

Interleukin-17 in Systemic Lupus Erythematosus and Rheumatoid Arthritis Patients: Correlation with Clinical Presentation, Laboratory Parameters and Activity Indices

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Abstract: Serum interleukin (IL)-17 concentrations have been reported to be increased in systemic lupus erythematosus (SLE), but associations with clinical characteristics are not well understood. Autoimmune diseases such as rheumatoid arthritis (RA), classically believed to be Th1-mediated, are predominantly driven by a Th17 immune response. The aim of the work is to compare the serum levels of IL-17 in patients with SLE and RA, its correlation with clinical presentations, laboratory findings and disease activity in both diseases. The study was carried out on 3 groups. Group I: 20 patients with SLE. Group II: 20 patients with RA. Group III: 10 of age and sex matched healthy subjects as a control group. In this study, there were no statistical significant differences between the three studied groups regarding disease duration, disease activity, laboratory investigations (except HB, WBC and platelet count). The mean serum level of IL-17 were 173.2 ± 52.11 , 82.6 ± 48.17 and 73.07 ± 41.05 for group I (SLE), II (RA) and III (Control) respectively, group I has values statistically higher than other groups, and group II has values statistically higher than group III. Serum IL-17 level was significantly higher in SLE patients compared to healthy group. We concluded that, Serum IL-17 concentration correlates with SLE and RA diseases activity but is significantly elevated in patients with SLE disease. The association of other cytokines with serum IL-17 suggests that IL-17 may drive activation of diverse immune pathways in SLE and RA.

Keywords: IL-17, SLE, RA

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic idiopathic systemic autoimmune disorder characterized by multiple organ damage, particularly the joints, skin, brain and kidneys. [1]

SLE is characterized by both innate and adaptive immune dysregulation, but the relative importance of cytokines operative in these systems is unknown. [2, 3]

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease associated with articular, extra-articular and systemic effects. It has been reported that RA affects ~0.5–1% of the adult population of developed regions. [4] Although some patients have mild self-limited disease, many experience joint destruction, severe physical disability and multiple co-morbidities. [5]

Mortality rates are more than twice as high in patients with RA as in the general population. [6]

T cells, B cells and the orchestrated interaction of pro-inflammatory cytokines play key roles in the pathophysiology of RA. [7, 8]

The cytokines most directly implicated in this process are TNF- α and IL-6; IL-1 and IL-17 may also play important, albeit arguably less so, roles in the disease process. [7]

Interleukin (IL)-17 is the prototypic T helper 17 (Th17) cell pro-inflammatory cytokine. Since the identification of Th17 cells as a third subset of CD4⁺ T effector cells, [2, 3] there has been much interest regarding the role of the Th17 axis in the pathogenesis of autoimmune disease. IL-17 has been associated with the pathogenesis of a range of autoimmune diseases, including rheumatoid arthritis (RA) [9], systemic sclerosis [10], multiple sclerosis (MS) [11], and SLE [12].

Correlations between serum IL-17 levels and SLE disease activity and anti- double stranded DNA (anti-dsDNA) antibody levels have been reported [13, 14]. However the potential relationships between IL-17 and the clinical expression of SLE is lacking. [15]

2. Aim of the Work

To compare the serum level of IL-17 in patients with SLE and RA, it's correlation with the clinical presentations, laboratory findings and disease activity in both diseases.

3. Subject and Methods

The study was carried out on 3 groups. Patients were enrolled from the outpatient clinic of the Rheumatology unit of the Main University Hospital in Alexandria and from the rheumatology ward of the Main Hospital.

Group I: 20 patients with SLE fulfilling systemic lupus international collaborating clinics (SLICC) 2012 criteria for diagnosis of SLE [16]

Group II: 20 patients with RA fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria of RA. [17]

Group III: 10 of age and sex matched healthy subjects as control group.

3.1. All Patients Were Subjects to the Following

1. Clinical study:
 - I. A detailed history taking and a thorough interrogation of different clinical manifestations of the disease.
 - II. Complete physical examination with thorough systemic evaluation particularly for:
 - a In rheumatoid arthritis special emphasis on joint examination for presence of swellings, tenderness or deformities. Also all patients were examined for extra-articular manifestations.
 - b In systemic lupus erythematosus special emphasis on malar rash, photosensitivity, cardiovascular, respiratory, neurological, renal, hematological affections and vasculitic lesions.
 - c The patients clinical charts were extensively reviewed to obtain clinical data and to detect the severity of the disease by:
 - i. SLE Disease activity Index (SLE DAI) score, [18] for lupus patients.
 - ii. Disease Activity score 28 CRP (DAS 28) [19] High disease activity relates to DAS 28 > 5.1, moderate to DAS 28 of 3.2 to 5.1, low disease activity is regarded in the range of 2.6 to 3.2 and remission to DAS 28 < 2.6.
2. Laboratory investigations done included:
 - I. Routine laboratory investigations:
 - a Complete blood picture. [20]
 - b Blood urea, serum creatinine
 - c Hepatic enzymes (AST, ALT)
 - d Complete urine analysis.
 - e Erythrocyte sedimentation rate (ESR)
 - f C-reactive protein (CRP) [21]
 - II. Immunological profile including:
 - a Antinuclear antibody (ANA) [22]
 - b Anti-double stranded antibodies (anti-DNA)
 - c Complement C3, C4. [23]
 - For RA
 - a Rheumatoid factor titre by Rose Waalar test. [24]
 - b Anti citrullinated peptide antibody (ACPA)
 - III. Specific laboratory investigations:
 - a Detection of serum interleukin-17 (IL-17) level using enzyme linked immuno-sorbant assay (ELISA). [25]
 - b Sera were obtained and stored at -20°C until the time of use.

3.2. Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Comparison between different groups regarding categorical variables was tested using Chi-square test. Normally quantitative data was compared using student t-test, or F test (ANOVA), abnormally distributed data was compared using Mann Whitney test or Kruskal Wallis test, Correlations between two quantitative variables were assessed using Pearson or Spearman coefficient according to test of normality. Significance of the obtained results was judged at level of 0.05.

4. Results

The study was carried out on 3 groups. Patients were enrolled from the outpatient clinic of the Rheumatology unit of the Main University Hospital in Alexandria and from the rheumatology ward of the Main Hospital. *Group I:* 20 patients with SLE fulfilling systemic lupus international collaborating clinics (SLICC) 2012 criteria for diagnosis of SLE. *Group II:* 20 patients with RA fulfilling the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria of RA. *Group III:* 10 of age and sex matched healthy subjects as a control group.

4.1. Demographic Data

Table (1) shows demographic data of the studied groups, it demonstrated that:

Age

Age ranged from 22-56, 28-58 and 30-55 years with the mean of 43.1±8.98, 46.8±8.17 and 41.98±8.25 for group I (SLE), II (RA) and III (control) respectively, there were no statistical significant differences between the studied groups regarding age. (P=0.105)

Sex

This study include 2 (10.0%), 3 (15.0%) and 2 (20.0%) males and 18 (90.0%), 17 (85.0%) and 8 (80.0%) females for

group I (SLE), II (RA) and III (control) respectively, there were no statistical significant differences between the studied groups regarding sex. ($P=0.589$)

Disease duration

Disease duration ranged from 3-11 and 2-12 with the mean of 5.11 ± 6.01 and 6.01 ± 3.68 for group I (SLE) and II (RA) respectively, there were no statistical significant differences between the studied groups regarding disease duration. ($P=0.152$).

Table 1. Demographic data of the studied groups.

	Group I "SLE" "n=20"	Group II "RA" "n=20"	Group III "control" "n=10"	p
Age				
Range	22-56	28-58	30-55	0.105
Mean \pm S. D.	43.1 \pm 8.98	46.6 \pm 8.17	41.98 \pm 8.25	
Sex				
Male	2 (10.0%)	3 (15.0)	2 (20.0%)	0.589
Female	18 (90.0%)	17 (85.0%)	8 (80.0%)	
Disease duration			-	
Range	3-11	2-12	-	
Mean \pm S. D.	5.11 \pm 4.19	6.01 \pm 3.68	-	0.152

4.2. Clinical Data

Table (2) shows clinical data of the two studied patients groups, it illustrated that, for group I, malar rash was found in 13 (65.0%), photosensitivity was found in 12 (60.0%), cardiovascular symptoms in 7 (35.0%), respiratory symptoms in 5 (25.0%), neurological symptoms in 6 (30.0%), renal symptoms in 2 (10.0%), hematological abnormalities in 2 (10.0%), for group II, deformities were found in 11 (55.0%), Rheumatoid nodules were found in 2 (10.0%), while swellings were found in 2 (10.0%) and 18 (90.0%), tender joints were found in 1 (5.0%) and 9 (45.0%) for group I and II respectively.

Table 2. Clinical data of the two studied patients group.

	Group I "SLE" "n=20"		Group II "RA" "n=20"	
	No.	%	No.	%
Malar rash	13	65.0	-	-
photosensitivity	12	60.0	-	-
Cardiovascular symptoms	7	35.0	-	-
respiratory symptoms	5	25.0	-	-
neurological symptoms	6	30.0	-	-
renal symptoms	2	10.0	-	-
hematological abnormalities	2	10.0	-	-
vasculitis symptoms	-	-	-	-
Swellings	2	10.0	18	90.0
Tender joints	1	5.0	9	45.0
Deformities	-	-	11	55.0
Rheumatoid Nodules	-	-	2	10.0

4.3. Disease Activity

Distribution of the studied patients regarding the disease

activity were presented in table (3), it showed that, high disease activity was found in 12 (60.0%) and 10 (50.0%), moderate disease activity in 3 (15.0%) and 6 (30.0%), low disease activity in 5 (25.0%) and 4 (20.0%) for group I (SLE), II (RA) respectively, there were no statistical significant differences between the patients groups regarding disease activity. ($P=0.425$).

Table 3. Distribution of the studied patients regarding the disease activity.

	Group I "SLE" "n=20" "SLEDAI"		Group II "RA" "n=20" "DAS-28"	
	No.	%	No.	%
High	12	60.0	10	50.0
Moderate	3	15.0	6	30.0
Low	5	25.0	4	20.0
p	0.425			

Table 4. Comparison between laboratory investigations in the two patients groups.

Laboratory investigations	Group I "SLE" "n=20"	Group II "RA" "n=20"	p
HB g/dl			
Range	8.3 – 11.4	9.5 – 12.7	
Mean \pm S. D.	10.32 \pm 1.41	11.41 \pm 1.31	0.041*
RBCs count			
Range	4.05-5.9	4.01-5.31	
Mean \pm S. D.	5.01 \pm 0.46	4.92 \pm 0.45	0.298
WBCs count			
Range	2.40 – 6.5	3.80 – 9.60	
Mean \pm S. D.	4.92 \pm 1.63	6.91 \pm 3.71	0.0311*
Platelet count			
Range	25.000 – 340.000	166.00 – 530.00	
Mean \pm S. D.	270.0 \pm 122.71	336.1 \pm 89.6	0.039*
ALT			
Range	13.0 – 55.0	15.00 – 43.0	
Mean \pm S. D.	35.11 \pm 19.86	38.00 \pm 11.66	0.125
AST			
Range	25.0 -40.0	21.0 -33.0	
Mean \pm S. D.	36.11 \pm 10.64	28.74 \pm 5.12	0.366
Blood urea			
Range	22-45	24-51	
Mean \pm S. D.	36.9 \pm 6.21	39.8 \pm 8.32	0.107
Serum creatinine			
Range	0.61-1.3	0.55-1.41	
Mean \pm S. D.	0.89 \pm 0.42	0.79 \pm 0.55	0.233
ESR (mm)			
Range	30-140	25-115	
Mean \pm S. D.	72.0 \pm 35.8	74.2 \pm 30.6	0.884
CRP (mg/dl)			
Negative	16 (80%)	0 (0.0%)	
Positive	4 (20%)	20 (100%)	0.000*

4.4. Laboratory Investigations

Distribution of the studied patients regarding the laboratory investigations were presented in table (4), it showed that,

Hg (g/dl)

It ranged from 8.3-11.4 and 9.5-12.7 with the mean of 10.32 ± 1.41 and 11.41 ± 1.31 for group I (SLE) and II (RA) respectively, group II has values statistically higher than group I. ($P=0.041$).

RBCs count

It ranged from 4.05-5.9 and 4.01-5.31 with the mean of 5.01 ± 0.46 and 4.92 ± 0.45 for group I (SLE) and II (RA) respectively, group I has values statistically higher than group II. ($P=0.298$).

WBCs count

It ranged from 2.40-6.5 and 3.80-9.60 with the mean of 4.92 ± 1.63 and 6.91 ± 3.71 for group I (SLE) and II (RA) respectively, group II has values statistically higher than group I. ($P=0.0311$).

Platelet count

It ranged from 25.0000-340.000 and 166.00-530.00 with the mean of 270.0 ± 122.71 and 336.1 ± 89.6 for group I (SLE) and II (RA) respectively, group II has values statistically higher than group I. ($P=0.039$).

CRP

Negative CRP was found in 16 (80%) and 0 (0.0%), while positive CRP was found in 4 (20%) and 20 (100.0%) for group I (SLE) and II (RA).

There were no statistical significant differences between the two studied groups regarding ALT, AST, blood urea and serum creatinine and ESR.

Table 5. Immunological profile for the two studied patients group.

Immunological investigation	Group I "SLE" "n=20"	Group II "RA" "n=20"	P
ANA			
Range	40-640	20-320	
Mean \pm S. D.	266.5 ± 86.5	165.6 ± 65.2	0.001*
Anti-DNA			
Range	30-275	-	
Mean \pm S. D.	125.6 ± 62.5	-	
C3			
Range	0.74-1.47	0.84-1.54	
Mean \pm S. D.	1.1 ± 0.2	1.2 ± 0.2	0.301
C4			
Range	0.09-0.26	0.12-0.23	
Mean \pm S. D.	0.2 ± 0.04	0.2 ± 0.03	0.771
Anti CCP			
-ve	20	7	
+ve	0	13	
RF			
-ve	20	14	
+ve	0	6	

4.5. Immunological Profile

Table (5) shows immunological profile of the two studied patients groups; it demonstrated that, distribution of the studied patients regarding the laboratory investigations were presented in table (4), it showed that:

ANA

It ranged from 40-640 and 20-320 with the mean of 266.5 ± 86.5 and 165.6 ± 65.2 for group I (SLE) and II (RA) respectively, group I has values statistically higher than group II. ($P=0.001$).

Anti-DNA

It ranged from 30-275 with the mean of 125.6 ± 62.5 for group I (SLE) only.

C3

It ranged from 0.74-1.47 and 0.84-1.54 with the mean of 1.1 ± 0.2 and 1.2 ± 0.2 for group I (SLE) and II (RA)

respectively; there were no statistical significant differences between the two studied groups. ($P=0.301$).

C4

It ranged from 0.09-0.26 and 0.12-0.23 with the mean of 0.2 ± 0.04 and 0.2 ± 0.03 for group I (SLE) and II (RA) respectively; there were no statistical significant differences between the two studied groups. ($P=0.771$).

Anti CCP

Negative Anti CCP was found in all patients for group I (SLE) and 7 for group II, while positive Anti CCP was found in 13 patients for group II (RA).

RF

Negative RF was found in all patients of group I (SLE) and 14 patients of group II (RA), while positive RF was found in only 6 patients of group II (RA).

IL-17

Table (6) shows the serum level of IL-17 in the studied groups, it illustrated that, IL-17 ranged from 52-340, 41-251 and 40-108 with the mean of 173.2 ± 52.11 , 82.6 ± 48.17 and 73.07 ± 41.05 for group I (SLE), II (RA) and III (Control) respectively, group I has statistically higher values than the other two groups, and group II has statistically higher values than group III. ($P=0.013$).

Table 6. IL-17 in different studied groups.

	Group I "SLE" "n=20"	Group II "RA" "n=20"	Group III "control" "n=10"
IL-17			
Range	52-340	41-251	40-108
Mean \pm S. D.	173.2 ± 52.11	82.6 ± 48.17	73.07 ± 41.05
p	0.013*		

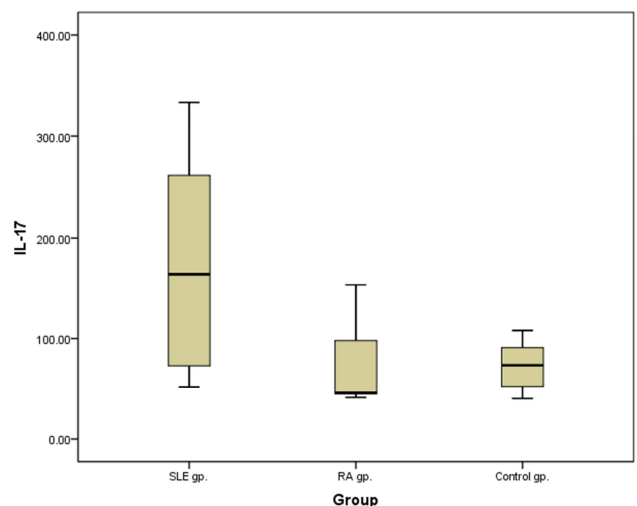


Figure 1. Box-plot illustrated the serum IL-17 levels observed in the three groups included in this study.

4.6. Correlation

Table (7) shows correlation between IL-17 and immunological profile and disease duration and disease activity in the group I and group II, it demonstrated that:

There was positive significant correlation between IL-17 with ANA for group I and II,

There was positive significant correlation between IL-17 with disease activity for both groups I and II.

Table 7. Correlation between IL-17 and immunological profile and disease duration and disease activity in the two patients group.

IL-17#	Group I "SLE" "n=20"		Group II "RA" "n=20"	
	r	p	r	p
ANA	0.442	0.0021*	0.405	0.008*
Anti-DNA	0.398	0.013	-	-
C3	0.109	0.217	0.12	0.311
C4	0.183	0.177	0.19	0.235
Disease duration	0.425	0.005	0.246	0.079
Disease activity	0.66	0.001*	0.42	0.007*

4.7. Relations

Relation between disease activity and IL-17 level was presented in table (8), it showed that, Regarding group I (SLE), the mean of IL-17 was 192.0±46.2, 170.3±36.2 and 160.3±48.2 for high, moderate and low disease activity, with statistical significant differences. (P=0.013)

Regarding group II (RA), the mean of IL-17 was

102.3±1.0, 82.6±39.5 and 67.8±41.0 for high, moderate and low disease activity, with statistical significant differences. (P=0.022).

Table 8. Relation between disease activity and IL-17 level.

	Group I "SLE" "n=20" "SLEDAI"	Group II "RA" "n=20" "DAS-28"
High	192.0±46.2	102.3±1
Moderate	170.3±36.2	82.6±39.5
Low	160.3±48.2	67.8±41.0
p	0.013*	0.022*

Relation between clinical data and IL-17 level was presented in table (9), it showed that,

Regarding group I (SLE), there was statistical significant relation between malar rash, photosensitivity, cardiovascular symptoms, hematological symptoms, swellings and tenderness with the high level of serum IL-17.

Regarding group II (RA), there was statistical significant relation between the presence of swellings and tenderness with the high level of serum IL-17.

Table 9. Relation between clinical data and IL-17 level.

	Group I "SLE" "n=20"		P	Group II "RA" "n=20"		p
	Present	Absent		Present	Absent	
Malar rash	198.3±50.2	168.3±42.3	0.021*	-	-	
photosensitivity	189.2±47.5	162.3±40.3	0.036*	-	-	
Cardiovascular symptoms	197.5±45.6	160.3±38.2	0.041*	-	-	
respiratory symptoms	178.3±41.6	170.3±38.2	0.685	-	-	
neurological symptoms	179.5±45.2	169.5±46.2	0.71	-	-	
renal symptoms	172.6±47.2	175.6±41.8	0.741	-	-	
hematological symptoms	199.2±45.6	160.3±48.2	0.012*	-	-	
vasculitis symptoms	-	-		-	-	
Swellings	204.3±4.98	152.3±57.2	0.002*	98.6±36.6	74.2±35.2	0.013*
Tenderness	189.6±47.2	160.2±45.2	0.004*	90.2±42.6	77.9±41.8	0.021*
Deformities	-	-		84.3±41.3	80.9±39.5	0.365
Rh. Nodules	-	-		86.2±38.7	79.1±39.8	0.175

5. Discussion

Serum interleukin (IL)-17 concentrations have been reported to be increased in systemic lupus erythematosus (SLE), but associations with clinical characteristics are not well understood. [26]

Autoimmune diseases such as RA, classically believed to be Th1-mediated, are predominantly driven by a Th17 immune response. IL-17 (IL-17A, IL-17F, IL-21, IL-22). This results in augmented infiltration of leukocytes, in particular neutrophils to the affected tissue where they induce organ inflammation and injury. [27]

Our study showed that, there were no statistical significant differences between the three studied groups regarding sex, disease duration, disease activity, laboratory investigations (except for HB, WBC and platelet count).

In agreement with our study, Daman, et al., (2014) demonstrated that, HB, and platelet count were statistically higher in RA than SLE. [28]

In this study, there were statistical significant differences between the patients studied groups regarding ANA, Anti-DNA, C3 and C4, SLE group has values statistically higher than RA group.

Jacobs, et al., (2001) demonstrated that, systemic lupus erythematosus patients have values of ANA, C3 and C4 higher than rheumatoid arthritis patients. [29]

In this study, the mean of IL-17 was 173.2±52.11, 82.6±48.17 and 73.07±41.05 for group I (SLE), II (RA) and III (Control) respectively, group I has values statistically higher than other groups, and group II has values statistically higher than group III. Serum IL-17 levels were significantly higher in SLE patients compared to healthy donors.

Fabien, et al., (2013) [26] showed that, the role of IL-17 in the pathogenesis of autoimmune diseases is now well accepted, and as such, IL-17 is a potential therapeutic target. In our study, we reported that serum IL-17 levels were significantly elevated in the serum of SLE patients compared to healthy controls, Fabien, et al., (2013) observed that SLEDAI-2k was positively correlated with IL-17. Serum IL-

17 was significantly increased in SLE patients. and this relationship was observed regardless of disease activity and persisted when integrating cytokine levels over the period observed. [26]

Conversely, other studies showed no correlation in any patient subset. The reason for these discrepancies is unknown, but may be partially attributable to the relatively small sample sizes used in some studies. [30, 31]

In the study on Egyptian RA patients, even though IL-17 serum level did not correlate with the DAS28 score yet it was significantly higher among severely active patients as compared to patients with moderate activity. [32]

In our study, regarding group I (SLE), the mean of IL-17 was 192.0 ± 46.2 , 170.3 ± 36.2 and 160.3 ± 48.2 for high, moderate and low disease activity, with statistical significant differences. Regarding group II (RA), the mean of IL-17 was 102.3 ± 1.0 , 82.6 ± 39.5 and 67.8 ± 41.0 for high, moderate and low disease activity, with statistical significant differences.

This is in agreement with the results of Metawi *et al.* (2011) [33], who reported that there was a direct relation between the serum level of IL-17 and disease activity and severity in RA patients.

Also, Sarkar *et al.* (2014) [34] found that IL-17A increases during inflammatory arthritis and that neutralization of IL-17A reduces the severity of arthritis. Moreover, significantly higher levels of IL-17A were detected in the peripheral blood of patients with rheumatoid.

This is commensurate with the results of Kim *et al.* (2013) [35], who suggest that IL-17 play an important role in RA pathogenesis, and that the level of IL-17A in the peripheral blood is associated with increased disease activity and articular destructive effects, and effusion in RA patients.

Pavlovic *et al.* (2014) [36] found that the mean serum IL-17A levels in patients with early RA corresponded with disease activity and severity. This might highlight the usefulness of the serum IL-17A level in defining the activity and predictive patterns, to aid in aggressive disease therapy, and it might express specific therapeutic targets.

An association between RA and systemic lupus erythematosus (SLE) has been suggested. Similar to RA, IL17 is elevated in the serum of patients with SLE compared to patients without SLE. [37]

6. Conclusions

Serum IL-17 concentration correlates with SLE and RA diseases activity but is significantly elevated in patients with SLE disease. The association of other cytokines with serum IL-17 suggests that IL-17 may drive activation of diverse immune pathways in SLE and RA. Our data raised the hope to use IL-17 as crucial biomarker and therapeutic target in autoimmune diseases specially SLE and RA.

However the limitation of our study was the small sample size, so we recommend further studies to be conducted over larger number of patients with special emphasis on the factors that may influence the serum level of IL-17 like infections other co-morbidities and the effect of some

medications especially biological therapies and Immunosuppressant drugs which have an impact on serum IL-17 concentrations, and thereby may by a confounding factor when analyzing correlation between serum cytokines and disease activity.

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