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Serum interleukin-19 level in vitiligo patients and its relationship with disease severity and activity

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Abstract

Vitiligo is induced by melanocyte destruction mediated by autoreactive cytotoxic CD8+ T cells. Interleukin-19 (IL-19) belongs to the IL-10 family of cytokines. It acts to enhance T-helper (Th) 2 cytokine release. The association between IL-19 (rs2243188) gene polymorphism and vitiligo development has been confirmed, but the serum level of IL-19 in vitiligo patients has been poorly studied. The aim of this study was to assess IL-19 serum level in vitiligo patients and its relationship with disease severity and activity. In this case-control study, 50 non-segmental vitiligo patients and 50 controls of similar age and sex were included. Vitiligo Extent Score (VES) and Vitiligo Disease Activity (VIDA) Score were used to assess disease severity and activity, respectively. An enzyme-linked immunosorbent assay (ELISA) was used to determine serum IL-19 level. Vitiligo patients had significant lower serum levels of IL-19 than those of healthy controls ($p<0.001$). These levels were negatively correlated with disease severity ($p=0.023$), and duration ($p=0.032$). Furthermore, the levels were significantly lower among patients with signs of activity than in patients who didn't have signs of activity ($p<0.05$). ROC curve analysis showed that IL-19 can be used to differentiate between patients with active and non-active vitiligo. Lower Il-19 serum level in vitiligo patients may have a role in vitiligo pathogenesis by enhancing the T-helper 1 mediated cytotoxic attack against melanocytes. Moreover, IL-19 may be an indicator of vitiligo activity.

Keywords: Vitiligo, Interleukin, Pathogenesis.

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1. Introduction

Vitiligo is a disorder of skin depigmentation clinically characterized by the appearance of disfiguring depigmented circumscribed skin macules and patches. It is hypothesized that the disease primarily results from the destruction of melanocytes**.** Vitiligo has a complex etiopathogenesis that includes genetic, metabolic, environmental factors, and autoimmune processes [1-2]. Innate immunity in vitiligo bridges the gap between oxidative stress and adaptive immunity. It is likely that the activation of innate immune cells occurs early in vitiligo, by sensing exogenously or endogenously induced stress signals released from melanocytes and possibly keratinocyte [3]. Cytotoxic CD8+ T lymphocytes that are specific for melanocytes have been closely linked to the demise of melanocytes. Histological evidence has shown CD8+ T cell infiltration of the epidermis and dermis, and compared to healthy controls, patients with vitiligo had greater blood levels of cytotoxic CD8+ T cells [4]. Interferon-γ, produced by cytotoxic CD8+ T cells in vitiligo patient skin lesions and blood, directly induces melanocyte apoptosis in vitro. Interferon-γ-induced chemokines CXCL9 and CXCL10 were significantly elevated in human vitiligo skin [5]. Cytokine secretion from CD4+ T cell subsets including Th1, Th2, and Th17 cells may contribute to the pathogenesis of the disease [6]. Interleukin-19 (IL-19) is a member of the IL-10 family of cytokines, forming a subfamily with IL-20 and IL-24, and is related more broadly with the type-I, -II and -III interferons [7]. IL-19 has been found to be a component of the T-helper (Th) 2 system.

Its expression in lipopolysaccharide stimulated monocytes was greatly enhanced by preincubation of the monocytes with IL-4 and, to a lesser extent, with IL-13 [8]. In addition, the induction of Th 2 cytokine expression (IL-4,

IL-5, IL-10, and IL-13) by IL-19 has been confirmed [9]. Furthermore, IL-19 has been shown to play a significant function in the pathogenesis of different autoimmune diseases, especially Th 2 allergic reaction, atopic diseases, and psoriasis [10-12]. The role of IL-19 in psoriasis, which is a Th 1 dependent autoimmune disease, could be explained by the fact that IL-19 mRNA expression in keratinocytes was induced by IL-17, and tumor necrosis factor (TNF)-α as well as by Th2 cytokines IL-4 and IL-13 [12]. Previous research has revealed the association between IL-19 (rs2243188) gene polymorphism and vitiligo development [13]. Therefore, it was crucial to determine the serum level of interleukin-19 in vitiligo patients and its relationship with disease severity and activity.

2. Subjects and methods

2.1. Study design

This case-control study was carried out at the Dermatology Outpatient Clinics, Suez Canal University Hospitals, Ismailia, Egypt from February 2022 to August 2023. The study protocol was approved by the Research Ethics Committee of Faculty of Medicine, Suez Canal University. The study included 50 patients with both stable and active non-segmental vitiligo aged 16 years or older. Patients with autoimmune disease, cancer patients, patients with other dermatological disease that causes depigmentation, as well as those taking immunosuppressive medications like methotrexate, those with inflammatory conditions, acute or chronic infections, and those receiving systemic or topical treatment for vitiligo for at least three months prior to enrollment were excluded from the study. A control group of 50 age and sex matched healthy persons without vitiligo, cancers, autoimmune illnesses, or inflammatory diseases was also included. Prior to inclusion in the study, all participants signed a written informed consent. All patients underwent a full history taking including age, sex, age at disease onset, disease course, duration, and site of lesions. Dermatological examination was done to assess vitiligo lesions site, size, and clinical type, as well as hair involvement (leukotrichia). Vitiligo was diagnosed clinically as skin depigmented macules or patches and the diagnosis was confirmed by Wood's lamp examination by which vitiligo lesions appear milky white. Examination of hair, nails and mucosal membranes was also done. Assessment of disease severity was evaluated by Vitiligo Extent Score (VES Score) [14]. Assessment of disease Activity was evaluated by Vitiligo Disease Activity Score (VIDA Score) and by signs of activity consisting of recent Koebner's phenomenon, confetti-like depigmentation, tri- and hypochromic lesions (including those with ill-defined borders), inflammatory borders/areas, and presence of itching [15-16].

2.2. Assessment of IL-19 serum level

Five mL blood samples were collected in plain test tubes from peripheral veins then it was left standing for 20 minutes at room temperature, centrifuged for 10 minutes at the speed of 3000 rpm. The serum was then isolated and put into storage at -20°C until it was time for testing. Human IL-19 enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Wuhan, China, Catalogue No: E-EL-H0254) was used to measure serum IL-19 levels according to the manufacturer's instructions.

2.3. Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Chi-square test was used for categorical variables, to compare between different groups. Student t-test was used for normally distributed quantitative variables, to compare between two studied groups. Mann-Whitney test was used for non-normally distributed quantitative variables, to compare between two studied groups. ANOVA test was used for normally distributed quantitative variables, to compare between more than two studied groups. Pearson coefficient was used to correlate between two normally distributed quantitative variables.

3. Results

3.1. Demographic and clinical characteristics of patients with vitiligo (n=50) and healthy controls (n=50)

Fifteen (30%) patients were males and 35(70%) were females, and in the control group; 13 (26%) individuals were males and 37 (74%) were females. The mean ± SD age of vitiligo patients was 32.22± 10.40 years (range 16-60 years), and in the control group was 33.64 ± 11.34 years (range 18-53 years). There were non-statistically significant differences in age and gender between patients and controls (Table 4). Clinical data of patients with vitiligo are summarized in Table 1. Acrofacial vitiligo was the most prevalent type presented in 30 (60%) patients, followed by generalized vitiligo that was presented in 17 (34%) patients. VES score ranged from 0.18 to 6.52 with the mean± SD 2.45±1.84. Regarding signs of activity, 44 (88%) patients had signs of activity including, Koebner's phenomenon that was presented in 22 (44%) patients, confetti like depigmentation that was present in 10 (20%) patients, hypochromic lesions presented in 21 (42%) patients, inflammatory border and itching presented in 4 (8%) patients.

3.2. Serum level of IL-19

The mean ± SD serum IL–19 level in vitiligo patients was 159.36 ± 305.43 pg/ml (range 5-1000 pg/ml), and in the control group was 1267.20 ± 1671.59 pg/ml (range 10-5100 pg/ml). Serum level of IL-19 was significantly lower in patients with vitiligo compared to healthy controls ($p<0.001$) (Figure 1 & Table 5). Serum IL-19 level was significantly lower among patients with advanced VIDA score ($p<0.05$). Furthermore, IL-19 serum level was significantly lower among patients with signs of activity than in patients who showed no signs of activity ($p<0.05$). There were statistically significant negative correlations between IL19 serum level and VES score ($p=0.023$) as well as vitiligo disease duration ($p=0.032$) (Table 2 & Table 3). Otherwise, serum level of IL-19 wasn`t influenced by patient's gender or disease clinical type.

The receiver operating characteristic (ROC) curve analysis of IL-19 was used to differentiate between patients with active and non-active vitiligo by examining the sensitivity, specificity, predictive values, and area under the

curve (AUC) based on the cut-off levels for serum IL-19 levels in vitiligo patients. IL-19 had an AUC of 0.785, showing 84% sensitivity and 70% specificity. Serum levels of IL-19 can thus be used to differentiate between patients with active vitiligo and those with non-active vitiligo using a cutoff value of ≤120 (Figure 2 & Table 6).

4. Discussion

Vitiligo has been confirmed as an autoimmune disease mediated by melanocyte specific CD8+ Cytotoxic T lymphocytes that trigger melanocyte apoptosis, and malfunction leading to depigmented macules and patches. Moreover, changes in cytokine release from CD4+ T cell subsets including Th1, Th2, and Th17 Cells could be involved in the disease's etiology [17]. IL-19 has been discovered to be expressed preferentially by monocytes, and its expression is up-regulated after stimulation with lipopolysaccharide, Pam3CSK4, or granulocyte-macrophage colony stimulating factor [8]. IL-19 binds to IL-20 receptor that is used by IL-20 and IL-24 [18]. IL-19 stimulates the expression of IL-10 in monocytes and boosts the production of Th2 cytokines in T-lymphocytes [19]. This study aimed to determine IL-19 serum level in vitiligo patients to highlight the possible role of this cytokine in the autoimmune pathogenesis of vitiligo. In the current study, patients with vitiligo had significant lower serum IL-19 levels than healthy controls. This level correlated negatively with vitiligo severity and duration. Moreover, IL-19 serum level was significantly lower among patients with signs of activity than in patients who showed no signs of activity. These findings may suggest the role of IL-19 in the autoimmune responses implicated in vitiligo. IL-19 is a cytokine that act to stimulate Th2 response with simultaneous attenuation of Th1 response. Besides, it induces the expression of IL-10, an anti-inflammatory cytokine released from monocytes [19]. Consequently, IL-19 low serum levels in patients with vitiligo may have enhanced Th1-cytotoxic T cells autoimmune attack against melanocyte. Thus, IL-19, as an anti-inflammatory cytokine, may be suggested as a possible therapeutic option in patients with vitiligo to ameliorate autoimmune cytotoxic responses and could be used as a predictor of vitiligo activity and severity. In contrast to these findings, a previous study found that IL-19 serum levels were higher in vitiligo patients than in healthy controls, particularly in those with active or generalized vitiligo. Moreover, IL-19 serum level was positively correlated with disease duration and severity [20]. The discrepancy between the results of this study and the present study findings may be due to the imprecise exclusion criteria. Ebrahim et al., (2020) only excluded patients with inflammatory skin conditions, burns and intralesional steroid injection [20]. The authors did not exclude patients with other autoimmune diseases, atopy, active or chronic infections, history of cancers or patients on treatment other than intralesional steroid. All these conditions are associated with alterations in IL-19 serum levels and may function as confounders, making it difficult to accurately measure IL-19 serum levels. According to a different study, patients with psoriasis had significantly higher serum levels of IL-19 than healthy controls. The authors therefore hypothesized that IL-19 may help develop and maintain the skin inflammation that characterizes psoriasis.

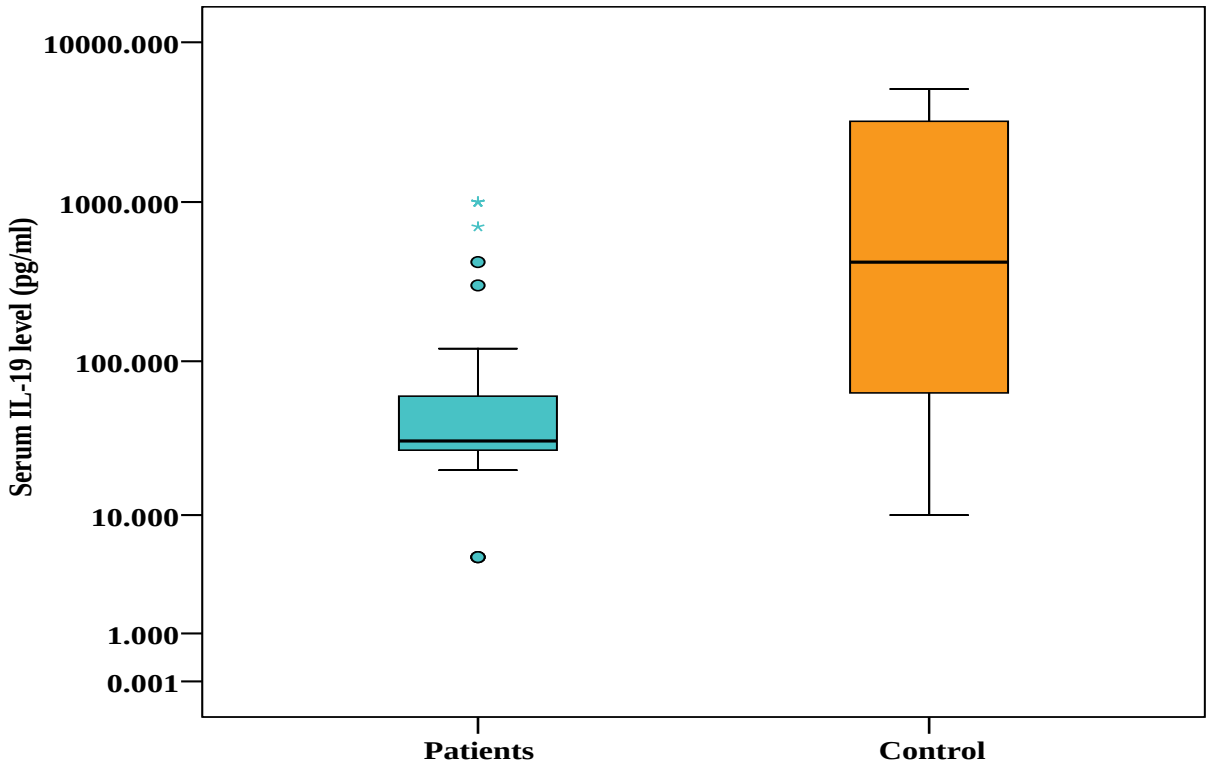

Figure 1: Comparison between the two studied groups according to serum IL-19 level (pg/ml).
Table 1: Distribution of the relevant clinical features of vitiligo patients (n = 50).

	No.	%
Age at disease onset (years)		
Min. – Max.	4.0 – 48.0	
Mean ± SD.	24.80 ± 9.91	
Median (IQR)	24.50 (17.0 – 30.0)	
Duration of the disease (years)		
Min. – Max.	0.50 – 24.0	
Mean ± SD.	7.39 ± 4.96	
Median (IQR)	6.0 (4.0 – 10.0)	
Clinical type		
Generalized	17	34.0
Acrofacial	30	60.0
Localized	3	6.0
Family history		
Negative	42	84.0
Positive	8	16.0
VES score		
Min. – Max.	0.18 – 6.52	
Mean ± SD.	2.45 ± 1.84	
Median (IQR)	2.53 (0.80 – 3.72)	
VIDA score		
0	7	14.0
+1	8	16.0
+2	9	18.0
+3	11	22.0
+4	15	30.0
Signs of activity		
No	6	12.0
Yes	44	88.0
Signs of activity		
Koebner`s phenomenon	22	44.0
Confetti like depigmentation	10	20.0
Hypochromic lesions	21	42.0
Inflammatory border and itching	4	8.0
Leukotrichia	4	8.0

IQR: Inter quartile range; SD: Standard deviation; VES: Vitiligo extent score, VIDA: Vitiligo disease activity score.

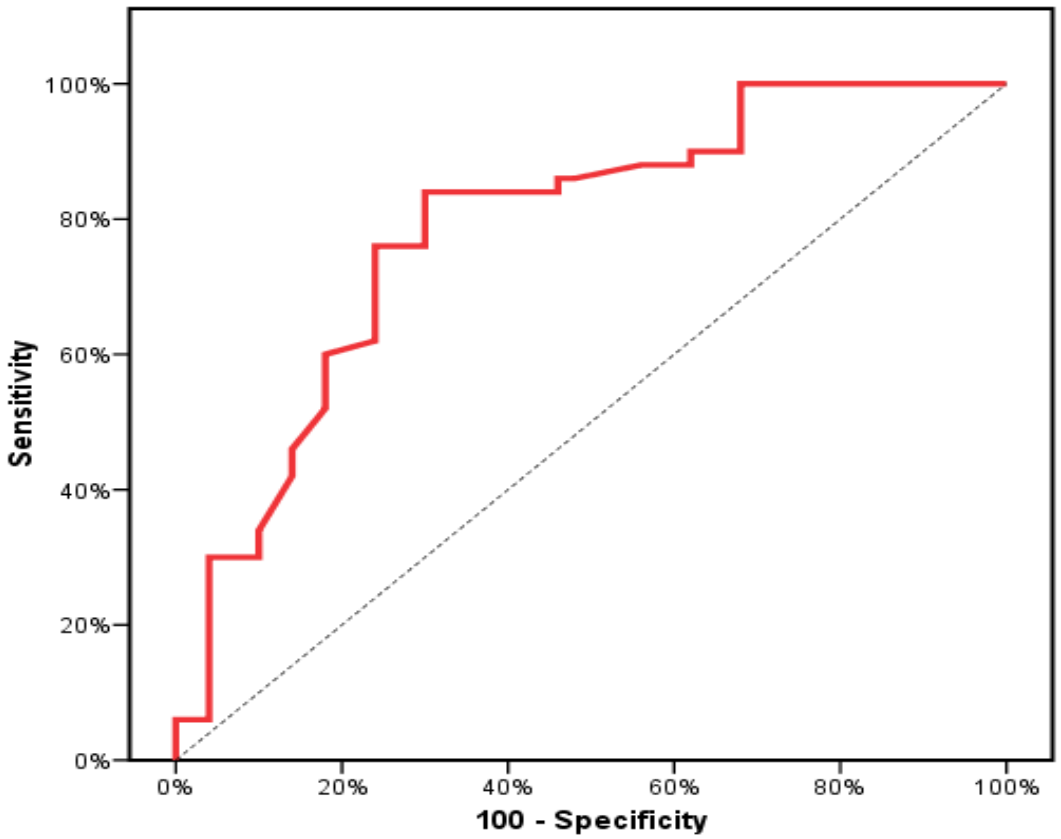

Figure 2: ROC curve for serum IL-19 level (pg/ml) to distinguish between patients with active and non-active vitiligo (n=50).

Table 2: Correlation between serum IL-19 level (pg/ml) and different clinical parameters of vitiligo patients (n=50).

	Serum IL-19 level (pg/ml)	
	r_s	P
Age (years)	0.148	0.306
Age at disease onset (years)	0.123	0.396
Duration of the disease (years)	-0.304	0.032*
VES score	-0.321	0.023*

r_s: Spearman coefficient; IL; Interleukin; VES: Vitiligo extent score.

Table 3: Relation between IL-19 serum level (pg/ml) and clinical characteristics of vitiligo patients (n=50).

	N	Serum IL-19 level (pg/ml)			Test of Sig.	p
		Min. – Max.	Mean ± SD.	Median		
Gender						
Male	**15**	5.0 – 300.0	46.10 ± 71.05	30.50	U= 199.0	0.178
Female	**35**	5.0 – 1000.0	207.91 ± 352.53	31.50		
Type of Vitiligo						
Generalized	**17**	5.0 – 1000.0	86.55 ± 235.71	30.50	H= 1.588	0.452
Acrofacial	**30**	5.0 – 1000.0	213.05 ± 345.37	31.50		
Localized	**3**	31.0 – 41.20	35.07 ± 5.40	33.0		
VIDA score(activity)						
0	**7**	31.50 – 1000.00	598.94 ± 439.31	700.00	H= 43.738*	<0.001*
+1	**8**	41.20 – 1000.00	229.90 ± 320.85	109.00		
+2	**9**	31.50 – 1000.00	143.47 ± 321.23	40.00		
+3	**11**	29.50 – 31.00	30.27 ± 0.56	30.00		
+4	**15**	5.00 – 28.00	20.81 ± 8.39	24.50		
Signs of activity						
No	**6**	31.50 – 1000.0	628.75 ± 473.44	850.0	U= 34.50*	0.002*
Yes	**44**	5.0 – 1000.0	95.36 ± 212.85	30.50		
Koebner`s phenomen						
No	**28**	5.0 – 1000.0	228.38 ± 352.93	41.0	U= 171.0*	0.007*
Yes	**22**	5.0 – 1000.0	71.53 ± 207.58	30.0		
Confetti like depigmentation						
No	**40**	20.0 – 1000.0	193.60 ± 333.40	31.60	U= 89.0*	0.006*
Yes	**10**	5.0 – 40.0	22.42 ± 12.78	26.10		
Hypochromic lesions						
No	**29**	5.0 – 1000.0	249.13 ± 377.92	41.0	U= 195.50*	0.032*
Yes	**21**	5.0 – 120.0	35.40 ± 27.94	30.0		
Inflammatory border and itching						
No	**46**	5.0 – 1000.0	171.59 ± 315.67	31.25	U= 34.50*	0.036*
Yes	**4**	5.0 – 41.0	18.75 ± 17.33	14.50		
Leukotrichia						
No	**46**	5.0 – 1000.0	171.73 ± 315.61	31.50	U= 31.50*	0.026*
Yes	**4**	5.0 – 30.50	17.13 ± 14.04	16.50		

U: Mann Whitney test; H: Kruskal Wallis test; IL: Interleukin; VIDA: Vitiligo disease activity score; p: p value for comparison between different categories; *: Statistically significant at $p < 0.05$.

Table 4: Demographic data of the study participants.

	Patients (n = 50)		Control (n = 50)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	15	30.0	13	26.0	χ^2= 0.198	0.656
Female	35	70.0	37	74.0		
Age (years)						
Min. – Max.	16.0 – 60.0		18.0 – 53.0		t= 0.653	0.515
Mean ± SD.	32.22 ± 10.40		33.64 ± 11.34			
Median (IQR)	32.50(24.0 – 39.0)		30.0(25.0 – 45.0)			

IQR: Inter quartile range; SD: Standard deviation; χ^2: Chi square test; t: Student t-test; p: p-value for comparing between the studied groups.

Table 5: Comparison between patients with vitiligo (n=50) and healthy controls (n=50) according to IL-19 serum level.

Serum IL-19 level (pg/ml)	Vitiligo patients (n = 50)	Controls (n = 50)	U	p
Min. – Max.	5.0 – 1000.0	10.0 – 5100.0	536.50*	<0.001*
Mean ± SD.	159.36 ± 305.43	1267.20 ± 1671.59		
Median (IQR)	31.0(27.0 – 60.0)	420.0(63.0 – 3200.0)		

IQR: Inter quartile range; SD: Standard deviation; U: Mann Whitney test; p: p-value for comparing between the studied groups; *: Statistically significant at $p < 0.05$.

Table 6: Validity (AUC, sensitivity, specificity) for Serum IL-19 level (pg/ml) to distinguish between patients with active and non-active vitiligo (n = 50).

	AUC	P	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
Serum IL-19 level (pg/ml)	0.785	<0.001*	0.695 – 0.876	≤120	84.0	70.0	73.7	81.4

AUC: Area under the curve.

This can be explained by the fact that IL-17A stimulates keratinocytes to produce IL-19, which is then enhanced by the essential cytokines for psoriasis TNF-α and IL-22. IL-19 affects keratinocytes as an autocrine mediator, causing aberrant proliferation and differentiation. Furthermore, IL-19 stimulates the synthesis of certain mediators that are both pro-regeneration (IL-20, matrix metalloproteinase 1) and inflammatory (IL-1, CXCL8) [21]. In another study, Li et al. observed that psoriasis patients had lower serum levels of IL-19 [22]. The authors explained that the decreased serum IL-19 level could be attributed to enhanced binding or faster consumption of keratinocytes in psoriasis patients. This study presents preliminary evidence that interleukin 19 serum level is lower among vitiligo patients than in healthy controls. However, there are certain limitations, such as the small sample size and the absence of assessment of IL-19 tissue expression in vitiligo lesions. Additional research with a greater sample size is needed to determine the expression of IL-19 in vitiligo lesions, especially before and after improvement with different treatment modalities.

5. Conclusions

Serum level of IL-19 in vitiligo patients was significantly lower than in healthy controls. Il-19 may therefore have a role in vitiligo pathogenesis via the enhancement of T-helper 1 mediated cytotoxic reactions against melanocytes. Moreover, serum level of IL-19 was found to be negatively correlated with disease severity, activity, and duration and to be capable of distinguishing between patients with active vitiligo and those with non-active vitiligo. Thus, IL-19 serum level may be an indicator of vitiligo activity.

6. Abbreviations

- IL: Interleukin.
- VES: Vitiligo Extent Score.
- VIDA: Vitiligo Disease Activity Score.
- ELISA: enzyme-linked immunosorbent assay.
- Th: T-helper.
- TNF: Tumor necrosis factor.
- ROC: Receiver operating characteristic.
- AUC: Area under the curve.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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