels and techniques for measuring IL-22 in the lesional skin could be the cause of this discrepancy.

IL-22 serum level correlated with age, the age at which vitiligo first appeared, the length of the disease, and the VES in the current investigation, but not statistically significantly. This agreed with Yasmin and colleagues who demonstrated that IL-22 serum levels and the severity of the disease did not correlate (Yasmin et al., 2021).

In our research, the best cut-off point for serum level of IL-22 to identify active vitiligo cases from stable cases was 11.64 with 96.7% sensitivity and 90% specificity. Also, the best cut-off point of serum level of IL-22 to identify cases with vitiligo from controls was 7.06 with 96.7% sensitivity and 96.7% specificity.

No previous researches has reported the cut-off point of serum IL-22 in identifying vitiligo cases from control or the determination of the disease activity.

This could be the main strength point of our study which provides a less invasive assessment

technique in the diagnosis of the disease and its severity. Of course, the determination of a certain cut-off point requires more and more studies.

In our study, the mean age of vitiligo cases was 31.37 ± 13.14 years. Dragoni *et al.* showed that the mean (±SD) and median age of the cases were 43.7 ± 16 and 45 years (Dragoni et al., 2017). Al Houssien *et al.* showed that the mean age was 45 ± 19 years (Al Houssien et al., 2017). In other studies, different mean ages were found. Our findings almost match research from Rome that revealed 63.9% of patients were under 40 (Paradisi et al., 2014). Abdallah *et al.* revealed that the age range between 10 and 29 was the most prevalent in their study (51.2%) (Abdallah et al., 2020).

Our findings indicated that female sex was more common in vitiligo cases (63.3%). This agreed with a recent study conducted in Damanhur city in Egypt that revealed among 86 cases complaining of vitiligo, there were 54 (62.8%) female patients, and 32 (37.2%) male patients (Abdallah et al., 2020). A recent study in Iran included 166 individuals (the case group was formed of 83 vitiligo cases and 83 individuals acted as control). The study revealed that there was higher female predominance in vitiligo cases (Females: 60.24%, males: 39.76%) (Namazi et al., 2020).

However, this disagreed with Wang *et al.* who showed a male to female ratio of 1.6:1 (Wang et al., 2013). Also, another research by Dragoni *et al.* revealed an equal sex distribution between the two groups (Dragoni et al., 2017).

The difference between the studies regarding the presence or absence of significance could be due to different sample sizes that could affect the level of significance.

The reason for the higher percentage of females is that women typically worry more about skin pigmentation changes because they typically have an impact on their social lives. This might be the cause of the study's female preponderance.

In the current study, there were 20 cases (23.3%) with a positive family history of vitiligo. 111 vitiligo patients (61 men and 50 women) were studied in the Qassim Region of Saudi Arabia. The results showed that 22.5% of the cases had first-degree cousin consanguinity and 32.4% of the cases showed consanguinity, indicating that vitiligo may be an inherited condition. Consanguineous cases began at a younger age (Alzolibani, 2009).

Positive family history was discovered in 11.6% of the participants in an Egyptian study (Abdallah et al., 2020). It nearly matches a Chinese survey of 815 probands, of which 15.7% reported having a family history (Sun et al., 2006).

In the current study, the cases with active vitiligo had a median age of onset that was statistically significantly higher than stable vitiligo. These results suggest that patients experience longer periods of stable disease as their illness worsens.

Our results corroborated those of Taneja and colleagues, who discovered that the duration of vitiligo activity and stability varied according to the severity of the condition. Both the active and stable periods of the disease's duration increased over time, as expected, but the stable periods' increase was notably larger than the active periods'. For each year that the disease persisted, the stable and active periods in NSV increased by 0.7 and 0.3 years, respectively; in segmental vitiligo, they increased by 0.9 and 0.1 years ($P < 0.001$) (Taneja et al., 2022).

These results were not previously reported and need more verification in further studies.

The sample size may be regarded as relatively small, which limits the power of conclusions. Additionally, the study was conducted in a single center with certain limitations. Consequently, in order to increase reliability, we advise conducting more large-scale, unlimited, controlled multicentric studies.

4.1. Conclusion

IL-22 might have great validity to be utilized as a biomarker for assessing activity but not the severity of vitiligo. IL-22 has an immune-modulatory role in vitiligo and can be considered as a new target for immune manipulation in managing vitiligo.

Publication Ethical Statement

Every participant provided informed consent. The research was performed in line with the 2013 Helsinki Standards revision (World Medical Association, 2013). The Mansoura Faculty of Medicine's institutional review board gave the study approval (MS.21.08.1639).

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Conflicts of interest

No conflicts of interest were disclosed by the writers.

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