Role of Interleukin-17 in Predicting Activity of Rheumatoid Arthritis and Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND: Although high serum levels of interleukin (IL)-17 and its producing cells have been found in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) in earlier research, it is still unclear how these findings relate to disease activity.

OBJECTIVES: This study examines the link between serum levels of IL-17 and the activity of both RA and SLE.

DESIGN: This pilot case–control study included 100 patients with RA, 100 with SLE, and 100 healthy controls.

METHODS: The Disease Activity Score-28 (DAS28) scores assessed the activity of RA, whereas the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores assessed SLE activity. All participants' data were compared and correlated.

RESULTS: Serum levels of IL-17 were significantly higher in RA and SLE patients compared with the controls ($P < .001$) and showed significantly positive correlations ($P < .001$) with rheumatoid factor titer, anti-cyclic citrullinated peptide (anti-CCP) and DAS28 score among the RA patients. Although among SLE patients, they were significantly positively correlated ($P < .001$) with anti-double-stranded DNA (anti-ds DNA) levels and the SLEDAI-2K scores, the best cut-off value of IL-17 for predicting moderate and high disease activity was > 175 pg/mL among RA patients and > 95 pg/mL among SLE patients.

CONCLUSIONS: There is a significant correlation between RA and SLE activity and serum levels of IL-17. This discovery emphasizes IL-17 as a potential therapeutic target.

KEYWORDS: Activity, DAS28, interleukin-17, rheumatoid arthritis, SLEDAI-2K, systemic lupus erythematosus

Introduction

The proinflammatory cytokine interleukin (IL)-17, a hallmark cytokine of T-helper 17 (Th17) cells, plays a significant role in host defense against infections, mainly against the extracellular pathogens, and in the pathogenesis of many autoimmune diseases. It is a pleiotropic cytokine that can induce the secretion of other proinflammatory factors.[1-3] It also promotes the activation and recruitment of immune cells, stimulates stromal cells, and induces angiogenesis and osteoclastogenesis.[4,5]

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are common autoimmune disorders that cause disability, poor quality of life and low survival rates. Both disorders have genetic, environmental, and immunological etiology.[6] SLE is a heterogeneous disorder that can affect multiple organs such as skin, brain, joints, and kidneys due to the production of autoantibodies and the deposition of immune complexes. It is characterized by immune dysregulation with remissions and exacerbations. On the contrary, RA mainly affects the joints and can lead to deformities due to chronic inflammation, synovial hyperplasia, and autoantibody production. It can affect other body systems such as the cardiovascular and pulmonary systems.[7,8] Previous studies have reported elevated serum levels of IL-17 and numbers of Th-17 cells in RA and SLE, but their association with disease activity is still uncertain.[9,10] Early management of these disorders could improve disease outcomes and increase survival rates and quality of life. Several treatment approaches approved for psoriasis, psoriasis arthritis, and ankylosing spondylitis target the Th17 cells and IL-17 pathway.[11,12] In an effort to identify a potential new target for treatment of RA and SLE, this study investigates the relationship between serum levels of IL-17 and the activity of both disorders.

Methodology

Ethics and participants selection

This pilot case–control study got ethical approval (# FMASUR10/2023) from the Research Ethics Committee, Faculty of Medicine, Ain Shams University. All participants or

Table 1. Comparison of the demographic characteristics of the study groups.

		GROUPS			P-VALUE
		CONTROL	SLE	RA	
Age (years)	Range	16-61	15-58	18-57	.630[a]
	Mean ± SD	27.950 ± 8.959	28.980 ± 9.353	27.760±9.226	
Sex, n (%)	Male	27 (27%)	14 (14%)	22 (22%)	.075[b]
	Female	73 (73%)	86 (86%)	78 (78%)	
Disease duration (years)	Range	—	0.58-20	0.52-22	.924[a]
	Mean ± SD	—	4.833 ± 3.978	5.023±4.122	

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.
[a]One-way analysis of variance (ANOVA) test.
[b]Chi-square test.

their legal guardians provided their written informed consent before the start. A total of 300 adults (100 healthy controls, 100 RA, and 100 SLE) participated in this study that was conducted over 6 months from March to August 2023. The RA and SLE patients were recruited from the Rheumatology Department of Ain-Shams University Hospital, whereas controls were recruited from the healthy sex- and age-matched attendees. The diagnosis of SLE followed the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria and the assessment of disease activity was done using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scoring system, whereas RA diagnosis followed the 2010 American college of rheumatology (ACR)/European league against rheumatism (EULAR) criteria, and the assessment of disease activity was done using the Disease Activity Score-28 (DAS28) scoring system.[13] Patients with chronic infections, malignancies, and other autoimmune diseases were excluded from the study.

Clinical evaluation and data gathering

All participants were subjected to complete clinical evaluation and history-taking stressing on disease duration, the presence of comorbid conditions (eg, diabetes, hypertension), and body systems affection (eg, cardiac, pulmonary, renal, articular, cutaneous, vascular, oral, and central nervous systems). In addition, data were collected from patients' medical reports, including routine lab investigations such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). As well as serum complement C3 and C4, anti-double-stranded DNA levels (anti-ds DNA) in SLE patients and rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) in RA patients.

Serum IL-17 level assessment

Three milliliters of whole blood from all participants were collected under strict sterile conditions into a gel-containing vacutainer tube. The collected blood was allowed to clot entirely before the serum was separated by centrifugation at 4000 r/min for 15 min. According to the manufacturer manual, the collected sera were used for serum IL-17 level assay by ELISA (Bioassay Technology Laboratory, Shanghai, China, Code: E0142Hu). The kit detection range is 2 to 600 pg/mL, and the sensitivity is 1.06 pg/mL.

Statistical analysis

SPSS version 20 (International Business Machines Corporation, New York, 2010) was used to analyze the data. For comparisons, one-way analysis of variance (ANOVA), independent T-test, and Chi-square test were employed. Using Spearman's approach for non-parametric data and Pearson's approach for parametric data, correlation studies were carried out. Finally, the predictive power of serum IL-17 levels for moderate and high RA and SLE activity was examined using receiver operating characteristic (ROC) curve analysis. A statistically significant P-value is less than .05.

Results

This study was performed on 100 patients with RA, 100 with SLE, and 100 healthy matched controls in age and sex. RA and SLE patients did not differ according to their disease duration (P = .924; see Table 1).

The IL-17 levels differed significantly between the study groups (P < .001); they were significantly higher in RA and SLE patients than in the control group. The mean (±SD) serum level of IL-17 among the RA patients was the highest, 362.76 ± 140.30 pg/mL, ranging from 67 to 600 pg/mL. Although among the SLE patients, it was 127.208 ± 81.310 pg/mL and ranged from 31 to 360 pg/mL, the control group's mean (±SD) serum level of IL-17 was 30.450 ± 9.537 pg/mL and ranged from 16 to 52 pg/mL (see Figure 1).

The DAS28 scores of the included RA patients ranged from 2.5 to 8.3 with a mean (±SD) of 4.967 ± 1.546. Of
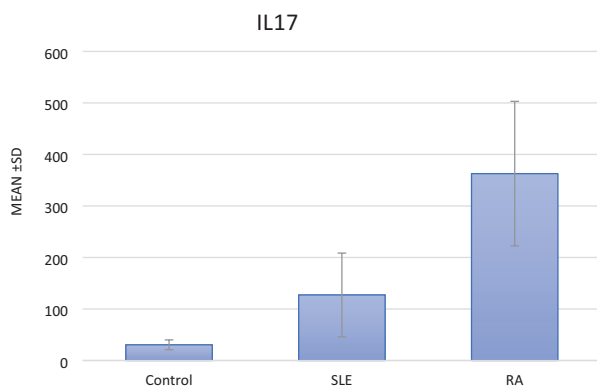
Figure 1. Box plot for comparison of serum levels of IL-17 (pg/mL) among the study groups (*P* < .001).

them, four patients were inactive, 11 had low, 42 had moderate, and 43 had high scores. On the contrary, according to the SLEDAI-2K scores of the included SLE patients, they ranged from 0 to 12 with a mean (±SD) of 5.360 ± 3.697. Of them, 51 patients had mild, 37 had moderate, and 12 had high scores. Serum levels of IL-17 differed significantly according to the DAS28 and the SLEDAI-2K scores; their levels increased significantly with higher scores (*P* < .001). Also, significantly higher serum levels of IL-17 among RA patients were associated with interstitial pulmonary fibrosis

(*P* = .002). Although in SLE patients, IL-17 levels were significantly higher with serositis (*P* = .001), cerebritis (*P* < .001), thrombosis (*P* = .003), bleeding (*P* = .016), pulmonary complications (*P* < .001), consumed complement C3 and C4 (*P* < .001), arthritis (*P* = .025), and kidney affection in renal biopsy (*P* < .001; see Tables 2 and 3).

Among the RA patients, IL-17 levels showed significantly positive correlations with ESR (*r*: 0.588; *P* < .001), CRP (*r*: 0.553; *P* < .001), rheumatoid factor titer (*r*: 0.507; *P* < .001), anti-CCP (*r*: 0.575; *P* < .001), and DAS28 score (0.797; *P* < .001; see Figure 2).

Among the SLE patients, serum IL-17 levels showed significantly positive correlations with ESR (*r*: 0.200; *P* = .046), anti-ds DNA levels (*r*: 0.490; *P* < .001), and the SLEDAI-2K scores (*r*: 0742; *P* < .001; see Figure 3).

The predictive ability of serum IL-17 levels for the severity of RA and SLE was tested using ROC curve analyses. Among the RA patients, serum IL-17 at a cut-off > 175 pg/mL had 100% diagnostic sensitivity, 100% specificity, and 100% accuracy for predicting moderate to high score disease. On the contrary, among the SLE patients, serum IL-17 at a cut-off > 95 pg/mL had 95.92% diagnostic sensitivity, 88.24% specificity, and 94.7% accuracy for predicting moderate to high score disease (see Figures 4 and 5).

Table 2. Serum levels of IL-17 according to the characteristics of the included RA patients (n = 100).

RHEUMATOID ARTHRITIS GROUP		IL-17 (PG/ML)		*P*-VALUE
		N	MEAN ± SD	
Diabetes	Positive	28	340.286 ± 129.389	.320[a]
	Negative	72	371.500 ± 144.244	
Hypertension	Positive	38	340.447 ± 118.230	.215 [a]
	Negative	62	376.435 ± 151.560	
Ischemic heart disease	Positive	11	354.545 ± 132.331	.838[a]
	Negative	89	363.775 ± 141.941	
Interstitial pulmonary fibrosis	Positive	26	435.000 ± 103.838	**.002**[a]
	Negative	74	337.378 ± 143.154	
DAS28 score	Inactive	4	80.500 ± 15.588	**<.001**[b]
	Low	11	143.273 ± 19.764	
	Moderate	42	325.262 ± 54.448	
	High	43	481.791 ± 85.331	

Abbreviations: DAS, Disease Activity Score; IL, interleukin; RA, rheumatoid arthritis.
[a]Independent T-test.
[b]One-way analysis of variance (ANOVA) test.
Bold *P*-value indicates statistical significance.

Table 3. Serum levels of IL-17 according to the characteristics of the included SLE patients (n = 100).

SYSTEMIC LUPUS ERYTHEMATOSUS GROUP		IL-17 (PG/ML)		P-VALUE
		N	MEAN ± SD	
Diabetes	Positive	8	112.250 ± 50.514	.590a
	Negative	92	128.509 ± 83.515	
Hypertension	Positive	38	121.474 ± 77.553	.583a
	Negative	62	130.723 ± 83.956	
Antiphospholipid syndrome	Positive	52	125.169 ± 71.075	.796a
	Negative	48	129.417 ± 91.840	
Malar rash	Positive	94	124.647 ± 80.232	.214a
	Negative	6	167.333 ± 95.475	
Oral ulcer	Positive	84	121.438 ± 70.585	.104a
	Negative	16	157.500 ± 122.070	
Photosensitivity	Positive	51	125.686 ± 83.623	.850a
	Negative	49	128.792 ± 79.665	
Alopecia	Positive	61	121.311 ± 79.934	.367a
	Negative	39	136.431 ± 83.621	
Serositis	Positive	26	171.685 ± 89.771	**.001a**
	Negative	74	111.581 ± 72.484	
Cerebritis	Positive	15	209.067 ± 88.841	<**.001a**
	Negative	85	112.762 ± 71.194	
Thrombosis	Positive	16	182.250 ± 109.444	**.003a**
	Negative	84	116.724 ± 70.893	
Bleeding	Positive	10	133.676 ± 82.960	**.016a**
	Negative	90	69.000 ± 21.960	
Cardiac complications	Positive	14	122.414 ± 75.346	.813
	Negative	86	127.988 ± 82.629	
Pulmonary complications	Positive	16	192.125 ± 98.183	<**.001a**
	Negative	84	114.843 ± 71.948	
Complement C3	Consumed	34	191.353 ± 76.308	<**.001a**
	Normal	66	94.164 ± 62.067	
Complement C4	Consumed	29	178.345 ± 60.469	<**.001a**
	Normal	71	106.321 ± 79.761	
Joint affection	Negative	4	107.500 ± 20.207	**.025b**
	Arthralgia	60	111.013 ± 70.664	
	Arthritis	36	156.389 ± 94.224	

Table 3. (continued)

SYSTEMIC LUPUS ERYTHEMATOSUS GROUP		IL-17 (PG/ML)		P-VALUE
		N	MEAN ± SD	
Renal biopsy	Normal	68	108.985 ± 70.550	**<.001**[b]
	Class 2	6	112.500 ± 37.891	
	Class 3	10	119.000 ± 30.441	
	Class 4	8	152.633 ± 102.129	
	Class 5	8	288.000 ± 45.981	
SLEDAI-2K score	Mild	51	70.251 ± 25.736	**<.001**[b]
	Moderate	37	169.081 ± 74.495	
	High	12	240.167 ± 58.913	

Abbreviations: IL, interleukin; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.
[a]Independent T-test.
[b]One-way analysis of variance (ANOVA) test.
Bold *P*-value indicates statistical significance.
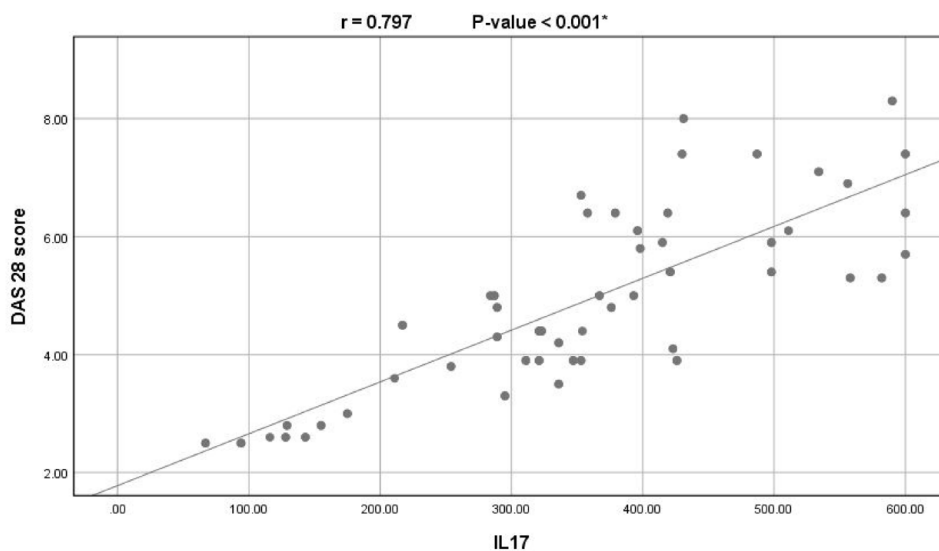

Figure 2. Correlation between serum levels of IL-17 and the DAS28 scores among the RA patients.

Discussion

Biologic therapy for rheumatologic diseases targets immune system molecules and offers an alternative to disease-modifying anti-rheumatic medicines and other immunosuppressive pharmaceuticals. They are not widely used as first-line pharmaceuticals due to their high costs, intravenous delivery, and side effects.[14]

This work aimed to investigate the association between serum levels of IL-17 and the activity of both RA and SLE to find a possible novel target for early intervention, better disease prognosis, and patient outcomes. We found that serum levels of IL-17 were significantly higher in RA and SLE patients compared with the controls. These elevated levels were significantly positively correlated with disease activity biomarkers and scores. This finding can propose IL-17 as an effective treatment target for these disorders as it might be essential in the pathogenesis of both diseases. In addition to its proinflammatory effects, IL-17 recruits monocytes and neutrophils by increasing chemokine production, facilitates T-cell infiltration into the inflamed tissues and its activation by enhancing expression of adhesion molecules, and boosts the immunological response by triggering the synthesis of other cytokines, such as IL-6. The IL-17 also synergizes the interplay between several proinflammatory cytokines. Its receptor is widely distributed; thus, IL-17 can impact the function of many cell types, including non-immune cells such as endothelium and epithelial cells.[15] The primary source of IL-17 is Th17 cells, which could be produced by the effect of IL-6, IL-1, and
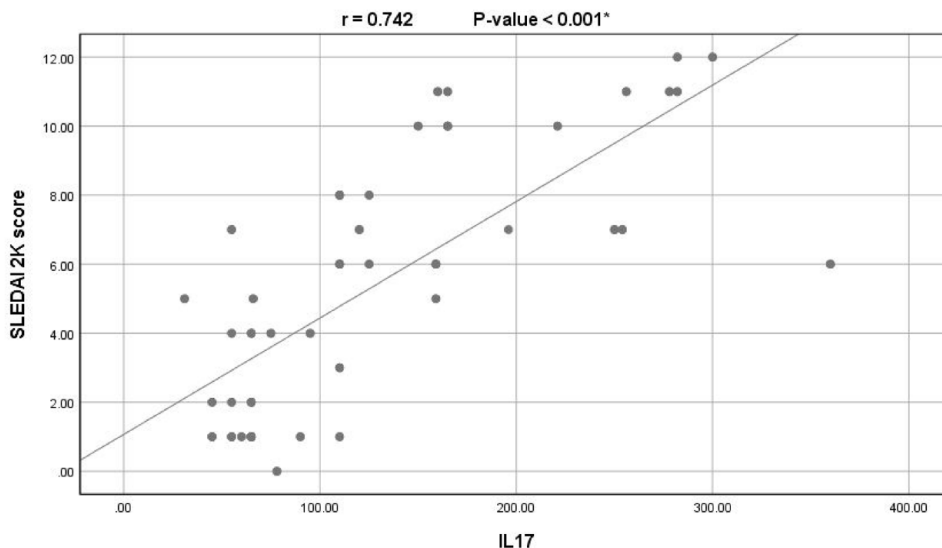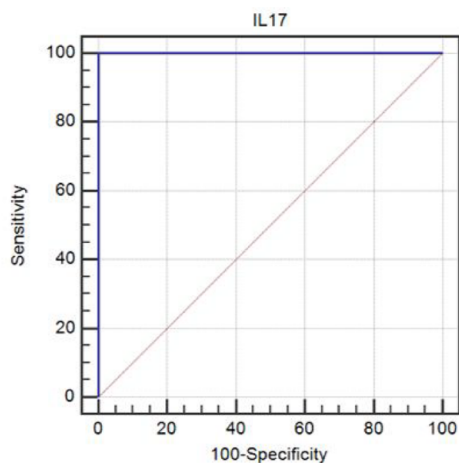
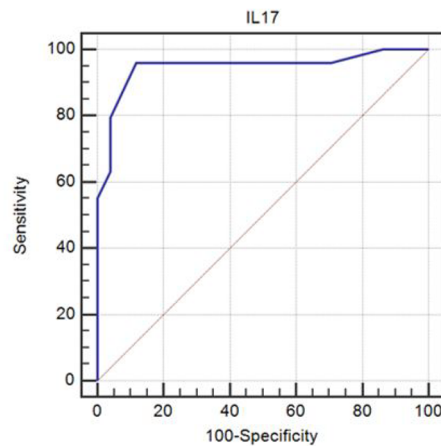**Figure 3.** Correlation between serum levels of IL-17 and the SLEDAI-2K scores among the SLE patients.

IL-17	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
	>175 pg/mL	100%	100%	100%	100%	100%

Figure 4. ROC curve analysis for the predicting ability of serum IL-17 levels between (moderate + high) and (inactive + mild) DAS28 scores among the RA patients.

transforming growth factor β. These cells have the orphan nuclear receptor RORγt as a key transcription factor and IL-23 as a major stabilization and maturation factor.[16] IL-17 could also be produced by various innate cells, including macrophages, and natural killer cells.[17]

Previous reports of the relationship between serum levels of IL-17 and the activity of autoimmune diseases have been inconsistent. Similar to this study, several other studies reported elevated IL-17 levels or IL-17-producing cells in the blood or the inflamed joints of RA patients. They also reported that these elevated levels were associated with disease activity and the extent of joint destruction.[4,18-20] Similarly, Chabaud et al[21]

reported that IL-17 and Th17 cells were present in the synovial tissue of RA lesions, indicating their role in the pathogenesis of RA. In addition, Kirkham et al[19] reported that IL-17 is predictive of joint destruction progression and poor outcome. Studies also found that introducing IL-17 to stromal cells, such as synoviocytes from RA patients, enhanced the production of IL-6 and IL-8.[22] Also, Meng et al reported that IL-17 is closely related to the occurrence of RA. They also reported that using IL-17 in relation to other cytokines could be more suitable in reflecting the treatment effectiveness of RA.[23] Furthermore, Pratama and Widyowati[24] found that IL-17 inhibition has an anti-RA potential. Although there is compelling evidence that

Figure 5. ROC curve analysis for the predicting ability of serum IL-17 levels between (moderate + high) and (mild) SLEDAI-2K scores among the SLE patients.

IL-17	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
	>95 pg/mL	95.92%	88.24%	88.7%	95.7%	94.7%

IL-17 plays a part in aggravating human RA, not all studies completely agree, and there is no solid evidence that IL-17 plays a part in osteoarthritis.[25]

Furthermore, numerous investigations have documented higher serum IL-17 levels in SLE patients compared with controls; these elevated levels were significantly positively correlated with anti-ds DNA titer and disease activity.[26-28] These findings are similar to our own. On the contrary, Vincent et al reported that despite serum IL-17 being significantly elevated among SLE patients compared with controls, its concentration correlated poorly with disease activity. However, IL-17 elevation was significantly associated with central nervous system involvement among their included SLE patients.[9] In addition, Lovato et al[29] reported that anti-IL-17 medications may be useful for treating cutaneous lupus erythematosus (CLE) lesions, as IL-17 expression was considerably greater in CLE/SLE patients. Also, Behiry et al found elevated levels of serum IL-17 in SLE cases. They suggested that IL-17 may have a role in the pathogenesis of SLE. However, they did not find any statistically significant correlations between IL-17 and lupus nephritis nor the SLEDAI score.[30] On the contrary, IL-17 serum levels and SLE activity were not related as well, according to other research.[31,32]

The discrepancy between studies could be attributable to the difference in sample sizes, ethnicity, the age of the included participants, the sensitivity of IL-17 detection methods, the immunosuppressive treatment regimen, and the disease duration. In addition, the production of IL-17 could be localized into the inflamed organs only, like the brain or joints; thus, measuring peripheral blood IL-17 level might not accurately indicate its true levels in the affected organs.[9,33]

Based on the available data, it has been demonstrated that treating autoimmune diseases such as psoriasis, psoriatic arthritis, and ankylosing spondylitis with monoclonal antibodies that target the IL-17 cytokine (secukinumab, ixekizumab) or its receptor (brodalumab) can effectively block the IL-17 secreted by auto-reactive Th17 cells and inhibit IL-17 signaling, leading to better treatment outcomes.[2,34-36] However, because IL-17 and neutrophils are linked, medications that target IL-17 may have unintended consequences that impact acute immune responses. Furthermore, IL-17 can be produced by cells other than TH17, and IL-17 from these cells may have unique (local) functions that make therapies targeting IL-17 less effective.[16] Therefore, a more thorough understanding of the mechanism of action of IL-17 and its inhibitors will help the development of an efficient, targeted therapy with fewer side effects. On the contrary, other studies reported that since several cytokines are implicated in the pathogenesis of autoimmune diseases, a single molecule suppression strategy—such as blocking IL-17—is unlikely to help treat the full range of clinical symptoms. Future research ought to determine which autoimmune disease patients qualify for medication that targets Th17.[37,38]

This study has several limitations being a single-center study with no close follow-up of the included patients. The study also did not look into the different patterns of other cytokines and their localization and did not consider other confounding factors that could have affected our results. Future studies, with proper sample size calculation, should get beyond these obstacles and produce more thorough and therapeutically relevant results by addressing these constraints through careful study design, exacting methodology, addressing clinical and laboratory features at the moment of enrollment, citing

concomitant therapies, and cooperation with other research centers.

Conclusions

Despite not taking into consideration the established treatment protocol for each included RA and SLE patient, this study found a strong association between serum levels of IL-17 and the activity of these autoimmune diseases. This finding highlights IL-17 as a viable therapeutic target for those conditions. For further proof and greater therapeutic benefits, larger-scale research and clinical trials utilizing IL-17-targeting medicines are required.

Declarations

Ethics approval and consent to participate

This study got ethical approval (# FMASUR10/2023) from the Research Ethics Committee, Faculty of Medicine, Ain Shams University. All participants or their legal guardians provided their written informed consent before the start.

Consent for publication

Not applicable.

Author contributions

Sara F Samaan: Conceptualization; Validation; Investigation; Formal analysis.
Sara I Taha: Writing – original draft; Methodology; Investigation; Supervision.
Fatma A Mahmoud: Writing – review & editing; Resources; Investigation; Formal analysis.
Yara Elsaadawy: Conceptualization; Investigation; Writing – review & editing; Resources.
Salma A Khalil: Conceptualization; Investigation; Writing – review & editing; Formal analysis.
Dalia M Gamal: Conceptualization; Investigation; Writing – review & editing; Formal analysis.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All the data needed to support the current findings will be available upon request.

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