Iraqi Journal of Biotechnology, 2026, Vol. 25, No. 1, 247-262.

Association betweenIL39 and IL41 with Susceptibility of Systemic Lupus Erythematosus

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Received: October 21, 2024 Accepted: January 8, 2025 Published March 30, 2026

Abstract

Background. Cytokines are regulators of host responses to trauma, inflammation, immune responses, and infection. **Aim.** Study the association between IL39 and IL41 in female subjects diagnosed with Systemic Lupus Erythematosus **(**SLE). **Methods.** One hundred women with SLE, with an average age of 30.93 ± 9.85 years, were included in this study. Along with 100 healthy control women (HCW) with an average age of 32.97 ± 9.13 years, they were sourced from Baghdad city (medical city, Baghdad Hospital/Iraq). Cytokine levels were measured using enzyme-linked immunosorbent assay kits. **Results.** According to medication, Individuals with SLE were distributed into two groups: group one (24%) of patients who were newly diagnosed (do not take any medications) and group two (76%) of patients with an illness duration (of 6.23±0.58 years who took medication. The result showed IL-39 values manifested a significant increase in Individuals with SLE when compared to HCW (190.3± 66.24 *vs*.133.5±43.53 ng/L; $p < 0.0001$) ROC curve analysis demonstrated that IL-39 scored 0.830 AUC (95% CI = 0.7740 - 0.8860; $p < 0.0001$). where IL-41 values manifested a significant decline in Individuals with SLE when compared to HCW (7.35± 0.63 *vs*.10.30±1.03 pg/mL; $p < 0.029$. ROC curve analysis demonstrated that IL-41 scored 0.693 AUC (95% CI = 0.6207 - 0.7652; $p < 0.0001$). **Conclusion.** Sera IL-39 and IL-41 concentrations were not associated with illness prevalence or severity in the current research.

Keyword: Cytokines, Interleukin-39, Interleukin-41, SLE, Autoimmune illness

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Introduction

Systemic lupus erythematosus (SLE) is a severe autoimmune illness impacting various systems in the body. It may manifest in a wide range of ways, cause a wide range of abnormalities in the body's laboratory and immunological systems, and have a wide range of possible results (1,2,3). A broad variety of autoantibodies are produced as a result of reduced immunological tolerance; these antibodies then assault self-antigens, including cellular components, immune complexes, DNA, and host nuclear antigens.

This is the major characteristic of the illness (4, 5). While SLE may affect every organ or tissue in the body, the specific clinical symptom pattern might vary greatly from person to person (2). Systemic lupus erythematous may cause damage to several end organs, including cardiovascular system, neuropsychiatric systems, kidneys, and the lungs. The most common cause of death is cardiovascular issues. Multiple environmental, hormonal, and genetic factors seem to have had a role in the onset of SLE,

but the specific cause of the condition is still a mystery. Minority women of childbearing age account for the vast majority of SLE cases (65%) (6). The fundamental hallmark of SLE is sex prejudice, which affects one out of every nine males (7). Fatigue, myalgia, fever, and weight loss or gain are classic lupus symptoms that impact half or more of Individuals with SLE. The term "constitutional symptoms" describes these signs and symptoms. The symptoms of lupus are comparable to those of other immunological illnesses, including: Spondylitis with ankylosing (AS) Lupus erythematosus, an autoimmune illness that shares symptoms with AS, causes discomfort in the sacroiliac and spinal joints, among others (8,9,10). Multiple studies have shown that alterations in the expression of certain cytokines play a crucial role in the progression of SLE (11). A heterodimer of 54 kDa mass is the IL-39 complex, SLE is one of the illnesses linked to IL-39, which is immunopathogenic because it triggers a proinflammatory response (12). Interleukin-41 is an immunoregulatory cytokinec, IL41 and METRN (Meteorin) exhibit a genetic similarity of approximately 40%.

The discovery of METRN, a neurotrophic factor, occurred in 2009 (13). The term IL-39 was previously employed to designate a substance similar to meteorin, however, this nomenclature has subsequently been assigned to one of the IL12 counterparts that have any connection to meteorin-like properties (14). SLE remains a difficult and disabling illness, but now have a better comprehension of its causes, earlier recognition of its symptoms and signs, and more effective and less toxic medications.

MATERIALS AND METHODS

Study subject

The study included 100 women diagnosed with SLE and 100 healthy women as control who were residing in Iraq, specifically in Baghdad City. These patients were recruited from the Medical City and Baghdad Hospital. The diagnosis of SLE was established by rheumatologists at the unit clinic, utilizing the diagnostic criteria for SLE developed by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) (15). All necessary clinical and laboratory procedures were conducted. The inquiry was carried out in Baghdad, Iraq, under the supervision of medical specialists at the City of Medical, Baghdad Hospital. The sample of 100 individuals without any known health conditions was acquired from the National blood transfusion facility. The demographic data and clinical presentations of each patient were extracted from their respective medical records. A series of laboratory investigations were undertaken to assess the efficacy of standard laboratory examinations as well as supplementary tests. During the sampling process, all hematological parameters were evaluated using the Erythrocyte Sedimentation Rate (ESR) and C-reactive protein tests. The values of complement (C3) and complement (C4) were assessed through the utilization of the Radial Immunodiffusion (RID) technique, while the enzyme-linked immunosorbent assay (ELISA) method (Human Company, Germany) was employed to quantify anti-nuclear autoantibodies (ANA) and anti-dsDNA.

Blood samples collection

Four milliliters of venous blood was collected from each subject. Each sample was divided into two parts:

1- The first part (2 ml) of whole blood was transferred into EDTA tube for laboratory tests.

2- The second part (2 ml) in gel tube for centrifugation was placed in a serum–separating tube and centrifuged for 10 min at 3000 rpm to separate for another laboratory tests that need sera for investigations.

Laboratory investigations

From each patient's medical record, demographic information was extracted and a number of clinical signs. The standard and additional laboratory tests were evaluated by laboratory examinations. Tests for complete blood count (CBC), (ESR) and (CRP) were performed simultaneously with sample collection. Relative concentrations of C3 and C4 were estimated using radial immunodiffusion (RID). In order to analyze the anti-dsDNA and ANAs, the researchers utilized immunosorbent assay (ELISA) technology developed by the Human Company in Germany.

Interleukins concentrations

Immunoassay of IL-39 and IL-41

In this study an ELISA assay was utilized to detect sera values of IL-39 and IL-41. Interleukin 39 and 41 concentrations were determined in patient and control samples using a sandwich ELISA kit according to the manufacturer's instructions (catalog number: E7444Hu, BT-LAB and In-Hu4260, INNOVA BIOTECH CO., LTD) respectively. The antibody utilized in this assay does not exhibit any detectable cross-reactivity with other relevant proteins.

Statistical analysis

Study results were subjected to a statistical evaluation with IBM SPSS Statistics 27.0 (Armonk, NY: IBM Corp.). Graphs were plotted with Graph-Pad Prism 9.4.1(San Diego, California USA). Categorical variables were expressed using numbers and percentages. The results reported in this study were expressed as mean ± SD. Independent t-test was utilized to test between two parameters. One-way ANOVA were utilized to test between study groups. Probability values less than 0.05 and 0.01 were considered significantly and highly significant different, respectively.

RESULTS

Characteristics of the study population

In this case-control study, 100 women with SLE had an average age of 30.93 ± 9.85 years, while 100 healthy control women (HCW) had an average age of 32.97 ± 9.13 years ($p = 0.13$), (Figure 1A). The mean BMI (± SD) of SLE patients was 28.62 ± 6.50 kg/m2, which was not significantly different from the HCW group (27.11 ± 5.60 kg/m2; $p = 0.07$), (Figure 1B). The ages of the healthy controls and patients with SLE ranged from fifteen to fifty. Patients with SLE were categorized into four age groups in this study: 15–23, 24-32, 33–42, and 42–50 (Figure 2). The prevalence of SLE was highest in the age range spanning 24–32 years, at 32.00%, compared to the age groups 15–23 years, 33–42 years, and 42–50 years, at 25.00%, 29.00%, and 14.00%.

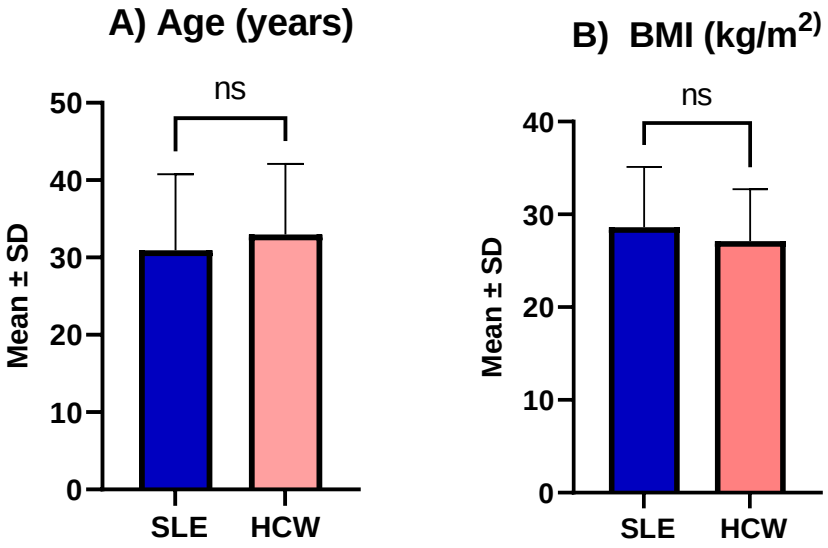


Figure 1: Comparison of (A) age and (B) BMI between SLE patients and healthy control women (HCW). Data are presented as Mean ± SD. ns: p-value > 0.05 (not significant).

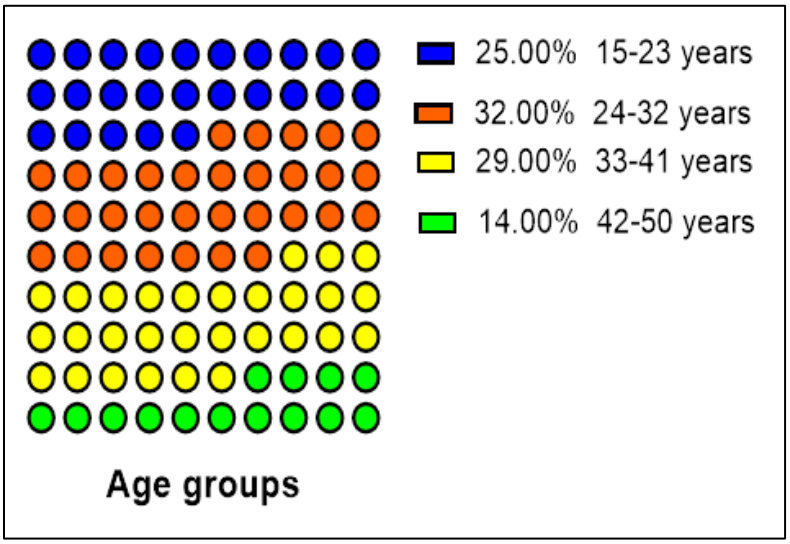


Figure (2): Distributing of Individuals with SLE according to the age groups.

Illness duration

According to medication, Individuals with SLE were distributed into two groups: group one (24%) of patients represented newly diagnosed (did not take any medications), and group two (76%) of patients with a illness duration (of 6.23±0.58years) who took medication.

Baseline laboratory data

All Individuals with SLE were subjected to the laboratory tests outlined in Table (1).

Table (1): Laboratory tests of Individuals with SLE

Parameter s	Patients (N=100) mean ± SD	Normal value
Hb g/dl	8.44±0.12	11.6-15
WBC x10^9/L	265±8.39	4000-11000
ESR (mm/h)	42±2.91	0-20
CRP mg/dl	17±1.86	<10
C3 mg/dl	15± 2.35	88-201
C4 mg/dl	8.04±1.30	16-48
Anti-dsDNA (AU/mL)	41± 4.03	<10
ANA (AU/mL)	4.86± 0.59	<40
PLTx10^9/L	361±0.11	150-450

Hb: Hemoglobin; C4: Fourth component of complement; CRP:C-reactive protein; PLT: platelet; ANA: Anti-nuclear antibody; ESR: Erythrocyte sedimentation rate; WBC: White blood cell; C3: Third component of complement; Anti-dsDNA: Anti-double stranded DNA antibody

Measurement of cytokines under study

In the current study, two interleukins, IL-39and IL-41, were determined in women with SLE (N = 100) and age matching HCW (N = 100). When it comes to the progression of autoimmune illnesses like psoriasis and SLE (SLE and PS, respectively), cytokines have a clear function. Because of their critical functions in the control of immune cells, specialization, and maturation, autoimmune illnesses may arise from a disruption in their production or activity (7). Findings from a variety of studies point to alterations in the expression of certain cytokines as important contributors to the progression of SLE (43).

Sera value of interleukin-39

Mean (SD) of IL-39 values manifested a significant increase in Individuals with SLE when compared to HCW (190.3± 66.24 vs.133.5±43.53 ng/L; $p < 0.0001$) (Figure 3). ROC curve analysis demonstrated that IL-39 scored 0.830 AUC (95% CI = 0.7740 - 0.8860; $p < 0.0001$). At a cut-off concentration of 144.7 ng/L (YI = 0.44), the sensitivity was 72.0% and the specificity was 72.0% (Figure 4).

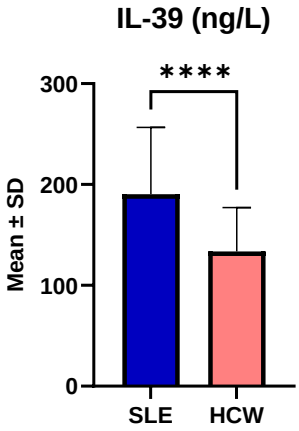


Figure (3): Column- bar plot of sera IL-39 values in patients with SLE and HCW. Column represent mean. Bar represent standard deviation (SD). Mann- Whitney test utilized to assess significant variations (** $p< 0.0001$)**

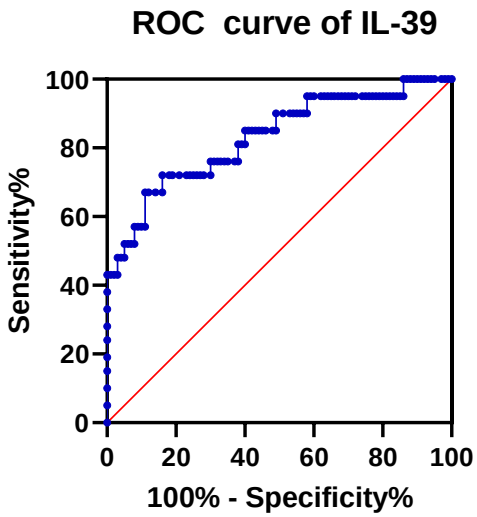


Figure (4): Receiver-operating characteristic curve analysis of IL-39 in women with SLE versus HCW

Analysis correlation of IL-39 with parameters under study

The analysis revealed that IL-39 had significant negative correlations were found with Anti-dsDNA and ESR ($\mathbf{r_{sp}}$ =-0.23; p=0.021; $\mathbf{r_{sp}}$ =-0.22; p=0.026) respectively (Table 2).

Table (2): Correlation analysis of IL-37 with baseline data parameters in SLE patients.

Parameters	Concentration of IL-39ng/L in Individuals with SLE	
	r_{sp}	*p-value*
Ages(years)	-0.09	0.356[ns]
BMI	-0.05	0.608[ns]
Illness duration	0.26	0.008**
ANA (AU/mL)	-0.005	0.956[ns]
Anti-dsDNA (AU/mL)	-0.23	0.021*
CRP mg/dl	-0.141	0.159[ns]
C4 mg/dl	-0.098	0.327[ns]
Hb g/dl	0.059	0.553[ns]
C3 mg/dl	-0.06	0.542[ns]
ESR mm/h	-0.221	0.026*
PLTx10^9/L	0.067	0.502[ns]
WBC x10^9/L	0.082	0.415[ns]

***p*: Probability (*$p < 0.05$; ns: Not significant); PLT: platelet; CRP:C-reactive protein; ANA: Anti-nuclear antibody; Anti-dsDNA: Anti-double stranded DNA antibody; Correlation coefficient (r), BMI: body mass index; C4: Fourth component of complement; Hb: Hemoglobin; WBC: White blood cell; C3: Third component of complement; ESR: Erythrocyte sedimentation rate.**

Sera value of interleukin -39 in newly diagnosis and medicated patients

According to medication, Individuals with SLE were distributed into two groups: group one (24%) of patients represented newly diagnosed (did not take any medications), and group two (76%) of patients. there was non- significant association between sera value of IL-39 in newly diagnosed and medication patients (195±8.31 *vs.* 175.3±7.81 ng/L; p=0.088), as shown in (Figure 5).

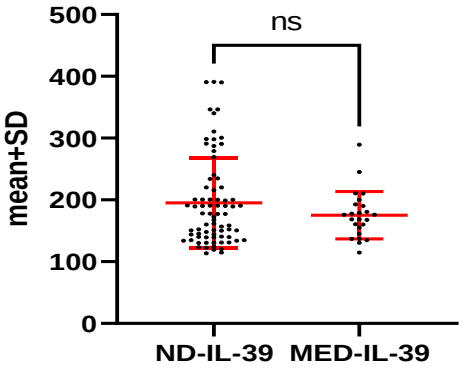


Figure (5): Comparison between newly diagnosis and medicated patients with SLE in IL-39 sera value.Sera interleukin-41 concentrations

Mean (SD) of IL-41 values manifested a significant decline in Individuals with SLE when compared to HCW (7.35± 0.63 *vs*.10.30±1.03 pg/mL; $p < 0.029$) (Figure 6). Receiver-operating characteristic (ROC) curve analysis demonstrated that IL-41 scored 0.693 AUC (95% CI = 0.6207 - 0.7652; $p < 0.0001$). At a cut-off concentration of 7.01 pg/mL (YI = 0.23), the sensitivity was 61.0% and the specificity was 62.0% (Figure 7).

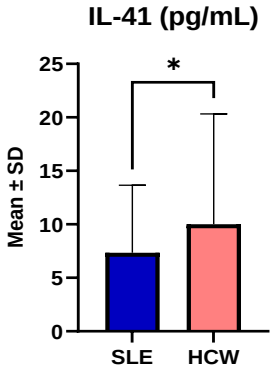


Figure (6): Column- bar plot of sera IL-41 values in patients with systemic lupus erythmatousus (SLE) and HCW. Column represent mean. Bar represent standard deviation (SD). Mann- Whitney test utilized to assess significant variations ($^{*}p< 0.05$)

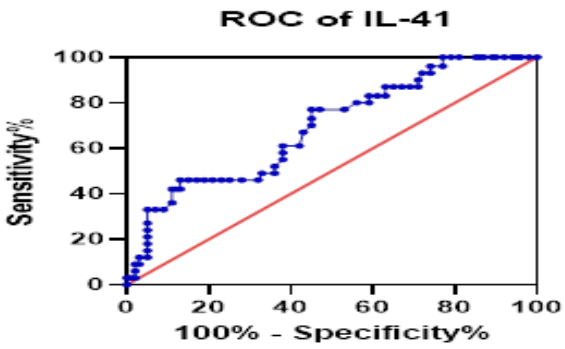


Figure (7): Receiver-operating characteristic (ROC) curve analysis of IL-41 in women with SLE versus HCW

Analysis correlation of IL-41 with parameters under study

The analysis revealed that IL-41 had only significant positive correlation with platelets (r_{sp} =0.252; *p*=0.011) (Table 3).

Sera value of interleukin -41 in newly diagnosis and medicated patients

According to medication, Individuals with SLE were distributed into two groups: group one (24%) of patients represented newly diagnosed (did not take any medications), and group two (76%) of patients. there were non-significant associations among sera value of IL-41 in newly diagnosed and medication patients (7.66±0.82 *vs.* 6.63±0.36ng/L; p=0.154), as shown in (Figure 8).

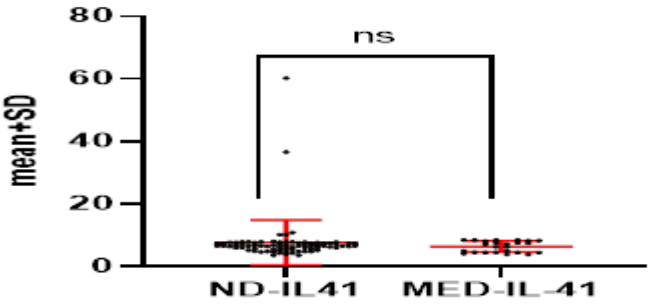
Discussion

In this case-control study, 100 women with SLE showed a high and low levels of Il-39 and Il-41, which will be discussed as follows; this study's age distribution shows that the illness mostly affects young people, particularly young women. Lupus erythematosus affects 0.09% of the European population, mostly affecting working-age women, with a median age of 33 years at diagnosis (14).Researchers in Japan found that SLE is most common in women between the ages of fifteen and forty-four (15).This age breakdown matched up with the results of the Iraqi research, which indicated that, compared to patients with an old onset (>45), the majority of patients were younger, namely adult-onset (≤45) (16). Furthermore, female patients from Iraq and other Arab communities have also shown a similar pattern in terms of age distribution (17) Nevertheless, the purpose of our research was not to examine age groups in Iraqi women with SLE; rather, we utilised patients' age classifications to collect HCW that were age-matched. Patients who had took the treatment regularly had fewer symptoms than those who were newly diagnosed, do not take any treatment, and suffered from more severe symptoms of the illness. Among the groups with SLE, there were no significant variations in terms of SLE duration, prednisone dosage, usage of antimalarials and immunosuppressants, and all of the individuals were female and of comparable age (18).

Table (3): Correlation analysis of IL-41 with baseline data parameters in SLE patients

Parameters	Concentration of IL-41pg/mL in Individuals with SLE	
	r_{sp}	*p-value*
BMI	-0.097	0.333[ns]
Ages (years)	-0.140	0.163[ns]
Illness duration	0.021	0.835[ns]
ANA (AU/mL)	0.029	0.771[ns]
Anti-dsDNA (AU/mL)	-0.130	0.196[ns]
Hb g/dl	-0.032	0.746[ns]
C4 mg/dl	-0.041	0.681[ns]
CRP mg/dl	-0.051	0.612[ns]
ESR mm/h	-0.146	0.145[ns]
C3 mg/dl	-0.101	0.316[ns]
PLTx10^9/L	0.252	0.011*
WBC x10^9/L	-0.061	0.546[ns]

***p*: Probability (*$p < 0.05$; ns: Not significant); PLT: platelet; CRP:C-reactive protein; ANA: Anti-nuclear antibody; Anti-dsDNA: Anti-double stranded DNA antibody; Correlation coefficient (r), BMI: body mass index; C4: Fourth component of complement; Hb: Hemoglobin; WBC: White blood cell; C3: Third component of complement; ESR: Erythrocyte sedimentation rate.**



Figurer (8) : Comparison between newly diagnosis and medicated patients with SLE in IL-41 sera value

All Individuals with SLE were subjected to the laboratory tests outlined in Table (1). Symptoms of SLE include the development of autoantibodies against self-antigens and a wide range of clinical presentations, including unexpected complete flares (19). Inflammation various markers were measured in patients with SLE; included: the haematological study included haemoglobin, WBC, and ESR tests. The mean Hb value was decreased (8.44±0.12) in the Individuals with SLE. People with SLE often have low red blood cell counts (anaemia), a condition that affects as many as half of all SLE patients. This condition is caused by autoimmune antibodies (20). This study was agreed with the study of (21) in the appearance of the mean of haemoglobin was lower in SLE. Table (2) shows an elevation in the WBC count in patients (2.65±8.39 10^9) with SLE. Previous studies have shown low white blood cell counts in SLE patients (22,23), but this research found the exact reverse. This might be because of the study's small sample size, the individuals' diverse backgrounds and symptoms, or the different approaches to treating the disease. According to (24), individuals with SLE often had an elevated white blood cell percentage as a result of bacterial or viral infections. On the other hand, the infection rate tends to rise owing to the treatment methods and the number of medicines used to suppress the immune systems. Treatment may have reduced neutropenia and leukopenia occurrence, according to another research, which also demonstrated that concomitant diseases may affect leukocyte levels. The researchers aimed to find a more accurate way to measure leukopenia frequency, therefore they ruled out individuals who had infections, liver cirrhosis, cancer, or other connective tissue diseases (25). The ESR result is listed in Table (2); the results showed an elevation (42±2.91) in ESR in Individuals with SLE. A popular haematology test, the ESR may reveal an increase in inflammatory activity in the human body caused by autoimmune disorders, infectious diseases, tumours, or a combination of these and other reasons. There is no specific disease for which ESR is useful. Nevertheless, when further tests are performed, it becomes possible to identify elevated inflammatory activity (26). Numerous investigations have shown a positive link between ESR and SLE (27,28,29,30), supporting the finding that individuals with SLE have a significantly elevated ESR relative to normal values. Autoimmune diseases, infections, and cancer are all associated with elevated ESR levels (31). ESR usually increases in patients with

SLE due to chronic inflammatory response and excessive production of immunoglobulins (32,33). This finding was in line with that of (34), which shown that Individuals with SLE may had an inflammatory response indicated by an increased CRP value. Reduced levels of complement proteins (C3 and C4) were seen in Individuals with SLE in this investigation. This was in line with what found in earlier research done in Iraq (35). Complement proteins decrease in SLE due to excessive production of autoantibodies and cytotoxicity mediation (36). This study also found that the mean sera of anti-dsDNA of Individuals with SLE was increased (41± 4.03). As a marker for tracking the course of the illness, the presence of the anti-dsDNA antibody is a standard diagnostic tool for SLE. This tool becomes even more useful when patients test positive for anaplastic anaemia (ANAs) (37). Multiple organ damage, including those to the skin, kidneys, and central nervous system, were associated with anti-dsDNA in SLE. Binding of anti-dsDNA to DNA or cross-reactive antigens in kidney cells triggers the complement cascade, leading to the infiltration of immune cells and the release of cytokines. Inducing autoantibody synthesis and breaking tolerance to auto antigen requires the presence of double-stranded DNA at immunological privilege sites. Elevated anti-dsDNA levels are indicative of a poor prognosis (37). The current study's findings showed that anti-dsDNA value was significantly greater in Individuals with SLE. Results for anti-ds-DNA positivity were comparable to those of the current investigation in Iraqi studies (35,37). This finding was consistent with earlier research that found elevated anti-dsDNA levels in Individuals with SLE (38). A rise of 4.86±0.59 was seen in the mean sera ANAs of Individuals with SLE. Studies that found a greater incidence of elevated ANA, reaching 90% to 99% positive in Individuals with SLE, were compared to the present research, which included a larger percentage of ANA-positive individuals (39). Women seem to have greater anti-nuclear antibody counts, and these levels tend to rise with age (40). The female reproductive system is more likely to have autoimmune illness recurrence due to the role of sex hormones, especially estrogens, in the progression of these conditions (41). In addition, the platelet value findings showed normal values in Individuals with SLE, with a mean of 361±0.11 x 109 /L. This finding was in agreement with the results of the previous study (42) which detected no significant differences between healthy persons and Individuals with SLE. Little known about IL-39 and their effect in autoimmune illness. This study was not consistent with (44) that found serum IL-39 levels were significantly higher in patients with SLE than in healthy controls and were correlated with disease activity. But in other studies, conducted on the relationship between IL39 and other immune diseases, it was found that Sera of IL-39 levels were much lower in RA patients, according to an Iraqi investigation ($p = 0.016$) (45). In mice with lupus-like symptoms, another research found that IL-39 activates STAT1/STAT3 to mediate inflammatory responses (46). Additionally, research conducted in Iraq revealed that the control group had substantially lower blood IL-39 concentrations compared to the RA patient groups ($p = 0.043$). Rheumatoid arthritis patients receiving treatment had much greater IL-39 concentration levels

compared to those who had an initial diagnosis but were not receiving medication. Assessment of the values of these cytokines may be useful in validating the activity of rheumatoid arthritis (47), as they have been related with an elevated value of IL-35 and IL-39 in RA patients (48). findings suggested that IL-39 may have a function in the immunopathogenic processes of SLE and may be a therapeutic target for this illness. An Iraqi study was found a positive correlation between IL39 levels with Anti-dsDNA and ESR (44). But in another study was found IL-39 values positively correlated with RF and ESR also revealed that there were no significant variations in age and sex between the two groups of participants (48) their result was agreed with an Iraqi study (49) , while significant negative correlations were found with Anti-dsDNA and ESR in this study. Another study showed that WBC count and free triiodothyronine value were positively correlated with sera IL-39 levels. In those diagnosed with Graves' illness (GD). White blood cell (WBC) count and CRP values were favorably linked with IL-39 sera levels (50). According to an Iraqi study, it was found that the level of IL39 gave varying rates in response to the treatments taken by the infected patients (44). Few research to support this findings, so will present some results of studies that have indicated a relationship of IL-39 with other immune illnesses such as (45) who found low sera value of IL-39 in 66 patients with RA under therapy. Different research found that individuals with Graves' illness (GD) and Hashimoto's thyroiditis (HT), excluding those with obvious hypothyroidism, had significantly lower blood IL-39 values. This study only included newly diagnosed HT patients. No AITD-related therapy had been administered to any of the newly diagnosed GD patients (50). An Iraqi study found that IL-41 had a significant function in the pathogenesis of SLE, as evidenced by elevated sera concentrations in Individuals with SLE compared to healthy controls, suggesting its involvement in illness susceptibility and activity also indicating its potential as a biomarker for the illness (27). But in another study that consistent with this current study found significantly lower concentrations of IL-41 were found in the sera of RA patients in comparison to healthy control (51). In contrast to individuals with osteoarthritis (OA), those with psoriatic arthritis (PsA) have elevated levels of the immunoregulatory cytokine IL-41, which is also called Meteorin-like protein, in their synovium (52). An Iraqi study showed the correlation between IL-41 values and platelet counts in patients with SLE is not directly established. However, several studies highlight the roles of both IL-41 and platelets in SLE pathology (27). One further research that looked at IL-41 levels revealed that they were positively correlated with DAS28, rheumatoid factor, and C-reactive protein levels, but not with ESR or ACCP antibodies (53). Highlighting several studies that have shown a correlation between IL-41 and other immunological disorders, as there was little evidence to back our claims. For example, one study (51) discovered that RA patients had substantially reduced blood IL-41 concentrations compared to normal women. One hundred and ten patients were already receiving therapy with methotrexate and the tumor necrosis factor inhibitor etanercept, whereas thirty patients were newly diagnosed

(ND). Another study displayed those individuals diagnosed with SLE demonstrate heightened concentrations of IL-41in their circulating blood plasma (27).

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