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Interleukin-17 as a biomarker for lupus nephritis: correlation with disease activity indices and histopathological classification

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Abstract

Background Lupus nephritis (LN) is one of the devastating manifestations of systemic lupus erythematosus (SLE). It is a leading cause of death in SLE patients. Interleukin 17(IL-17) is involved in the development of several autoimmune diseases. It causes inflammation and organ damage by exaggerating the immune response and augmenting antibody production by B cells. We assessed the role of IL-17A in LN and its relation to other markers of disease activity and different histopathological classes.

Results We evaluated serum IL-17A in forty LN patients and thirty SLE patients without LN (non-LN). We found that LN patients had a significantly higher IL-17A level in comparison to non-LN. In the LN group, IL-17A was positively correlated with the systemic lupus erythematosus disease activity index (SLEDAI), protein/creatinine (P/C) ratio, 24-hour urinary proteins, anti-nucleosome, and anti-dsDNA antibodies and negatively correlated with C3 and C4. IL-17A was higher in class III and IV compared to class II and V LN. ROC curve analysis of IL-17A revealed 75% sensitivity and 76.7% specificity for LN, and the AUC was 0.791.

Conclusion Lupus nephritis patients have a higher serum level of IL-17A than those without LN, which is more pronounced in patients with class-III and IV LN. Moreover, IL-17A has good sensitivity and specificity for LN and correlates with the disease activity indices; hence, it may be a prognostic marker for LN in SLE patients.

Keywords SLE, IL-17A, LN

Background

Systemic lupus erythematosus is a systemic autoimmune disease marked by reactivity to autoantigens, modification of the immune response to a pro-inflammatory profile, autoantibodies production, and immune complexes deposition in the tissues [1]. It is suggested that genetically susceptible individuals lose their tolerance to nuclear antigens on exposure to certain environmental factors, leading to the activation of immune responses [2]. The disease is characterized by dysregulation of the local and systemic immune reactions and the production of inflammatory mediators, with the subsequent accumulation of inflammatory cells leading to tissue damage in various organs [3]. Women of childbearing age are most commonly affected by SLE, with a prevalence rate ranging from 20 to 70 per 100,000 [4]. SLE manifestations are heterogeneous, ranging from simple skin rashes to more aggressive multi-organ involvement. The most commonly involved organs are the kidneys and the brain [5].

Lupus nephritis is one of the most critical organ affection and the strongest predictor of bad outcomes in SLE patients, which is responsible for a higher disease burden, mainly in low-income populations [6].

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LN occurs in up to 60% of SLE patients [7] and unless promptly treated, it rapidly progresses to end-stage renal disease [8]. The exact mechanisms for the pathogenesis of LN are unclear. Still, the hallmark in pathogenesis is the autoantibody production and formation of immune complexes with subsequent infiltration of the renal tissue by inflammatory cells. Cytokines also participate in the development and progression of LN [7].

Interleukin-17 was discovered twenty years ago at a transcriptional site from rodent cytotoxic T-cell hybridoma [9]. T-helper 17 (Th17) cells are the main producers. Still, it is also produced by other immune cells including group three innate lymphoid cells, mast cells, neutrophils, Gamma delta T cells, and natural killer T cells [10]. The family of IL-17 includes a group of six homologous cytokines (IL-17A, B, C, D, E, and F), of which IL-17A is the most generous, potent, and best characterized [11]. IL-17A binds to a functional IL-17 receptor. IL-17RA expression is omnipresent and abundant in hematopoietic cells. However, its response occurs mainly in epithelial cells, fibroblasts, macrophages, and dendritic cells (DCs) [12]. IL-17 has several biological functions, providing protective immunity against pathogens and promoting inflammation during infection and autoimmunity [13]. IL-17 is a potent pro-inflammatory cytokine that amplifies T-cell activation and stimulates fibroblast cells, endothelial, and epithelial cells to produce several pro-inflammatory mediators, including IL-1β, IL-6, and TNF-α. IL-17 receptor signaling enhances the expression of multiple pro-inflammatory mediators. Hence, IL-17 enhances the production of neutrophil-attracting chemokines [14].

IL-17 signaling contributes to the pathogenesis of autoimmune diseases such as spondyloarthritis (SpA) and rheumatoid arthritis (RA), where IL-17 stimulates the immune cells, producing matrix metalloproteinases, prostaglandins, and pro-inflammatory cytokines, that aggravate the inflammation [15]. Aberrant production of IL-17 has also been implicated in SLE, inflammatory bowel disease, and psoriasis [16]. The inner kidney cells, including renal endothelial cells, renal tubular epithelial cells, podocytes, and mesangial cells, express IL-17 receptors. Thus, these receptors may promote a pro-inflammatory environment, disrupt the function and morphology of nephrons, and activate multiple pro-fibrotic pathways, leading to fibrosis and loss of architecture, with subsequent loss of function [3]. Few studies focused on the importance of IL-17 in SLE, particularly LN, and its relation to different disease activity parameters, so we aimed to explore the role of IL-17A as the most abundant cytokine of the IL-17 family in LN, and its relation to other markers of disease activity and different histopathological classes.

Methods

Data collection

In our study, the data from seventy patients with SLE were obtained from the Rheumatology department from October 2021 to September 2022. Our patients were diagnosed according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [17]. We excluded patients with autoimmune diseases other than SLE, systemic diseases, malignancy, or pregnancy. All patients gave written informed consent, and we got the committee's ethical approval.

Patients' classification and evaluation

We classified the patients into two groups: The first group included forty SLE patients with LN (LN group). The second group included thirty SLE patients without LN (Non-LN group). LN patients were diagnosed based on renal biopsy results. The renal biopsy was performed, and the histopathological classes were determined in the Pathology department. Our patients were evaluated for their demographic data, medical history, and clinical and rheumatological examination. We assessed the disease activity using the SLEDAI. The grades were classified as zero with no activity, 1-5 with mild activity, 6-10 with moderate activity, 11-19 with high activity, and > 20 with very high activity [18].

Laboratory assessment

Laboratory assessment was done for all patients, including CRP, ESR, CBC, urine analysis, P/C ratio, 24-hour urinary proteins, serum urea, creatinine, C3, C4, ANA, anti-nucleosome, anti-dsDNA, and the serum level of IL-17A. We used the immunofluorescence technique for measuring the ANA and the ELISA for measuring the anti-dsDNA and anti-nucleosome. The level of IL-17A was measured in the serum of the patients using the Human IL17A ELISA Kit (Sino Gene Clon Biotech Co., Ltd (Catalog No: SG-10278)) according to the manufacturing protocol.

Statistical analysis

We used the statistical package (IBM-SPSS), version 24, to analyze data. Data were represented as percentages, numbers, mean, and standard deviation (SD). For quantitative data, we used the Student's t-test to compare the means between two groups and the ANOVA test to compare the means of more than two groups followed by the Tukey multiple comparison test. When the data were non-parametric, we used the Mann-Whitney test instead of the Student's t-test. We used the chi-square test to

compare percentages of qualitative variables. We used the Spearman's Rho test for correlations. The receiver operating characteristic (ROC) curve was implemented; *P* values ≤ 0.05 indicate significance.

Results

Demographic and clinical data of the participants

Our study included 70 adult SLE patients: forty patients with LN [37 females (92.5%) and 3 males (7.5%)], and thirty patients without LN [29 females (96.7%) and 1 male (3.3%)]. Age, sex, and disease duration were comparable in the two groups. Regarding the clinical manifestations, constitutional, mucocutaneous, musculoskeletal, serositis, hematological, and neurological manifestations were comparable in the two groups, except for mucosal ulcers and hypertension which were present more frequently in the LN group (p=0.04, and p=0.003). The SLEDAI score was significantly higher in the LN group (p<0.001) compared to the non-LN group, as shown in Table 1. Regarding the medications, 90% of our patients were receiving steroids, 87.1% were receiving hydroxychloroquine, 54.3% were receiving azathioprine, 20% were receiving cyclophosphamide, 12.9% were receiving mycophenolate mofetil, 15.7% were receiving methotrexate, and 1.4 were receiving leflunomide.

Table 1 Demographic and clinical data of LN patients compared to Non-LN patients

Parameters	LN (n=40)	Non-LN (n=30)	*P* value
Sex No. (%):			0.45
Male	3 (7.5%)	1 (3.3%)	
Female	37 (92.5%)	29 (96.7%)	
Age (years) mean ± SD	33.4 ± 10.03	35.67 ± 10.4	0.30
Disease duration (years) mean ± SD	4.86 ± 2.3	4.62 ± 1.27	0.604
Fever No. (%)	5 (12.5%)	1 (3.3%)	0.175
Arthralgia No. (%)	16 (40%)	11(36.66%)	0.778
Arthritis No. (%)	9 (22.5%)	6 (20%)	0.80
Malar rash No. (%)	13 (32.5%)	7 (23.3%)	0.40
Discoid rash No. (%)	1 (2.5%)	3 (10%)	0.184
Vasculitis rash No. (%)	3 (7.5%)	1 (3.33%)	0.461
Photosensitivity No. (%)	21 (52.5%)	14 (46.7%)	0.63
Alopecia No. (%)	18 (45%)	11 (36.7%)	0.48
Raynaud's No. (%)	4 (10%)	2 (6.66%)	0.625
Mucosal ulcers No. (%)	12 (30%)	3 (10%)	***0.04****
Hematologic No. (%)	31 (77.5%)	19 (63.3%)	0.19
Mood disorders No. (%)	6 (15%)	2 (6.66%)	0.282
Lupus headache No. (%)	5 (12.5%)	3 (10%)	0.747
Serositis	2 (5%)	0	0.217
Hypertension No. (%)	17 (42.5%)	3 (10%)	***0.003****
SLEDAI score mean ± SD	12.45 ± 5.74	5.53 ± 4.7	***<0.001****

SLEDAI score Systemic Lupus Erythematosus Disease Activity Index

Where *the difference is significant at p≤0.05, **the difference is significant at p≤0.01, and ***the difference is significant at p≤0.0001. Independent sample *t*-test, and chi-square test were used

Laboratory data of the participants

The ESR, CRP, and CBC parameters were comparable in both groups. Serum creatinine, urea, P/C ratio, and 24-hour urinary proteins were higher among LN patients with statistically significant differences (p=0.013, p=0.009, p<0.001, and p<0.001, respectively). C3 level was lower in the LN group, with a statistically significant difference (p=0.006). Despite that, both groups were comparable regarding C4 level (p=0.146). The positivity of anti-dsDNA and anti-nucleosome antibodies was higher among the LN than non-LN patients (p=0.033 and p=0.045). IL-17A expression was significantly higher among the LN group than the Non-LN group (p<0.001), as shown in Table 2.

Correlation of IL-17A with the SLEDAI and laboratory parameters

In the LN group, IL-17A was positively but weakly correlated with the SLEDAI score (r=0.356, p=0.024), and strongly correlated with the renal components of the SLEDAI (r=0.561, p<0.001). Regarding the laboratory

Table 2 Laboratory data of LN patients compared to Non-LN patients

Parameters	LN (n=40) mean ± SD	Non-LN (n=30) mean ± SD	*P* value
WBCs (*10^3/mm^3)	6.56 ± 2.46	5.79 ± 1.87	0.146
Hemoglobin (g/dl)	10.7 ± 2.07	11.64 ± 2.1	0.067
PLTs (*10^3/mm^3)	265.13 ± 93.35	257.5 ± 89.9	0.731
Creatinine (mg/dl)	0.86 ± 0.37	0.67 ± 0.26	***0.013****
Urea (mg/dl)	36.6 ± 5.68	32.8 ± 5.97	***0.009****
P/C ratio	2.14 ± 1.96	0.12 ± 0.067	***<0.001*****
24hrs urinary proteins (mg/24hrs)	686 ± 391.5	98.33 ± 38.7	***<0.001*****
ESR (mm/h)	38.75 ± 29.09	36.86 ± 22.44	0.761
CRP (mg/L)	18.7 ± 20.13	19.29 ± 20.55	0.905
C3 (mg/dl)	91.98 ± 48.94	116.01 ± 18.34	***0.006****
C4 (mg/dl)	16.4 ± 9.76	19.28 ± 6.57	0.146
IL-17 (ng/L)	41.4 ± 5.79	35.04 ± 6.16	***<0.001*****
ANA	39 (97.5)	28 (93.3%)	0.667
Anti-dsDNA	31 (77.5%)	16 (53.3%)	***0.033****
Anti-nucleosome	23 (57.5%)	10 (33.3%)	***0.045****

WBC white blood cell, *PLTs* platelets, *P/C ratio* protein /creatinine ratio, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *C* complement, *IL-17* Interleukin 17, *ANA* anti-nuclear antibody (ANA), *Anti-dsDNA* anti-double-stranded- DNA

Where *the difference is significant at p≤0.05, **the difference is significant at p≤0.01, and ***the difference is significant at p≤0.0001. Independent sample *t*-test and Mann-Whitney were used

parameters, there were positive correlations between IL-17A and both P/C ratio (r=0.409, p=0.009) and 24-hour urinary proteins (r=0.459, p=0.003). On the other hand, IL-17A was negatively correlated with both C3 (r=-0.455, p=0.003) and C4 (r=-0.314, p=0.048). In addition, IL-17A was positively correlated with anti-dsDNA (r=0.469, p=0.002) and anti-nucleosome (r=0.403, p=0.01) antibodies, as shown in Table 3.

Comparison of IL-17A expression among different LN classes

Regarding renal biopsy results, 27.5% of LN patients had class II LN, 25% had class III LN, 35% had class IV LN, and 12.5% had class V LN. On comparing IL-17A levels among LN patients, we found that IL-17A levels were higher in LN patients with class III compared with class II and V (P<0.001 and P=0.011, respectively). Also, we found that IL-17A level was higher in LN patients with class IV compared to those with class II and V (P<0.001 and P=0.027, respectively), as shown in Table 4.

Table 3 Correlation of IL-17A with the SLEDAI score and laboratory parameters in the LN group

Parameters	Correlation coefficient (r)	*P* value
SLEDAI	0.356*	***0.024***
Renal SLEDAI	0.561**	**<0.001**
WBC	-0.038	0.817
Hemoglobin	-0.139	0.394
PLTs	-0.122	0.454
Serum creatinine	-0.063	0.697
Urea	-0.101	0.536
P/C ratio	0.409**	***0.009***
24-hour urinary proteins	0.459**	***0.003***
C3	-0.455**	***0.003***
C4	-0.314*	***0.048***
ANA	-0.210	0.193
Anti-dsDNA	0.469**	***0.002***
Anti-nucleosome	0.403**	***0.010***

WBC white blood cell, *PLTs* platelets, *P/C ratio* protein /creatinine ratio, *C* complement

Where *means mild correlation, and **means moderate correlation. The Spearman's rho correlation was used

ROC curve analysis of IL-17A in lupus nephritis

Data from ROC curve analysis exhibited that at a cut-off value of 39.01(ng/L), IL-17A showed 75% sensitivity and 76.7% specificity for LN, and the AUC was 0.791 (P<0.001), as shown in Fig. 1 and Table 5.

Discussion

Lupus nephritis develops as a result of a complex process of an abnormal immune response involving the deposition of autoantibodies in the glomeruli, complement, and macrophages activation, and pro-inflammatory cytokines and chemokines production, causing tubular damage, tubular interstitial inflammation, and fibrosis [19]. Cytokine dysregulation is one of the mechanisms participating in the pathogenesis of SLE, including LN [20]. IL-17 receptors are expressed by the renal cells; this may propose a possible role for IL-17 in triggering inflammation in the renal tissue [3]. Hence, our study aimed to explore the role of IL-17A in LN and its relation to other

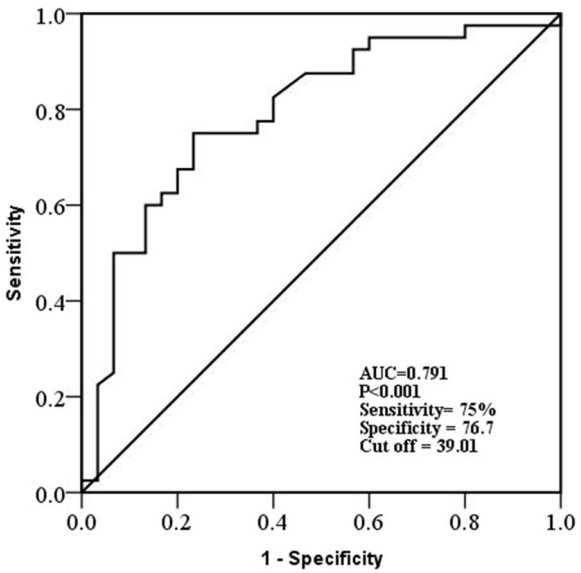

Figure 1 ROC curve analysis of IL-17A in lupus nephritis patients

Table 4 Comparison of IL-17A expression among different LN classes

Parameters	Class II	Class III	Class IV	Class V	*P* value
IL-17A (mean± SD)	34.9 ± 4.29	45.58 ± 4.07	44.54 ± 2.55	38.8 ± 4.57	<0.001***
Tukey's *p*-value					
II: III	II: IV	II: V	III: IV	III: V	IV: V
<0.001***	<0.001***	0.231	0.906	0.011*	0.027*

IL-17A interleukin 17A

Where *the difference is significant at $p \leq 0.05$, and ***the difference is significant at $p \leq 0.0001$. One-way ANOVA was used followed by Tukey multiple comparison test

Table 5 ROC curve analysis of IL-17A in LN patients

Cut-off	AUC	Sensitivity	Specificity	95% CI		*P* value
				Lower bound	Upper bound	
39.01 (ng/L)	0.791	75%	76.7%	0.682	0.900	<0.001***

CI Confidence interval, *AUC* Area under curve

*** the significance is very high

markers of disease activity and different histopathological classes.

In our study, when we compared the LN patients with those without LN, IL-17A expression was higher among the LN group (p<0.001). This was in line with Chen et al., who found that the LN patients had higher IL-17 levels than those without renal involvement [21]. Also, Dedong et al. found that the baseline levels of IL-17 were more elevated in active LN patients compared with inactive LN patients and controls [22]. In addition, Peliçari et al. found an association between serum IL-17A levels and the active LN [23] and Zickert et al. found that IL-17 level is a marker of poor outcome in patients with LN [7]. Also, Mok et al. found significant differences in IL-17 levels between patients with active LN, active non-renal disease, inactive SLE, and normal controls [24]. On the other hand, Hristova et al. and Zhao et al. found no significant differences in serum IL-17 levels between patients with LN and those without nephritis [25, 26].

Our LN patients had higher SLEDAI scores than non-LN patients (p<0.001). In accordance, Farres et al., Kwon et al., and Hafez et al. found that the LN patients had higher disease activity scores than the patients without nephritis [27–29]. In our study, both groups were comparable regarding CBC parameters. Our LN patients had higher serum creatinine, urea, P/C ratio, and 24-hour urinary proteins than those without LN (p=0.013, p=0.009, p<0.001, and p<0.001, respectively). In agreement with us, Hafez et al. found that the LN group had a higher serum creatinine, urea, P/C ratio, and 24-hour urinary proteins than the non-LN group [28]. In addition, Dedong et al. found that serum creatinine and 24-hour urinary proteins were higher in the LN group than those without nephritis [22]. Also, Farres et al. reported that patients with LN had higher creatinine levels than patients without LN [27].

According to our findings, the C3 level was lower in the LN group than in those without LN (p=0.006), but both groups were comparable regarding the C4 level (p=0.146). In accordance, Kwon et al. found that SLE patients who developed LN had lower C3 than those who didn't develop nephritis. However, they found a lower C4 level in the LN group [29]. Dedong et al. found that LN patients had lower C3 and C4 levels than the controls [22]. However, Farres et al. and Hafez et al. did not find significant differences between both groups regarding C3 and C4 [27, 28]. These different results may be due to variable sample sizes and patients' characteristics.

Our LN patients had a higher percentage of positive anti-nucleosome and anti-dsDNA antibodies than those without LN (p=0.033 and p=0.045). Similarly, Sui et al., Yang et al., and Elsayed & Mohafez found that SLE patients with LN had a higher positivity of anti-dsDNA and anti-nucleosome antibodies than SLE patients without nephritis [30–32]. In accordance, Farres et al. and Kwon et al. reported that patients with LN had significantly higher anti-dsDNA levels than patients without nephritis [27, 29]. Also, Mok reported that anti-nucleosome antibodies were associated with renal involvement [33].

Among our LN patients, IL-17A was negatively correlated with C3 (r=-0.455; p=0.003) and C4 (r=-0.314, p=0.048). In line with our result, Dedong et al. and Wang et al. found that IL-17 was negatively correlated with C3, but they found that IL-17 wasn't correlated with C4 [22, 34]. Regarding our findings, IL-17A was positively correlated with the P/C ratio (r=0.409, p=0.009) and 24-hour urinary proteins (r=0.459; p=0.003). In agreement with our results, Chen et al. found a positive correlation between IL-17 levels and proteinuria in SLE patients with LN [21]. Similarly, Galil et al. found that IL-17 positively correlated with 24-hour proteinuria levels, and this correlation was manifest in the LN group during periods of activity and remission [16]. In addition, Hammad et al. found a positive correlation between IL-17A level and urinary P/C ratio [35] Also, Wang et al. found that the serum level of IL-17A was correlated with proteinuria in LN patients [34]. In addition, IL-17 was positively correlated with anti-dsDNA (r=0.469, p=0.002), and anti-nucleosome (r=0.403, p=0.01). Galil et al. found that IL-17 correlated positively with anti-dsDNA in LN patients [16]. IL-17A was positively but weakly correlated with the SLEDAI score (r=0.356, *p=0.024*); our findings agree with Yin et al [36]. Also, Nasser et al. found a positive correlation between IL-17A and SLEDAI in SLE patients [37].

In our study, when we compared IL-17A levels among different classes of LN, we found that IL-17A levels

were higher in LN patients with class III compared to class II and V (P<0.001 and P=0.011, respectively). Also, we found that the IL-17A levels were higher in class IV LN compared to class II and V (P<0.001 and P=0.027, respectively). This low significant difference in IL-17A expression between class III and V and class IV and V may be due to the small number of patients having class V lupus nephritis (12.5%) and the relatively increased expression of IL-17A in patients with proliferative LN. In agreement with our findings, Yazici et al. found that when the staining of IL-17 was compared among the LN classes, more intense staining was found in classes III and IV when compared with class II [38]. Additionally, Zickert et al. found that the baseline level of IL-17 was higher in patients with classes III, IV, and V than in classes I and II LN [7]. Despite our promising findings regarding the prognostic value of IL-17A in LN, the renal biopsy remains the gold standard for diagnosing LN. However; IL-17A may be useful in predicting the degree of disease activity in LN patients, helping early recognition of renal flares, guiding treatment decisions, and assessing the responsiveness to therapy.

The pathogenic role of IL-17 in LN was supported by studies in animal models, revealing that the production of IL-17 is high in mice having lupus-like diseases, and T cells expressing IL-17 infiltrate their kidneys. Examples of these cells include CD3+CD4-CD8- DNT (double negative T) cells. The authors found that DNT cells in mice express large amounts of IL-17, and as the disease progresses, the lymphocytes express more IL-17 and IL-23 receptors [39]. Kwan et al. found increased expression of Th17-related genes involving IL-17 and IL-23 in SLE patients' urine, associated with active LN [40]. Also, IL-17-producing T cells were found in the kidneys of LN patients. They migrate to the kidneys and have a significant role in inducing inflammation [23, 41]. Moreover, it has been suggested that, in patients with LN, a high level of IL-17 after immunosuppressive therapy is a predictor of poor histopathological outcome [7].

In our study, the ROC curve analysis of IL-17A in LN patients revealed that at a cut-off value of 39.01(ng/L), IL-17A has 75% sensitivity and 76.7% specificity for LN (P <0.001), this was in line with Susianti et al., who found that the ROC curve analysis of IL-17 for the diagnosis of LN showed 66.67% sensitivity and 72% specificity [42].

Limitations of the study

Small sample size and lack of follow-up period to assess the effect of therapy on the serum level of IL-17A.

Recommendations

Future studies with large sample sizes and prolonged follow-up periods are recommended.

Conclusion

Lupus nephritis patients have a higher serum level of IL-17A than those without LN, which is more pronounced in patients with class-III and IV LN. Moreover, IL-17A has good sensitivity and specificity for LN and correlates with the disease activity indices; hence, it may be a prognostic marker for LN in SLE patients.

Abbreviations

AUC	Area under the curve
DCs	Dendritic cells
IL-17	Interleukin-17
LN	Lupus nephritis
ROC	Receiver operating characteristic
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
Th17	T-helper 17

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None.

Authors' contributions

Conceptualization and diagnosis: Faten Ismail, Sahar A. Elsayed and Abdullatif A. Ahmed. Data collection: Aya M. Ahmed. Laboratory investigations: Abdullatif A. Ahmed. Statistical analysis and manuscript writing: Sahar A. Elsayed and Aya M. Ahmed. Review, editing and approval: All authors.

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Availability of data and materials

The data of the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its later amendments in 2000, and approved by The Medical Research Ethics Committee, Faculty of Medicine - Sohag University under IRB registration number**:** Soh-Med-21-09-22. All patients included in this study gave written informed consent to participate in this research.

Consent for publication

Not applicable.

Competing interests

None.

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