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Research Article

Impact of Phototherapy on the Immunological and Protein Profile Markers in Iraqi Patients with Vitiligo: Application of Principal Component Analysis

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Abstract

Background: Vitiligo is an autoimmune disease characterized by the loss of melanin pigment in the body, while interleukin-6 is a key indicator in activating the immune response associated with autoimmune diseases. ***Objective***: The current study aims to understand vitiligo patients' immune and protein mechanisms using principal component analysis (PCA). ***Methods***: The study involved 150 participants divided into three groups: patients treated with NB-UVB (PUV), newly diagnosed patients (PN), and healthy controls (C). Serum IL-6 concentrations were measured using ELISA, while total protein, albumin, and globulin were determined using colorimetric analysis. Principal component analysis (PCA) was used to identify statistically significant trends in the variables' distribution among various groups. ***Results***: PCA analysis shows that biological variation among participants was primarily attributable to specific variables, most notably the albumin/globulin ratio and IL-6 concentration. A clear distinction was observed between healthy individuals and vitiligo patients, while the two disease groups (PUV and PN) showed similar biochemical and immunological characteristics, with some minor differences remaining. IL-6 and globulin levels significantly increased in both patient groups compared to the control group, although total protein, albumin, and A/G ratio levels significantly decreased. ***Conclusions***: PCA analysis revealed IL-6 and albumin-to-globulin ratio as key factors influencing biological variation in vitiligo, highlighting immune responses and proteomic abnormalities as potential biomarkers for disease assessment and treatment.

Keywords: Albumin, Globulin, Interleukin-6, Total proteins, Vitiligo.

تأثير العلاج بالضوء على العلامات المناعية والبروتينية لدى المرضى العراقيين المصابين بالبهاق: تطبيق تحليل المكونات الرئيسية

الخلاصة

الخلفية: البهاق هو مرض مناعي ذاتي يتميز بفقدان صبغة الميلانين في الجسم، بينما يعد الإنترلوكين 6 مؤشرا رئيسيا في تنشيط الاستجابة المناعية المرتبطة بأمراض المناعة الذاتية. **الهدف**: فهم الآليات المناعية والبروتينية لمرضى البهاق باستخدام تحليل المكونات الرئيسية (PCA). **الطرائق**: شملت الدراسة 150 مشاركا مقسمين إلى ثلاث مجموعات: المرضى الذين عولجوا ب NB-UVB (PUV) ، والمرضى الذين تم تشخيصهم حديثا (PN)، والضوابط الأصحاء (C). تم قياس تركيزات IL-6 في المصل باستخدام ELISA، بينما تم تحديد البروتين الكلي والألبومين والجلوبيولين باستخدام التحليل اللوني. تم استخدام تحليل المكونات الرئيسية (PCA) لتحديد الاتجاهات ذات الدلالة الإحصائية في توزيع المتغيرات بين المجموعات المختلفة. **النتائج**: يظهر تحليل PCA أن التباين البيولوجي بين المشاركين يعزى بشكل أساسي إلى متغيرات محددة، أبرزها نسبة الألبومين / الجلوبيولين وتركيز IL-6. لوحظ تمييز واضح بين الأفراد الأصحاء ومرضى البهاق، بينما أظهرت مجموعتا المرضين (PUV و PN) خصائص كيميائية حيوية ومناعية متشابهة ، مع بقاء بعض الاختلافات الطفيفة. زادت مستويات IL-6 والجلوبيولين بشكل ملحوظ في كلتا مجموعتي المرضى مقارنة بالمجموعة الضابطة، على الرغم من انخفاض مستويات البروتين الكلي والألبومين ونسبة A/G بشكل كبير. **الاستنتاجات**: كشف تحليل PCA أن IL-6 ونسبة الألبومين إلى الجلوبيولين كعوامل رئيسية تؤثر على التباين البيولوجي في البهاق، مما يسلط الضوء على الاستجابات المناعية والتشوهات البروتينية كمؤشرات حيوية محتملة لتقييم المرض وعلاجه.

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INTRODUCTION

Vitiligo (or achromia) results from the melanocytes' defective functioning in the skin's epidermal layer. When the melanocytes die, the melanin pigment that gives normal skin its characteristic color disappears, robbing the vitiligo patient of skin coloring at various body parts [1]. It is a disease that reduces the normal functions of the skin, hair, and other organs' tissues, causing social, emotional, and psychic disturbances, particularly in dark-skinned individuals. Significant variations in prevalence have been found across different geographic regions, age groups, genders, and research methods, with bigger differences in anecdotal reports. At first sight, vitiligo can appear as a cluster of white spots in a stipulated area; as it progresses, the cluster can spread across different body parts, in some extreme cases, leaving nothing unpigmented. Vitiligo can affect every body part but most often occurs in sun-exposed areas, such as the face and hands [2]. Rapid advances in genetics, molecular biology, immunology, and intracellular

signaling, in addition to oxidative stress, have provided new information concerning the mechanisms implicated in vitiligo pathogenesis [3-5]. Familial forms of vitiligo have been reported in most populations, with several studies revealing that about 20% of affected individuals have a positive family history. Genes implicated in pigmentation and immune responses were the first to be associated with vitiligo, supporting the critical role of autoimmunity in vitiligo's pathogenesis [6]. One popular method of treating vitiligo is phototherapy, often known as light therapy, which stimulates melanocyte activity to encourage regimentation. Narrowband UVB therapy is one type of phototherapy that exposes skin to UVB rays [7]. Interleukin-6 (IL-6) is a pleiotropic cytokine that regulates host defense, inflammation, and immune homeostasis [8]. Fibroblasts, endothelial cells, activated leukocytes, monocytes, and adipocytes are its primary producers. Most people know IL-6 as the primary regulator of the acute-phase inflammatory response. It was also established that IL-6 plays a crucial part in the transition from acute to chronic inflammation [9]. Increasingly, studies have indicated that immune inflammation, particularly cytokines such as IL-6, plays a prominent role in the pathogenesis and progression of the disease [10]. Moreover, alterations in serum protein markers might indicate a breakdown in the disease's associated inflammatory state [11]. The immunological and biochemical characteristics of vitiligo patients were the subject of several international studies, but there are nevertheless few local studies, especially in Iraq. Given the possible variations in environmental and genetic factors, neighborhood research is desperately needed to understand the biological changes connected to vitiligo in this geographic context. This will assist with better diagnosis and individualized remedies. This has a look at goals to investigate the underlying patterns of relationships between immune and protein markers in vitiligo sufferers with the aid of making use of essential factor evaluation (PCA) to pick out the variables that are most influential within the biological variance between PUV and PN, as compared to C, which contributes to improving the pathological understanding of vitiligo and linking immune responses to protein changes.

METHODS

Study design and setting

The current study was conducted on 150 participants (27-40 years old) divided into three groups. The first group (n = 50) were patients treated with NB-UVB (50 to 100 sessions) (PUV), the second group (n = 50) were patients newly diagnosed (PN), while the third group (n = 50) were healthy individuals (C). The patients' samples were collected by the Dermatology and Venereology Department, Baghdad Teaching Hospital, in the Medical City Complex, and Al-Imamain Al-Kadhimain Teaching Hospital, Iraq, from October 2024 to February 2025.

Exclusion criteria

The exclusion criteria of samples include presence of other autoimmune diseases, cataracts or skin cancer, psoriasis and history of cutaneous photosensitivity, pregnancy, lactation, diabetes, and anemia.

Sample collection

Ten milliliters of venous blood were collected, deposited in a tube at room temperature, and centrifuged for five minutes at 3,000 cycles per minute. Before being examined, the serum was placed in an Eppendorf tube and kept in a freezer at -20°C. Following their consent, each participant underwent a face-to-face interview with a specially created questionnaire format that included comprehensive information, including their medical history.

Outcome measurements

Laboratory tests include interleukin-6, determined using an immunological method (ELISA). Measurement of total protein and albumin by using colorimetric analysis and globulins by using the following equation: $C_{\text{globulins (g/dl)}} = C_{\text{total proteins (g/dl)}} - C_{\text{albumin (g/dl)}}$

Ethical considerations

The study protocol was approved by the local Research Ethics Committee of the College of Science, University of Baghdad, Iraq (Ref: CSEC/1224/0123).

Statistical analysis

Statistical analysis was performed using SPSS version 26. The normality of the data distribution was confirmed using goodness-of-fit tests, and all studied variables exhibited a normal distribution, allowing parametric inferential tests. One-way ANOVA was applied to test for differences between the three groups. Receiver operating characteristic (ROC) curves were used to assess the accuracy of biomarkers in distinguishing between groups. Principal components analysis (PCA) was used to uncover underlying patterns in the data and identify the most influential variables in biological variation between groups. *p*-values less than 0.05 were considered statistically significant.

RESULTS

Table 1 shows the general anthropometrics of the participants are represented. The age of the PUV, PN, and C groups ranged from 27 to 40 years. Also, the individual's BMI (an anthropometric assessment based on their weight and height that aids in determining their obesity status) was shown in Table 1.

Table 1: The demographic characteristics of the three groups (n=50 in each group)

Characteristics	PUV group	PN group	C group	*p*-value
Sex				
Male	25(50)	25(50)	25(50)	1.0
Female	25(50)	25(50)	25(50)	
Vitiligo stability				
Active	16(32)	38(76)	-	<0.001
Stable	34(68)	12(24)	-	
Age (year)	32.8±3.9	32.23±4.17	32.35±4.16	0.764
Height (cm)	166.25±10.93	168.03±10.65	166.4±8.89	0.690
Weight (kg)	69.5±8.08	73.15±11.61	70.25± 9.55	0.221
BMI (kg/m²)	26.13±1.66	26.75±1.65	26.35±2.73	0.410

Values were expressed as frequency, percentage, and mean±SD.

A non-significant variance (p> 0.05) in the mean of age, height, weight, and BMI between the three groups was indicated; the results showed that the participants of all groups have a BMI value > 26. Table 2 shows the significant increases in IL-6 levels for both PUV and PN groups compared to the control group, with no significant differences between the two groups. A significant decrease in total protein levels was observed in the PN group compared to the controls, while no significant differences were observed in the PUV group. A significant decrease in albumin levels was observed in both PUV and PN compared to the control group. Conversely, globulin levels significantly increased in both disease groups compared to the controls. The albumin/globulin ratio indicators also showed a significant decrease in the PUV and PN groups compared to the controls, with no significant differences observed between the two disease groups. Receiver operating characteristic (ROC) is a statistical approach that determines a diagnostic test's ideal specificity and sensitivity by plotting the relationship between sensitivity and 1-specificity.

Table 2: Comparison of serum interleukin-6, total proteins, albumin, globulins, and albumin/globulin ratio of the three studied groups

Parameter	PUV group	PN group	C group	*p*-value (ANOVA)
IL-6 (pg/ml)	39.47±13.7[a]	44.13±10.44[a]	10.60±2.59[b]	<0.0001
Total proteins (g/dl)	7.25±0.55[a]	7.04±0.53[a]	7.52±0.89[a,b]	0.0416
Albumin (g/dl)	3.44±0.54[a]	3.22±0.76[a]	4.17±0.64[b]	<0.0001
Globulins (g/dl)	3.80±0.5[a]	3.82±0.59[a]	3.23±0.97[b]	<0.0001
Albumin/Globulin	0.93±0.25[a]	0.88±0.34[a]	1.50±0.78[b]	<0.0001

Values were expressed as mean±SD. Values with different superscripts (a,b) are significantly different within the same parameter among groups (Tukey *post hoc* analysis, p<0.05).

Figures 1 and 2 show the ROC curve of interleukin-6 in PUV and PN. Principal Component Analysis (PCA) is a statistical technique that transforms original variables into uncorrelated principal components, reducing data dimensionality and improving analysis, visualization, and modeling by retaining variance [12]. Table 3 shows that the first and second components together explained 84.631% of the total variance in the data, reflecting the analysis's effectiveness in summarizing information on the studied variables. The first component contributed 54.508%, while the second contributed 30.123%.

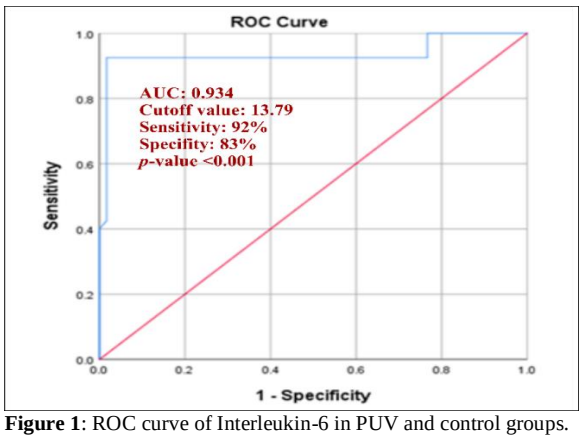

Figure 1: ROC curve of Interleukin-6 in PUV and control groups.

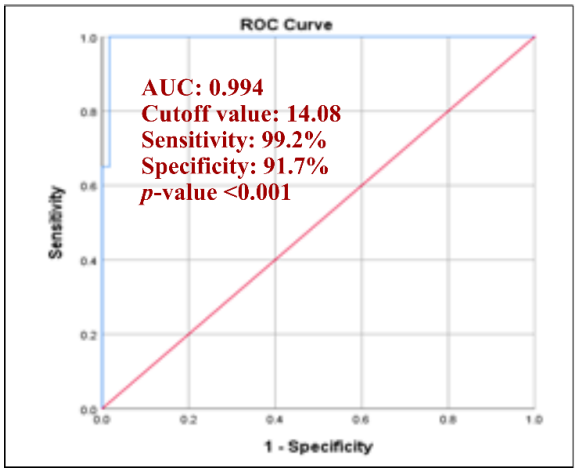

Figure 2: ROC curve of Interleukin-6 in PN and control groups.

Table 3: Percentage of variance explained by principal components (Total Variance Explained).

Component	Initial Eigenvalues	Variance (%)	Cumulative (%)
1	2.725	54.508	54.508
2	1.506	30.123	84.631

Figure 3 shows the relationship between the number of components on the horizontal axis and the percentage of explained variance on the vertical axis. It can be seen that the first and second components explain the highest rate of variance, with the curve

initially steep and then flattening after the second component.

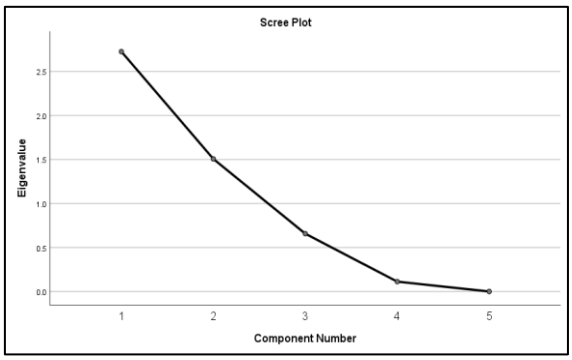

Figure 3: A visual trace of principal component contributions, highlighting where additional components offer diminishing explanatory value.

This pattern is called the "elbow point," which shows how many components are to keep in the analysis. As shown in Table 4, the PCA was applied to reduce dimensionality and explore the relationships between biochemical markers (IL-6, total protein, albumin, globulin, and albumin/globulin ratio).

Table 4: Pattern of Variable Loadings Reflecting Their Influence Across Principal Dimensions

Parameter	Component 1 (PC1)	Component 2 (PC2)
IL-6	-0.619	-0.307
Total proteins	-0.100	0.982
Albumin	0.813	0.501
Globulins	-0.881	0.425
Albumin/Globulin Ratio	0.994	-0.130

Two principal components were extracted, explaining 84.631% of the total variance in the data. The first component (PC1) explained 54.508% of the variance. It was characterized by high positive loadings for the albumin/globulin ratio (0.994) and albumin (0.813), as well as high negative loadings for globulin (-0.881) and IL-6 (-0.619), suggesting that this dimension reflects a balance between protein pattern and systemic inflammation. The second component (PC2) explained 30.123% of the variance and was primarily influenced by total protein (0.982), reflecting overall nutritional or liver functional status. Figure 4 shows a relative overlap between PN and PUV patients, reflecting a similarity in immune responses and proteins studied between these two groups. In contrast, the C group differed from the patient groups, especially on the first axis (PC1), indicating a pattern of immune differentiation between healthy individuals and those with vitiligo. We also observed outliers within each group, reflecting individual heterogeneity in immune expression.

DISCUSSION

Descriptive data showed clear homogeneity in demographic characteristics across the studied groups, enhancing the power of statistical comparison and reducing the possibility of bias. No significant differences were recorded in age, gender, or BMI of patients (PUV and PN) compared with the control group, which adds greater reliability to the results of subsequent analyses. Since vitiligo is classified as an autoimmune disorder associated with imbalances in inflammatory cytokines, the elevation of IL-6 in both patient groups reinforces this understanding and reflects the underlying inflammatory activity in different stages of the disease.

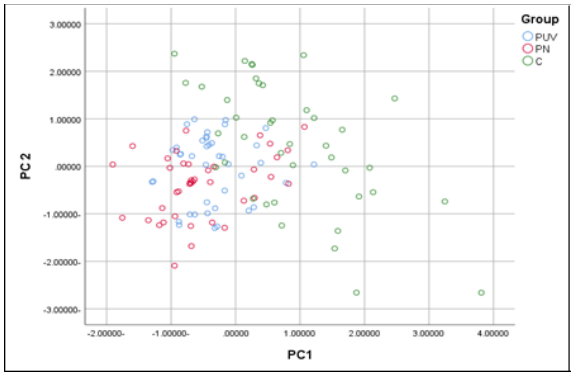

Figure 4: Spatial projection of individual samples along extracted principal components, revealing latent group-specific distribution patterns within the dataset.

The results (Table 2) show significant increases in IL-6 of PUV and PN when compared with the control, while no significant difference was observed between PUV and PN. Growing clinical data has shown that the level of IL-6 can be elevated in vitiligo patients, indicating a positive correlation of IL-6 with disease severity [13]. IL-6 produced in the skin impacts keratinocytes and influences inflammation, angiogenesis, and collagen deposition [14]. Considering the close relation between melanocytes and keratinocytes, the IL-6 may indicate a biomarker of skin disease, premised on severe impairment in melanogenesis and continual melanocyte dysfunction seen in chronic tissue damage and a variety of the inflammatory processes existing in the same geographical location of melanocytes [15]. In the discrete microenvironment of vitiligo, dysregulated IL-6 production has been implicated in the development of increased melanocyte injury. Pathological analysis suggests that IL-6 can be regarded as a nexus of multiple pathophysiological mechanisms contributing to melanocyte damage [16]. On the other hand, phototherapy modulated the amount of IL-6 produced in the test systems, which affected the intensity of the inflammatory stress. After the highest dose of UVB irradiation, keratinocytes produced more IL-6 and in higher concentrations than stressed cells without irradiation [17]. Studies have suggested a relationship between IL-6 and the early onset of vitiligo [18]. Prompting future studies that include vitiligo samples before and after phototherapy and newly diagnosed models to understand the mechanism more comprehensively. Moreover, results showed a significant decrease in total proteins of PN when compared with the control, while no significant difference was observed with PUV. The study also found significant increases in serum

globulins in patients (PUV and PN) compared to the C group. In contrast, the albumin and albumin/globulin ratio significantly decreased for both PUV and PN compared with C. However, no significant differences were observed between PUV and PN for all studied parameters. Serum proteins are among the most prominent biomarkers reflecting the inflammatory and functional status of the body, particularly in the context of chronic and immune-mediated diseases. Total serum protein consists of two main components: albumin and globulin. In some autoimmune diseases, there are clear disturbances in the ratio between albumin and globulin. Studies indicate that globulin levels are often elevated due to persistent immune system stimulation, leading to B-cell activation and increased antibody production, a condition known as hypergammaglobulinemia. Conversely, albumin levels are often low due to chronic inflammation affecting the liver, impairing its ability to synthesize this protein. This imbalance results in a decrease in the albumin/globulin ratio to less than 1.0, an important laboratory marker used to assess immune-inflammatory activity. Total protein may remain within normal levels or appear slightly increased, depending on the balance of components [19-21]. These changes in serum proteins are of clear clinical and diagnostic importance, as they reflect an immune dysfunction, which is also associated with vitiligo, which is classified as an autoimmune disease [22]; patients are expected to exhibit similar changes, particularly a decreased albumin/globulin ratio, enhancing their value as a prognostic marker in vitiligo. ROC curve analysis of IL-6 showed excellent results in assessing its accuracy as a biomarker for differentiating vitiligo patients from healthy controls in patients who underwent phototherapy (PUV) and newly diagnosed patients (PN). In the PUV group, the AUC value reached 0.934, within the excellent range of diagnostic excellence, with an optimal cutoff value of 13.79 pg/mL, a sensitivity of 92%, and a specificity of 83%. In the PN group, the predictive value of IL-6 was superior, with an AUC of 0.994, which is close to perfect, demonstrating the superior ability of this marker to detect the disease early. The results showed that sensitivity and specificity improved to 99.2% and 91.7%, respectively, with the usage of a cutoff price of 14.08 pg/ml. This shows that IL-6 may be vital in effectively diagnosing and staging vitiligo, specifically in early instances. The excessive predictive fee of IL-6 within the patient populace (PN) shows that improved stages are related to the onset of inflammatory processes inside the early levels of the disorder, making it a potential early indicator that may be used earlier than initiating any treatment. These findings are regular with current research demonstrating the position of IL-6 in stimulating the inflammatory immune response and influencing the immune device balance in autoimmune skin illnesses, inclusive of vitiligo [10,23]. As validated by way of the ROC outcomes, a clean hyperlink became located between IL-6 stages and disease activity in vitiligo sufferers. The analysis showed that IL-6 ranges were drastically better in PN sufferers, suggesting it is able to assist in discovering the situation early. In PUV patients, IL-6 additionally confirmed scientific significance, suggesting its usefulness in tracking treatment effectiveness. The slight distinction in sensitivity and specificity between the two businesses can be related to the biological progression of the ailment. Based on these observations, IL-6 appears to be an important parameter in the scientific evaluation of vitiligo, whether used by myself or in combination with different biomarkers. Principal additives analysis (PCA) provided additional insights into the underlying styles of variation among businesses. It showed that the primary aspect (PC1) defined 54.508% of the entire variance and became considerably positively correlated with the albumin/globulin ratio and albumin itself. In comparison, it negatively correlated with globulin and IL-6, suggesting that this axis reflects the balance between the inflammatory reaction and serum proteins. The 2D aspect (PC2), which explained 30.123% of the variance, turned into an association with general protein tiers, which can also replicate patients' protein synthesis. The distribution of variables throughout the axes showed that IL-6 had an excessively terrible loading on PC1, making it an awesome immune marker among sufferers and wholesome people. This multidimensional analysis revealed that the two corporations (PN and PUV) had a comparable biochemical profile, without a doubt distinct from the healthful institution, helping the idea of a not unusual pathway of inflammatory and protein abnormalities within the pathogenesis of vitiligo. These consequences are regular with [24], who indicated that vitiligo is not only a pore and skin disorder, but a systemic immune disorder related to huge serological adjustments. Hence, this takes a look at underscores the importance of combining immunological and biochemical markers whilst evaluating vitiligo instances. It additionally helps to use advanced analytical tools consisting of PCA and ROC to benefit from a deeper expertise of the disease and develop destiny evaluation signs.

Study limitations

The small sample size weakens the dependability of the findings. Future research should include larger and more varied populations to boost sample size and statistical power, which will raise statistical significance.

Conclusion

PCA effects display immunological and protein components, which include albumin/globulin ratio and IL-6, that are related to organic range in vitiligo sufferers, with some commonplace tendencies but fantastic discrepancies. ROC curve evaluation indicates that IL-6 is a touchy and trustworthy marker for vitiligo tiers, increasing its applicability in clinical assessment. These findings help the

development of unique organic evaluation tools that aid in diagnosis and remedy efficacy monitoring, mainly for phototherapy, through confirming that immune response dysfunctions and protein metabolism problems are vital elements in the development of vitiligo.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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