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Research Article

Interleukin 26 in patients with systemic lupus erythematosus

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Abstract

Purpose of study: Systemic lupus erythematosus (SLE) is an autoimmune disease affecting all body organs. Beside genetic, hormonal and environmental variables, unbalance between pro-inflammatory and anti-inflammatory cytokines leads to alteration of the immune system and promote tissue damage. Interleukin 26 is a pro inflammatory cytokine that has a function in the pathophysiology of autoimmune diseases like SLE. **The aim of this study** was to assess the level of interlekin-26 in SLE patients and correlate IL-26 with SLE activity. **Basic procedures:** The study was conducted on eighty-five subjects: 20 seemingly healthy individuals as control group and 65 patients of SLE, they were subdivided into 2 subgroups (SLE patients in active state disease and SLE patients in inactive state). SLE patients were diagnosed according to The European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2019 criteria for SLE. Interleukin 26 level was assessed EIA method. **Main findings**: results revealed that patients with SLE showed statistically significant higher IL-26 levels than control group and SLE patients in active state had statistically significant higher IL-26 levels than SLE patients in inactive state. Also, results showed significant positive correlation between IL-26 and (SLEADI score, A/C ratio, ESR and Anti –ds DNA) and significant negative correlation between IL-26 and (C3 and C4). **Principle conclusion:** The findings of this study showed correlation between IL-26 and SLE activity, therefore measurement of IL-26 can help in assessment of SLE activity. Also, IL-26 may be useful marker in predicating lupus nephritis because IL-26 serum level correlated positively with A/C ratio.

Key words: SLE, interleukin 26, SlEADI

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting many organs. It is having a relapsing and remitting pattern. It exhibits variable clinical manifestations. Usually, the onset appears within the third and fourth decades of age. The female to male ratio is 10:1[1].

SLE can present with variable manifestations from mild to life threating conditions. Most SLE patients represent by constitutional, muco-cutaneous and musculoskeletal manifestations, these manifestation are the most prevalent and earliest[2].

SLE pathogenesis is related to many factors and not accurately determined. It involves an interlinkage between genetic predisposition, hormonal and environmental variables causing change of both innate and adaptive immunity[3]. This disease is linked to the presence of

multiple autoantibodies and immune compl-exes formation and deposition leading to tissue damage[4]

In addition to genetic, hormonal and environ-mental variables, presence of unbalance

between pro-inflammatory and anti-inflammatory cytokines results in alteration of the immune system and promote tissue damage[5].

Interleukin 26 (IL-26) is thought to be one of IL-10 family[6]. It is firstly detected in herpesvirus-transformed T cells[7]. It is produced by T helper (Th17), natural killer cells, macrophage and fibroblast like cells[8].

IL-26 consist of one hundred- seventy one amino acids, including lysine or arginine 30 residues with formation of six highly cationic α-helices[9]. Even though IL-26 contains one of the IL-10 receptor subunits and shares around 25% of its amino acid sequence with IL-10, the functions of IL-26 are not alike to those of IL-10[6]. It works through binding to a heterodimer receptor (a complex of IL-10 receptor 2 and IL-20 receptor 1) to produce its effects[7].

Interleukin-26 is a cytokine that stimulate the release of inflammatory cytokines through myeloid cells that participate in the transformation of naïve CD4 T Cells into T helper "Th17" cells. Th17cell also produce IL-26 causing an inflammatory amplification loop [10]. Interleukin-26 is involved in the pathophysiology of chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, SLE and other infectious diseases through stimulation of release of inflammatory cytokines like type I interferon leading to tissue inflammation and damage [11] .

Aim of the work

The aim of the study was to evaluate IL-26 level in SLE patients and its correlation to disease activity.

Subjects and methods

Subjects: Eighty-five subjects were participating in our study: 20 apparently healthy individuals (group III) with matched age and sex who act as a control group. Also 65 SLE patients whom were diagnosed according to (EULAR/ACR) 2019 criteria for SLE, they were further subdivided into 2 subgroups: group I (45 SLE patient in active state) and group II (20 SLE patients in inactive state). The activity of the disease was assessed using SLEADI. They were considered active with SLEADI > 4 and inactive with SLEADI ≤ 4. Patients were selected from the rheumatology Clinic, Faculty of Medicine, Minia University from April 2022 to October 2022. The hospital ethics committee licensed this study and a written consent was gained from all patients (Approval number: 204: 12/2021, Date of approval: 27 December 2021). Patients of other autoimmune diseases and patients with hepatic and renal impairment were ruled out from study. All patients and control groups were subjected to the following: Complete history taking, complete clinical examination and laboratory investigations including a) routine investigations (CBC, ESR, CRP, renal function test, liver enzymes, A/C ratio, ANA, Anti-ds DNA, C3 and C4). b) specific investigation (Interleukin 26. **Blood sampling protocol:** about 7ml of venous blood was withdrawn from each participant by using a disposable plastic syringe after disinfection of skin with isopropyl alcohol (70%) swaps, and this sample was divided as follow: (a) 0.8 ml of blood on a tube containing 0.2 ml trisodium citrate for detection of ESR (dilution 4:1). (b) 1 ml in EDTA containing tube for CBC. Then 5 ml of blood was transferred into two plain tubes, each tube was allowed to be clotted for 20 min at room temperature then Centrifuged at 2000-3000 for 20 min, the expressed serum of first tube was used for determination of CRP, renal function tests, liver enzymes, C3 and C4.the remaining serum of other tube was stored refrigerated at -20°C for assay of interleukin-26. **methods**: CBC: It was performed using Celltac G, Nihon Kohden Corporation, Automated Hematology Analyzer, Tokyo, Japan. Renal function tests (blood urea and serum creatinine), liver enzymes, C3 and C4: using auto-analyzer Selectra PRO XL, ELITech Group, clinical chemistry automation systems, the Amsterdam, the Netherlands, using the commercially available kits according to manufacturer's instructions. CRP: using Genrui, Biotech Inc., Kinetic Assay, China. ESR: determined by conventional Westergren method. Interleukin 26 was assayed by **enzyme–linked immunosorbent assay (EIA)**. Kit was supplied by **Bioassay Technology Laboratory**

(catalog no. E0053Hu), **China**. **China**. Statistical analysis was done using the IBM SPSS version 20 statistical package software (IBM; Armonk, New York, USA). Normality of the data was tested using the Kolmogorov-Smirnov test. Data were expressed as median (IQR) for non-parametric quantitative data, in addition to both number and percentage for qualitative data. Kruskal Wallis test was done for non-parametric quantitative data between the three then Mann Whitney test between each two groups. The Chi-square test and Fisher's exact test were used to compare categorical variables. Spearman's rank correlation was done for non –parametric data. A p-value was considered significant when it was less than 0.05 was.

Results

Patients age in group I was from 18 to 40 years with mean 28.4±6.1 years, In group II was from 18 to 40 years with mean 27± 4.9. 20 years. In control group, age was from 19 to 40 years and the mean of age was 27.8 ± 4.9 years. All studied groups showed that disease was more in females, female ratio was (88.9%, 95% and 80 % respectively). No statistical difference concerning age or sex between all groups (as shown in table I).

Table I: demographic data in different groups

	Group I	**Group II**	**Group III**	**p value within 3 groups**		
	n= 45	**n=20**	**n=20**	**I vs II**	**I vs III**	**II vs III**
Age(years)				0.739		
Mean ± SD	28.4 ± 6.1	27.0 ± 4.9	27.8 ± 4.9			
(Range)	(18.0 – 40.0)	(18.0 – 40.0)	(19.0 – 40.0)			
Median	27.0	27.0	28.0			
(IQR)	(25.0 – 31.0)	(24.3 – 29.8)	(24.3 – 29.8)			
Gender (N%)						
Males	5 (11.1%)	1 (5.0%)	4 (20.0%)	0.43		
Females	40 (88.9%)	19 (95.0%)	16 (80.0%)			

Concerning disease duration, it was shorter among SLE patients in active state than in inactive one (p=0.105).
Group I show high SLEADI score with significant difference than group II (p<**0.0001**).
Regarding treatment, 91.1% of SLE patients with activity were treated with steroid and hydroxychloroquine plus immunosuppressive. On the other hand,75% of SLE patients in inactive state were treated with steroid and hydroxychloroquine (Fig.1 and table II)

Table II: SLEADI score and disease duration in patients groups

	Group I n= 45	**Group II n=20**	**p value**
Disease duration (years)			
Range	(0.5-5)	(2-10)	
Median	1	5.5	0.105
SLEADI score			
Range	(5.0 –26)	(0 – 4.0)	
Median	11.0	2.0	**<0.0001**

Hemoglobin level was significantly low when comparing SLE patients and control group, group II and group III (p<0.0001 and p<0.004 subsequently). Platelets count was significantly lower in SLE patients than control group and in group II than group III (p=0.031 and p<0.018 subsequently).

Absolute lymphocytic count was significantly lower in group I than group II and in group I than group III.
There was no statistically significant difference concerning total leucocytic count.

Table III: Hematological data between all studied groups

	Group I n= 45 Median IQR	**Group II n=20 Median IQR**	**Group III n=20 Median IQR**	**p value within 3 groups**		
				I vs II	**I vs III**	**II vs III**
Hemoglobin(g/dL)	10.0 (7.8 – 11.0)	10.3 (9.3 – 12.2)	12.0 (12.0 – 12.1)	**<0.0001***		
				0.067	**<0.0001***	**0.004***
Total leucocyte count (*x10^3/µl*)	5.0 (4.0 – 8.4)	6.0 (4.0 – 8.8)	6.0 (5.0 – 7.0)	0.747		
Platelets(*x10^3/µl*)	205.0 (169.5–283.0	205.5 (166.5 – 276.5)	250.0 (215.0–305.0)	**0.031***		
				0.865	**0.019***	**0.018***
Absolute lymphocytic count*(µl)*	1500 (1200 – 2000)	1815 (1625 – 2625)	1775.0 (1625–1915)	**0.013***		
				0.015*	**0.026***	0.321

In table IV, ESR level showed highest level in SLE patients. Also, it was higher in group I than group II (p<**0.0001**). CRP level showed significant difference between SLE patients in active state and control group only (p<**0.0001**). A/C ratio was significantly high in SLE patients than healthy subjects and higher in group I than group II (p<**0.0001**).

Table IV: Comparison between studied groups regarding inflammatory markers and A/C ratio

	Group I n= 45 Median IQR	**Group II n=20 Median IQR**	**Group III n=20 Median IQR**	**p value within 3 groups**		
				I vs II	**I vs III**	**II vs III**
ESR *(mm\hour)*	90.0 (80.0 – 110.0	40.0 (23.8 – 50.0)	5.0 (5.0 – 10.0)	**<0.0001***		
				<0.0001*	**<0.0001***	**<0.0001***
CRP (mg/L)	6.0 (3-9)	3.0 (3 – 6.0)	3.0 (2 – 4)	**0.002**		
				0.133	**<0.0001**	0.12
A/C ratio	3.0 (2.1 – 6.1)	0.1 (0.03 – 0.13)	0.02 (0.01 – 0.02)	**<0.0001***		
				<0.0001*	**<0.0001***	**<0.0001***

ANA exhibited significant difference between all studied groups (p<0.0001). Anti-ds DNA level was significantly higher in SLE patients than control and higher in SLE patients in active state than in inactive one (p<0.0001). There was significant decrease in C3 and C4 level when comparing all groups to each (p<0.0001) (as shown in table V).

Table V: immunological markers between different studied groups

	Group I n= 45 Median (IQR)	Group II n=20 Median (IQR)	Group III n=20 Median (IQR)	p value within 3 groups		
				I vs II	I vs III	II vs III
ANA:				**<0.0001***		
Positive	45(100%)	20(100%)	0	0.99	**<0.0001***	**<0.0001***
Negative	0	0	20(100%)			
Anti-ds	801.0	203.0	90.0	**<0.0001***		
DNA(IU/mL)	(705 – 1348)	(105 – 210)	(87.0 – 93.8)	**<0.0001***	**<0.0001***	**<0.0001***
C3(mg/dL	70.0	128.0	138.0	**<0.0001***		
	(61.5 – 72.0)	(118.5 – 131)	(134 – 139)	**<0.0001***	**<0.0001***	**<0.0001***
C4(mg/dL)	8.0	30.0	33.0	**<0.0001***		
	(5.0 – 9.0)	(27.0 – 31.0)	(33.0 – 34.0)	**<0.0001***	**<0.0001***	**<0.0001***

Regarding Interleukin 26 its level was significant high in SLE patients than control and between two patients' subgroups (p<0.0001) (Fig 2). It was noted also that IL-26 levels show highest level among patients receiving combination therapy of immunosuppressive treatment plus steroid and hydroxychloroquine than patients receiving steroid and hydroxychloroquine or hydroxychloroquine only (p<0.0001) (Fig 3).

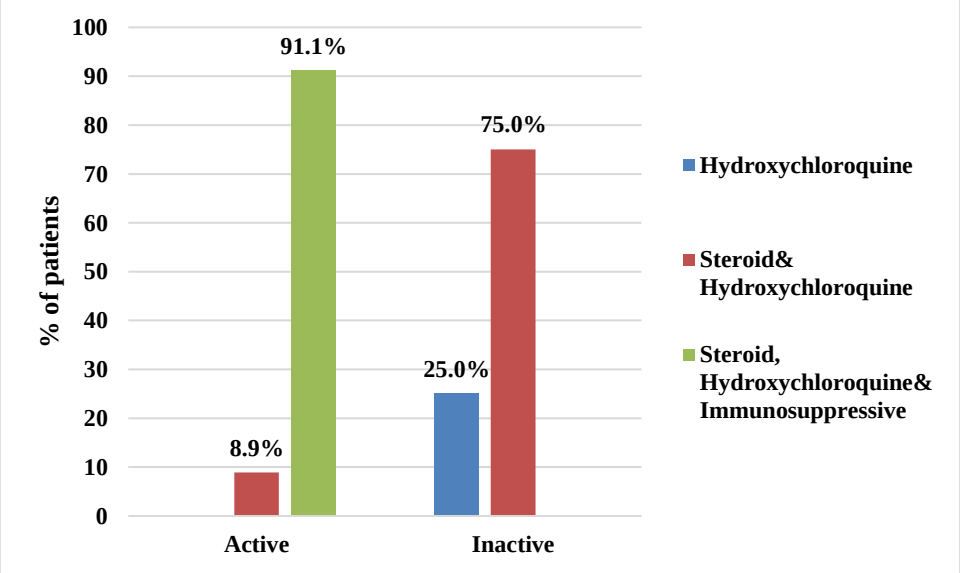

Figure 1: Treatment pattern in studied groups.

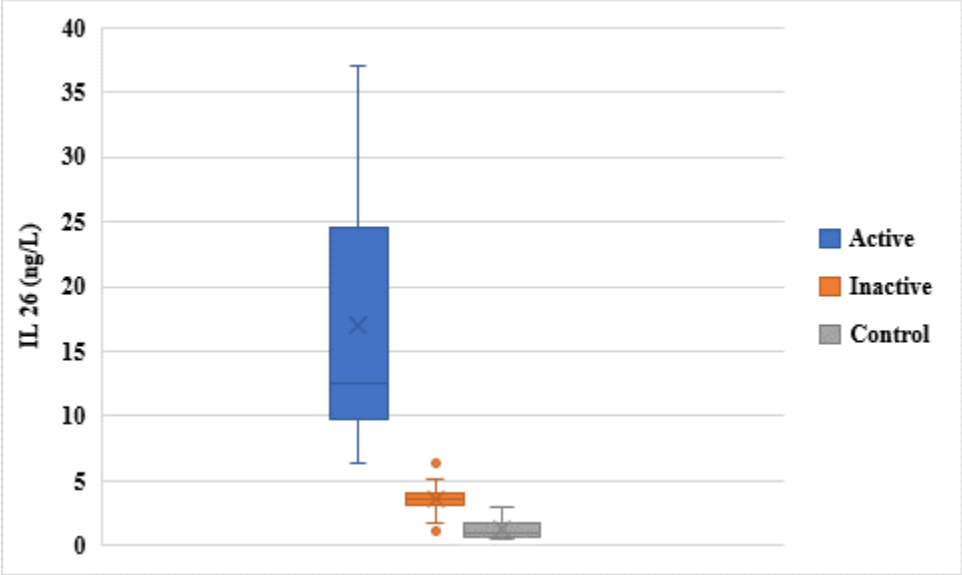

Figure 2: IL 26 comparison between different studied groups.

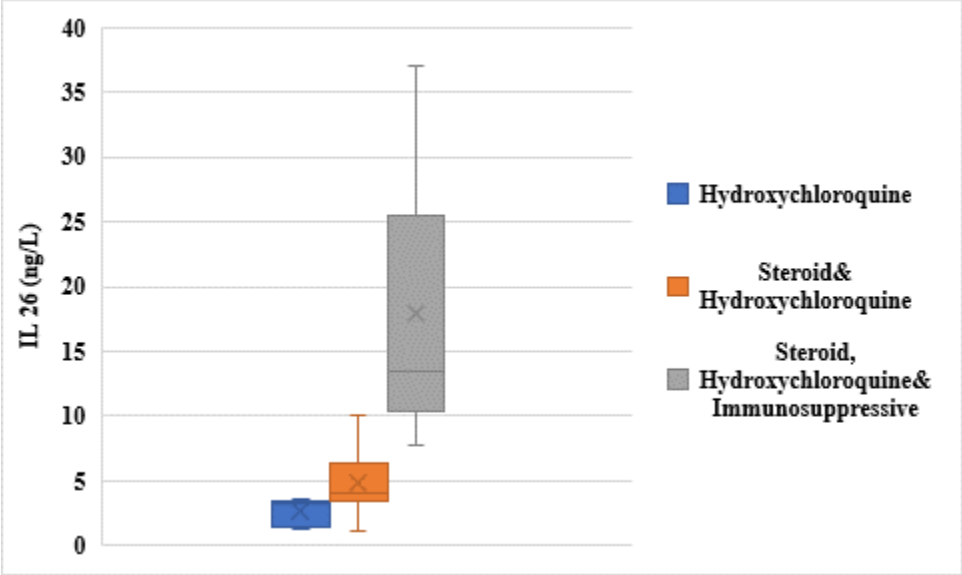

Figure 3: IL-26 level comparison based on treatment classification.

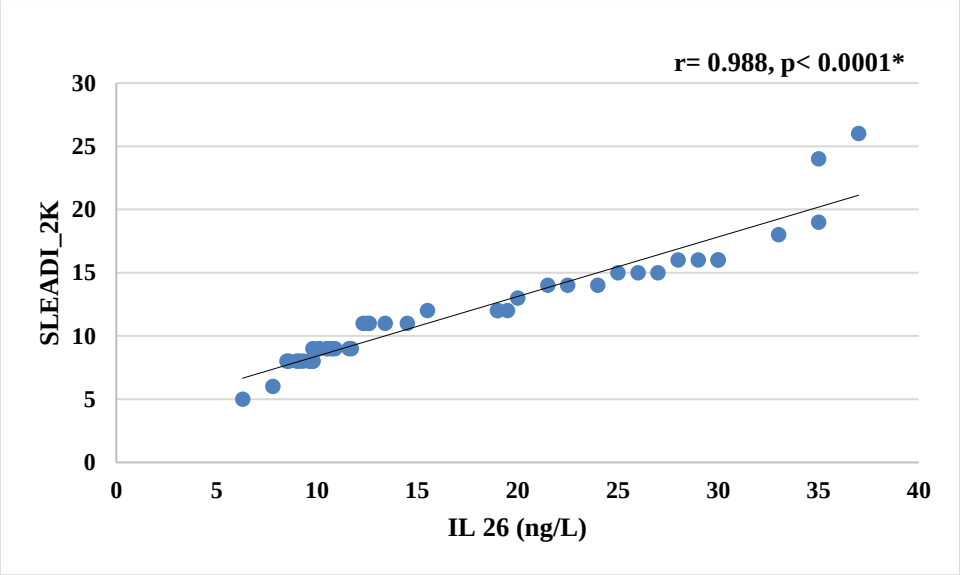

Figure 4: Correlation of IL 26 and SLEADI-2K in active group of patients.

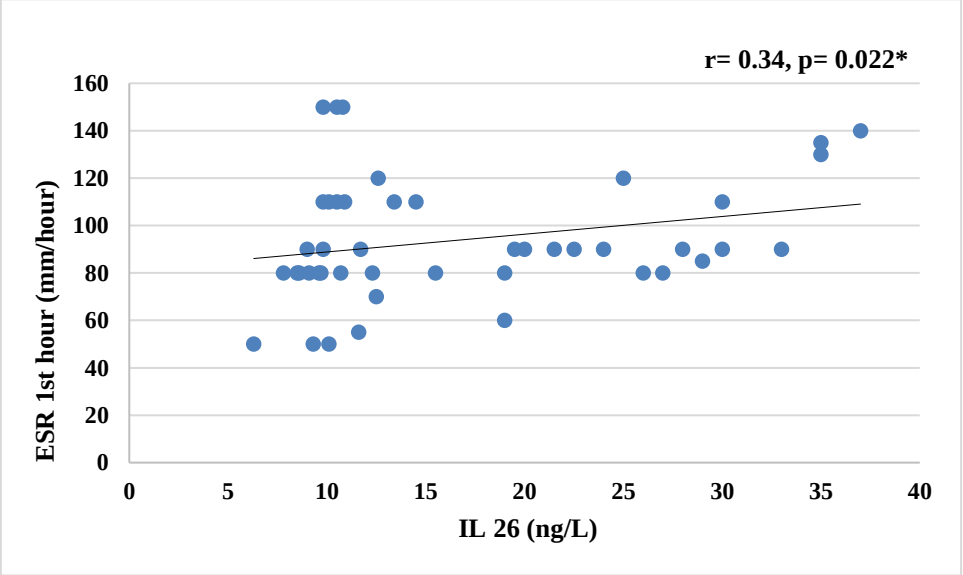

Figure 5: Correlation of IL 26 and ESR in active group of patients.

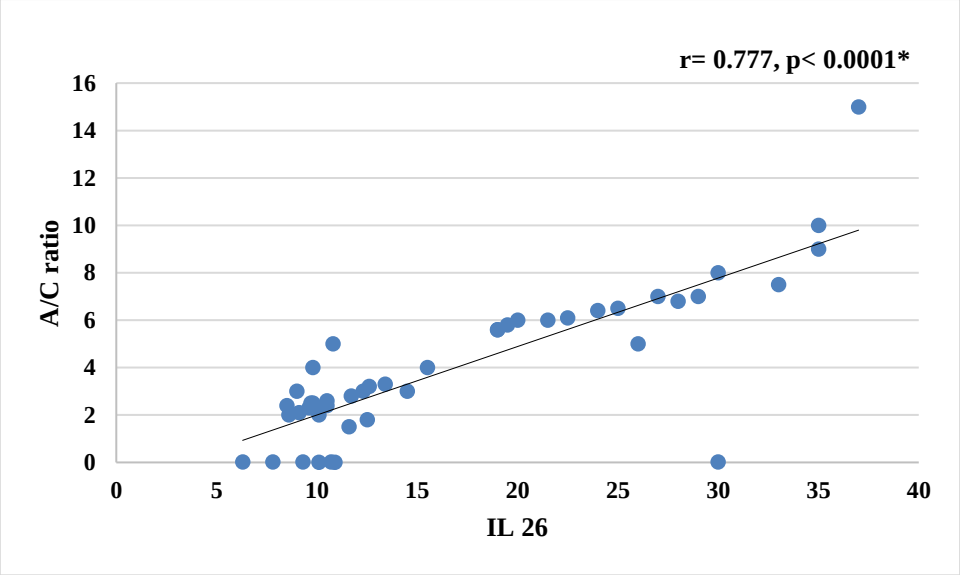

Figure 6: Correlation of IL 26 and A/C ratio in active group of patients.

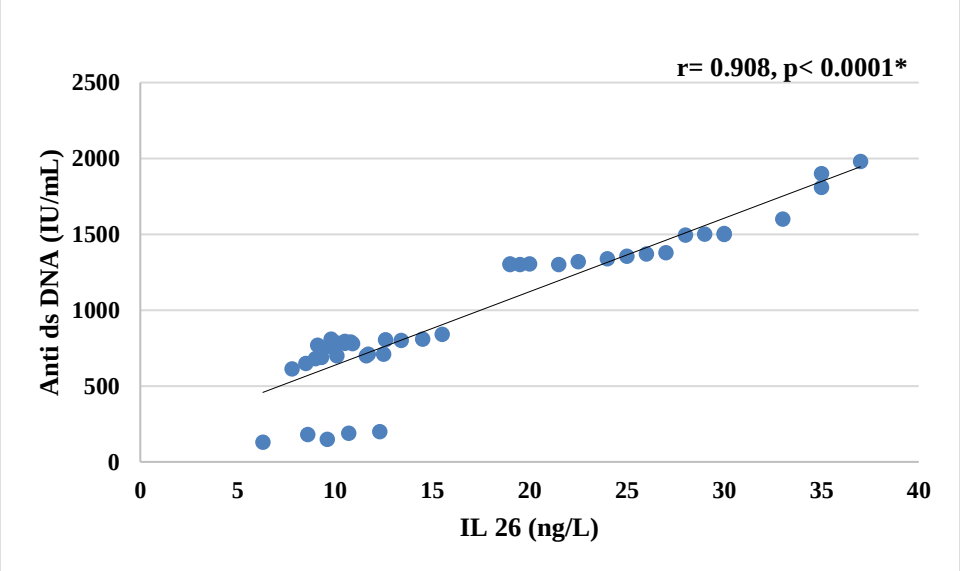

Figure 7: Correlation of IL 26 and Anti ds DNA in active group of patients.

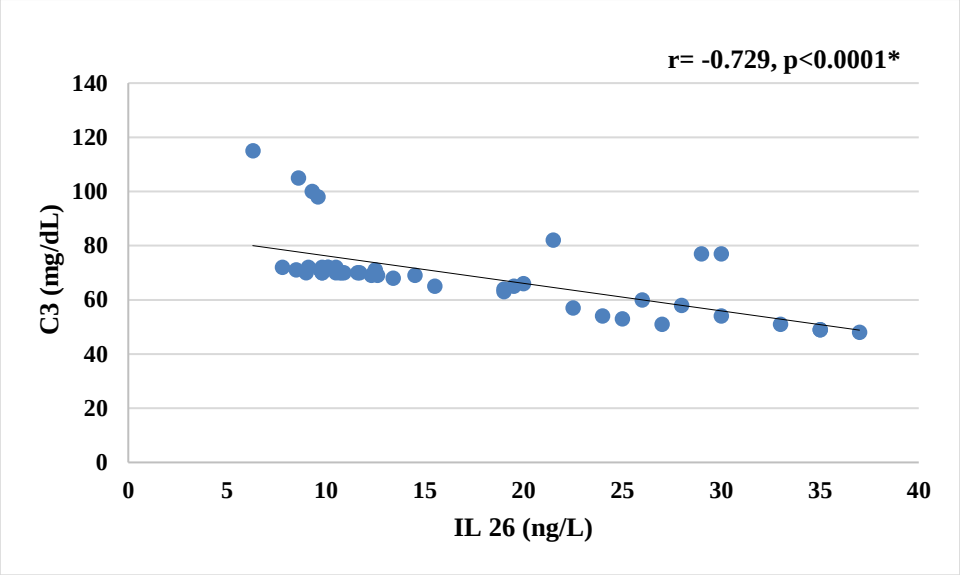

Figure 8: Correlation of IL 26 and C3 in active group of patients.

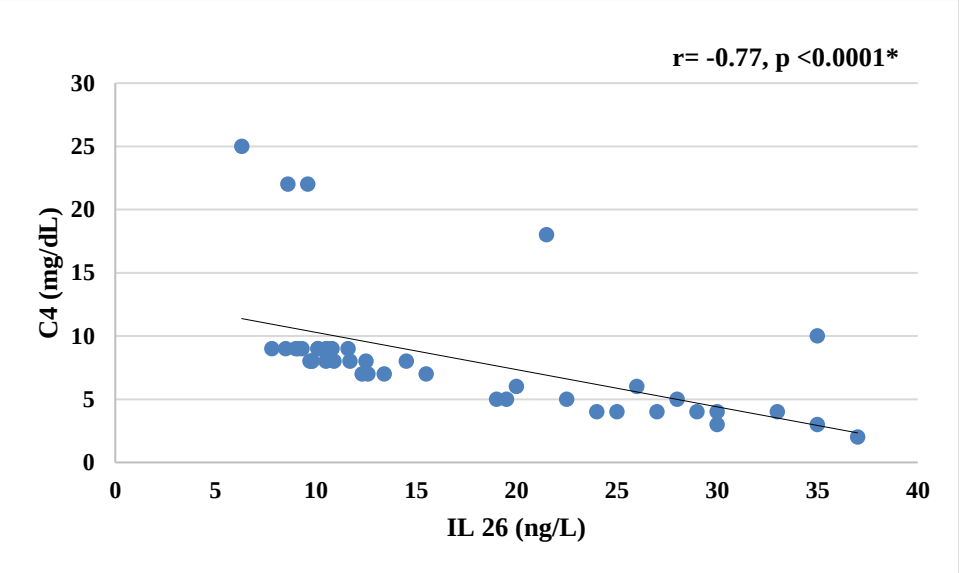

Figure 9: Correlation of IL 26 and C4 in active group of patients.

There was strong significant positive correlation between IL-26 and (SLEADI score, A/C ratio and Anti –ds DNA) (r=0.988, r=0.777, r=0.908 respectively) (Fig 4.6.7 respectively) and fair positive correlation between IL-26 and (ESR) (r=0.34) (Fig 5).
There was strong significant negative correlation between IL26 and (C3 and C4) (r=-0.729, r=-0.77 respectively) (Fig 8.9 respectively).

Discussion

SLE is an autoimmune disease of undetermined etiology affecting all body systems. Along with genetic, hormonal and environmental variables, presence of unbalance between pro-inflammatory and anti-inflammatory cytokines results in alteration of the immune system and promote tissue damage[5].

Interleukin-26 is a cytokine that stimulate the release of inflammatory cytokines by myeloid cells that shared in the transformation of naïve CD4 T Cells into T helper (Th17) cells. Th17 cell also produce IL-26 causing an inflammatory amplification loop[10].

Interleukin-26 is involved in the pathophysiology of chronic inflammatory diseases such as rheumatoid arthritis, Crohn's disease, SLE and other infectious diseases through stimulation of release of inflammatory cytokines like type I interferon leading to tissue inflammation and damage [11]

The present study showed that IL-26 level was highest among SLE patients in active state, then SLE patients in inactive state than control group. **Brilland and his colleagues** study illustrated that IL-26 levels were higher in SLE patients than control and in patients with disease activity than those with inactive lupus. This may be illustrated by the fact that IL-26 binds to circulating DNA released through tissue damage during chronic inflammation causing its invagination into myeloid cells where they bind to DNA sensors, this accelerate the release of interferon-I (IFN-I) and cytokines of inflammation causing more tissue damage[10]. In harmony, a previous study found that level of interleukin 26 was higher in SLE patients than control with significant correlation with disease activity and this is attributed to pro inflammatory property of interleukin 26[11], also it is similar to **yang and his colleagues** study that showed that interleukin 22 which is one of interleukin 10 family such as interleukin 26 was in high levels in patients of lupus nephritis and correlated with the severity of disease[12]. **Poli and his colleagues study** reported that IL-26 was highly expressed in chronic inflammatory disorders (Crohn's disease, rheumatoid arthritis and psoriasis), so IL-26 can be considered as a good inflammatory marker for autoimmune diseases[13].

We observed that level of interleukin 26 was higher in patients receiving steroid and immunosuppressive therapy than patients receiving steroid only and this is in agreement with **Brilland and his colleagues** study that concluded, IL-26 levels were high in patients receiving steroids and immunosuppressive medications as combination therapy is used for management of SLE flare and is found that IL-26 level is correlated with SLE activity[10].

In the present study, it was noticed that hemoglobin level was lower among patients of SLE than healthy subjects, this is similar to **Devia and his colleagues** study who documented that anemia is frequent in patients of SLE due to multifactorial causes such as anemia of chronic disease, iron deficiency anemia (caused by bleeding due to use of non-steroidal anti-inflammatory medications (NSAID)), autoimmune hemolytic anemia and aplastic anemia due to (bone marrow suppression)[14]. Our study showed that platelets count were significantly lower in SLE patients than control**,** in harmony, **Moysidou and his colleagues** study showed that Mild thrombocytopenia has been observed in about 25 to 50 percent of patients with SLE and severe thrombocytopenia <50,000/microL occur in about 10 percent of SLE patients due to increased peripheral destruction of platelet and decreased bone marrow production[15].

Regarding lymphocytic count, it was significantly lower in SLE patients in active state than inactive one. **Schur and his colleagues** study reported that Lymphocytopenia (absolute lymphocyte count <1500/microL), has been noted in about 20 to 75 percent of patients with SLE especially during disease activity ,this may be due to production of autoantibodies against lymphocytes [16], also this is similar to **Sobhy and his colleagues** study that showed that Lymphopenia is a frequently observed in SLE patients ,this is may be attributed to many factors such as infections ,medications as well as production of autoantibodies against lymphocytes[17].

Concerning CRP, it was significantly higher in SLE patients in active state than control group ,while there was no difference between patients subgroups regarding its level .This is compatible with **Littlejohn and his colleagues** study reporting that CRP values >6.0 mg/L in SLE patients are linked to infection and higher CRP levels were linked to SLE infection in comparison to SLE activity without infection

due to the release of autoantibodies directed toword CRP and the consequence of interferon-a that is increasingly released during SLE activity which may participate in lowering CRP levels through suppression of promoter activity and secretion of CRP[18]. However, **Pesqueda-Cendejas and his colleagues** study clarified that there is a significant correlation between CRP levels and disease activity as during SLE activity, there is an increase of cytokines of inflammation like IL-6 which cause an increase of CRP serum levels resulting in presence of association between the increase of IL-6 during SLE activity and higher CRP serum levels[19].

Regarding ESR , it was significantly higher in SLE patients than control and higher in SLE patients in active group than in inactive one ,this is in accordance with **Littlejohn and his colleagues** study who reported that ESR elevation is associated strongly with disease flare in SLE [18] ,also it is similar to **Aringer study** that showed ESR is commonly elevated in active SLE[20], but it is contrary to **Bruera and his colleagues** study reporting that ESR is used for detection of infection and not used as a marker for SLE activity[21] .

Through our study, we noted that A/C ratio was significantly higher in SLE patients than control and higher in patients in active state than inactive one, in contrary, **Wang and his colleagues** study showed that patients of lupus nephritis with active lesions by histological examination have proteinuria of low-grade [22]. **Kamel and his colleagues** study mentioned that patients with active renal nephritis have significantly higher 24h urinary protein excretion than healthy persons and positively correlates with activity, because there is an increase in severity of glomerulonephritis leading to more excretion of urinary protein[23] .

Our study revealed that all patients of SLE have positive ANA test, this in agreement with **Aringer and his colleagues** study that clarified that the (EULAR/ACR) 2019 criteria for SLE include positive ANA as obligatory item for diagnosis of SLE[24].However, **Choi and his colleagues** study showed that among recently diagnosed patients of SLE, 6.2% of patients were antinuclear antibody negative[25].

Results of the current study showed that Anti-ds DNA antibodies level was significantly higher in SLE patients than healthy subjects and higher in group I than group II ,this is similar to **Mummert and his colleagues** study that showed that Anti-ds DNA antibodies are linked to SLE disease activity and renal affection as Anti-ds DNA antibodies are considered autoantibodies that directed against body tissues causing tissue inflammation due to alteration in immune system[26].In contrary, **Brilland and his colleagues** study found that anti-DNA antibodies were elevated within only (40-70%) of SLE patients presented with an active state[10].

Regarding C3 and C4, they were significantly lower in SLE patients than healthy subjects and lower in group I than group II. **AL-Mughales and his colleagues** study found that decreased levels of C3 and or C4 (complement consumption) was associated with the disease activity specially lupus nephritis due to consumption of complement in formation of immune complex that deposit in glomeruli causing glomerulonephritis[27], while it is in disagreement with **Brilland and his colleagues** study that reported that C3 and C4 levels were decreased in only about (10-30%) of SLE patients presented with an active state[10].

In current study, it was noted that there is positive correlation between interleukin 26 and (SLEADI score, A/C ratio, Anti-ds DNA antibodies**),** this is compatible with **Brilland and his colleagues** study showing that patients with high IL-26 levels had higher SLEDAI score, anti-DNA antibodies levels, A/C ratio and more C3 or C4 complement consumption[10]. The correlation between IL-26 and A/C ratio, pointed to IL 26 can be helpful to detect the possibility of occurrence of renal injury. **Khalil and his colleagues** study also reported that there was positive correlation between IL-26 and (SLEADI score, A/C ratio) and negative correlation between it and C3 and C4[11]**,** also these findings are similar to **Xu and his colleagues** study who found presence of positive correlation between SLEADI score and DNA released from cells in SLE patients (there is positive correlation between cell free DNA and IL-26 that is considered as DNA

shuttling molecule)[28]. These findings suggest presence of relation between IL-26 and SLE activity because patients with activity have higher SLEADI-2K score, A/C ratio and lower C3 and C4 than inactive patients.

Conclusions

Overall, the findings of this study indicate presence of correlation between IL-26 and SLE activity, so as well as other serological markers, IL-26 can be considered as a good marker for assessment of SLE activity. IL-26 can also be considered as a marker for lupus nephritis due to presence of positive correlation between IL-26 and A/C ratio.

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