Sohag University Sohag Medical Journal Faculty of Medicine

Original Article

Study of Interleukin-17 and Fc Gamma Receptor in SLE Patients and Its Relation to Disease Activity and Clinical Presentation

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Abstract

Background: Systemic lupus erythematosus (SLE), a chronic multiorgan systemic autoimmune disease, damages and inflames numerous organs. Interleukin-17 (IL-17) is involved in lupus, its levels are often high in SLE patients. The Fc gamma receptor (FcRs) is crucial for immune system regulation and for allowing communication between humoral and cellular immune responses. **Objective:** In this study, the blood levels of IL-17 and FcR in people with lupus erythematosus were examined, and their relationships with various clinical manifestations, disease activity, and laboratory results were assessed. **Patients and methods:** 100 SLE patients who satisfied the diagnostic criteria for the disease in September 2019 from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) . All of them proceeded to the Sohag University Hospital's outpatient clinic or inpatient unit, where they had comprehensive clinical and medical examinations as well as standard laboratory tests including ANA, anti-dsDNA, C3,C4, and urine albumin creatinine.IL 17 & FcR ELISA assay and renal biopsies are further tests. **Results:** IL-17 was significantly different between mild, moderate and severe SLE with ($p < 0.05$). FcγR had significant positive correlation with Systemic Lupus Erythematosus ($P<0.05$). The results of the analysis for the predicted probability of combined biomarkers in discerning moderate/severe from mild cases of SLE are highly significant, indicates that the combined biomarkers have a very high level of accuracy in distinguishing between these two groups. **Conclusion:** IL17 and FcγR had significant positive correlation with SLE activity indicating their role in activity of SLE.

Keywords: Systemic lupus erythematosus, Interleukin 17, Fc Gamma Receptor, disease activity

DOI: 10.21608/SMJ.2023.211392.1392

Introduction:

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition that affects a variety of organs and is defined by the generation of autoantibodies and the deposition of immune complexes. SLE is thought to be caused by genetic, environmental, and hormonal factors.(1)

Effective targeted therapies have been developed as a result of the interleukin (IL)-17 axis's well-established function in a number of inflammatory and autoimmune diseases. Its significance in the illness is less clear since several other immunological players are weakened in SLE. Blood levels of IL-17 are greater in lupus patients, and organ lesions can be stained to identify the presence of cells that produce IL-17. The vast diversity of clinical symptoms and disease heterogeneity are caused by the IL-17 axis, which promotes the development of autoantibodies, immune complex deposition, complement activation, and tissue destruction through a number of mechanisms.(2)

Immunoglobulin G (IgG) antibody communication with the immune system is regulated and moderated by Fc gamma receptors (FcR), membrane-bound proteins that transmit the data gathered and sensed by antibodies to the immune system. These receptors, which are also glycoproteins, are necessary for this interaction

with the immune system and the stimulation of effector actions such as antibody-dependent cell cytotoxicity (ADCC), complement activation, and phagocytosis.[3]

Patients and Methods:

Study population

- This prospective study recruited 100 SLE patients who satisfied the criteria for the September 2019 SLE diagnosis from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR).[4], attending the outpatient clinic or the inpatient section at Sohag University Hospital.

All patients were subjected to:

- Detailed history& clinical examination.
- Assessment of disease activity index (SLEDAI): Clinical history, physical examination, organ-specific functional tests, and serologic testing will all be used to determine the disease activity. On the day that the serum sample is collected, the overall SLEDAI score will be calculated. Three levels of grading are frequently used: no or mild flare (0 to 3), moderate flare (4–12), and severe (12).[5]
- **The following investigations were performed:**

1. Cobas c311 Chemistry Analyzer System (Roche Diagnostics GmbH, Indianapolis, IN, USA) was used to measure blood glucose and serum creatinine using biochemical tests.
2. Complete Blood Count (CBC): The CELL-DYN 3700 (Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA) was used to perform the CBC .
3. By using the Westergren Method, the 3- erythrocyte sedimentation rate (ESR) was calculated.
4. The Cobas c311 Chemistry Analyzer System (Roche Diagnostics, GmbH, Mannheim, Germany) was used to quantify C-reactive protein (CRP).
5. Physical, chemical, and microscopic study of urine .
6. Protein for 6 to 24 hours: The collection of the 24-hour urine sample for protein estimation began at 8 am on the first day (without the first morning urine sample), and ended at 8 am on the second day (with the first morning urine sample). Between urine samples, the container was stored in the refrigerator. Using a turbidimetric assay and the Cobas c311 Chemistry Analyzer System from Roche Diagnostics, GmbH in Mannheim, Germany, total protein concentration levels were determined. The 24-hour protein concentration was computed as the product of its concentration and the total volume of 24 hours in dl, and it was reported in milligrams (mg.)
7. Urine albumin/creatinine ratio (uACR ratio): Urinary albumin and creatinine concentrations were determined using the Cobas c311 Chemistry Analyzer System (Roche Diagnostics, GmbH, Mannheim, Germany) and immunoturbidimetric assay and kinetic colorimetric Jaffé methods, respectively. By dividing the urinary albumin concentration by the urine creatinine concentration, the uACR ratio in urine samples was determined and represented in mg albumin/mmol creatinine with categories for normal albuminuria (uACR 3 mg/mmol), microalbuminuria (3–30 mg/mmol), and macroalbuminuria (30 mg/mmol).[6]
8. Anti-Nuclear Antibody (ANA) employing HEp-2 cells in an indirect immunofluorescence test (IFA): On fixed HEp-2 cells (ANAFLUOR, DiaSorin, Stillwater, Minnesota 55082-0285, U.S.A.) for 30 minutes at room temperature in a covered damp chamber, 20 to 30 l of diluted serum 1/40 in phosphate buffered saline (PBS) were applied. Slides were thoroughly washed in PBS before being put into a Coplin jar with PBS for about 10 minutes, gently stirred at intervals, and then removed. The excess PBS was then drained from the slides and blotted from the area around the wells using blotting strips after they had been taken from the wash buffer. Antihuman immunoglobulin (FITC)-conjugated fluorescein isothiocyanate (20–30 l) was added to each well and incubated for an additional 30 minutes under cover away from direct sunlight. The slides were read using a fluorescence microscope at 40X power after washing with PBS as previously, a little drop of mounting material was added to each well, and then a coverslip was carefully put over the slide. Every day, tests were conducted along

with positive and negative controls. A serum was deemed affirmative if the nuclei of the cells glow at a level greater or equal to that of the endpoint reference control and if the pattern of fluorescence is easily identifiable. Any positive patient specimen should be verified by running the test again with serum that has been diluted twice. The serial dilution that most closely resembles the fluorescence intensity of the endpoint reference control response is known as the endpoint titer. To identify potential mixed antinuclear responses that might not be seen when evaluating a single screening dilution, all positive ANA patterns should be tittered to endpoint dilution.

9-Anti-double stranded DNA (anti-dsDNA): Anti-ds DNA by IF method was detected by using a commercial kit from (ALPHADIA SA/NV, Avenue Vésale 26, 1300 Wavre, BELGIUM). Crithidia lucilliae was used as the substrate and Approximately 20 – 30 µl of controls and 1:10 diluted patient sera were added to each well. The slide was incubated for 30 minutes in a moist chamber at room temperature. Slides was rinsed carefully with phosphate buffer saline (PBS), then slide was placed into a Coplin jar filled with PBS for about 5 minutes and was repeated using fresh PBS. Then, slide was removed from the wash buffer and the excess PBS was drained and blotted from around the wells using blotting strip. 1 drop (20-30 µl) of FITC IgG Conjugate was delivered per antigen well and incubated for an additional 30 minutes in a moist chamber at room temperature. After washing with PBS as before, 4–5 drops of mounting media were applied to the slide and then a coverslip was placed gently over the slide, and the slide was read using a fluorescence Zeiss-Axiostar plus microscope at 40X power. A positive test was considered at a titer of 1:10 or above.

10- Complement 3 (C3) and complement 4 (C4): Both C3 and C4 were measured by nephlometric immunoassay by using Mispa-i2 (Agappe Diagnostics, GmbH, Knonauerstrasse 54 - 6330 Cham Switzerland). The serum sample reacts upon specific antibody for either human complement C3 or C4 and cause change in absorbance which is directly proportional to concentration of either C3 or C4 consequently in the sample. The reference range for C3 in adults is 90-180 mg/dL while for C4 in adults is 9-36 mg/dL

11- IL -17 & Fc-gamma receptor biomarkers were assessed by Enzyme Linked-Immuno-Sorbent (ELISA):

Using an ELISA kit from SinoGeneClon Biotech Co.,Ltd. in Hangzhou, China, IL -17 and Fc-gamma receptor biomarkers were found in serum samples. Tetramethylbenzidine (TMB) substrate was added and incubated for 15 min. at 37 °C without light for both biomarkers. As the HRP enzyme catalyzed, the TMB substrate became blue. By adding a stop solution that changed color from blue to yellow, the enzyme process was stopped. Thermo Fisher Scientific Oy, FI-01621 Vantaa, Finland) Multiskan EX Microplate Reader was used to detect the absorbance of the color change at 450 nm. Comparing the O.D. of the samples to the standard curve allowed researchers to quantify the amount of human EGF present in the samples.

Detection range:

a-IL-17 :0.5 ng/L -15 ng/L
b-Fc-gamma receptor: 0.78 ng/mL-50 ng/mL

Other investigations also was done

1. Abdominal ultrasound.
2. Electrocardiogram (ECG) & echocardiography (Echo).
3. Renal biopsy. The updated International Society of Nephrology/Renal Pathology Society (ISN/RPS) categorization of lupus nephritis (LN) was applied to renal biopsies from individuals with LN.

Results:

The current study included 100 SLE patients with mean age of 31.5±6.9 years with higher percentage of females (87%) among SLE patients. Regarding clinical presentation, severe cases were significantly associated with fever (88.9%), oral ulcer (83.3%), pleural effusion (69.4%), and neurophsychatric SLE(NPSLE) (52.8%), while mild cases were significantly associated with arthralgia (77.8%) ($P<0.05$).

Pericardial effusion was the only cardiac affection presented in mild, moderate and severe cases of SLE but with no significant difference between groups.

IL-17 was significantly different between mild, moderate and severe SLE with ($p < 0.05$).

FC gamma receptor had significant positive correlation with SLEDAI score (R +ve, P.<0.05). Significant positive correlation between FC gamma receptor and SLEDAI score in all group, as correlation coefficient (r) was positive and P. value <0.05.

IL17 had significant positive correlation with ESR, alb/creat ratio, FC gamma receptor (R +ve, P.<0.05).

FC gamma receptor had significant positive correlation with ESR, serum creatinine, alb/creat ratio, C3, and Anti-dsDNA (R +ve, P.<0.05).

Within all group, IL17 had significant positive correlation with SLEDAI score (R +ve, P.<0.05).).

The results of this study showing that the IL17 level in discerning moderate/severe from mild cases of SLE are highly significant and indicative of a strong discriminatory power.

The results of this study showing that the FC gamma receptor in discerning moderate/severe from mild cases of SLE are highly significant, suggesting a strong discriminatory power.

The results of the analysis for the predicted probability of combined biomarkers in discerning moderate/severe from mild cases of SLE are highly significant, suggesting a very strong discriminatory power indicating that the combined biomarkers have a very high level of accuracy in distinguishing between these two groups.

Table 1 Comparing clinical presentation between groups

Clinical presentation	**Group**						**P.value**
	Mild (n=36)		**Moderate** (n=28)		**Severe** (n=36)		
	N	**%**	**N**	**%**	**N**	**%**	
Fever	12	33.3	4	14.3	32	88.9	< 0.0001*
Alopecia	0	0	2	7.1	5	13.9	0.0694
Oral ulcer	22	61.1	14	50	30	83.3	< 0.0001*
Subacute cutaneous lupus	2	5.6	0	0	0	0	0.1630
Acute cutaneous lupus	0	0	0	0	3	8.3	0.0640
Arthralgia	28	77.8	14	50	9	25	< 0.0001*
Avascular hip necrosis	0	0	2	7.1	0	0	0.0725
Pericardial effusion	14	38.9	8	28.6	16	44.4	0.4267
Pleural effusion	0	0	10	35.7	25	69.4	< 0.0001*
NPSLE	0	0	2	7.1	19	52.8	< 0.0001*

NPSLE: neuropsychiatric lupus
*****P ≤ 0.05 is considered significant

(Table 2) Comparing biomarkers IL17 and FC gamma receptor between groups.

Laboratory results	**Group**			**P.value**
	Mild (n=36)	**Moderate** (n=28)	**Severe** (n=36)	
IL 17 ng /L	217.48±49.35	243.98±12.81	339.07±331.58	0.032*
FcγR ng /L	56.16±4.17	65.66±3.69	73.51±9.97	< 0.001*

IL 17: Interleukin 17, FcγR: FC gamma receptor
Mean ±SD, *P ≤ 0.05 is considered significant

(Table 3): Pearson correlation between biomarkers and laboratory data within all groups:

Laboratory data		**All group**			
		IL17		FcγR	
		R	P.value	R	P.value
ESR	mm/hr	0.7429	<0.0001*	0.450	<0.0001*
S.Creatinine	mg/dl	0.128	0.2059	0.518	<0.0001*
24 h protein		0.065	0.5228	0.145	0.1512
(uACR)	mg/mmol	0.216	0.0308*	0.510	<0.0001*
C3	mg /dl	-0.455	0.0114*	-0.252	<0.0001*
C4	mg/dl	-0.364	<0.0001*	-0.505	0.0002*
AntidsDNA	IU/L	0.160	0.1122	0.461	<0.0001*
IL17		--	--	0.272	0.0061*
FcγR		0.272	0.0061*	---	---

ESR: Erythrocyte Sedmintation Rate, S. Creatinine: Serum Cereatinine, Urine Alb/cereat ratio (uACR), C3&C4: Complement 3 and Complement 4, AntidsDNA: Anti-double Stranded DNA, IL 17: Interleukin 17, FcγR: FC gamma receptor
*P ≤ 0.05 is considered significant

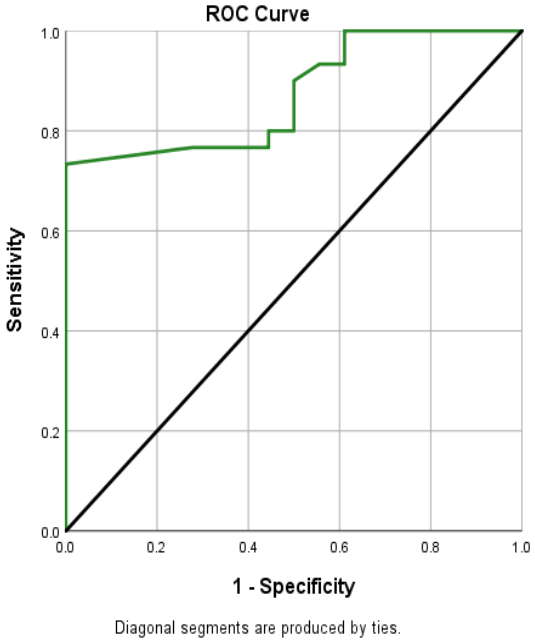

Figure (1): Roc curve of IL17 and for severity of SLE to discern moderate/severe from mild

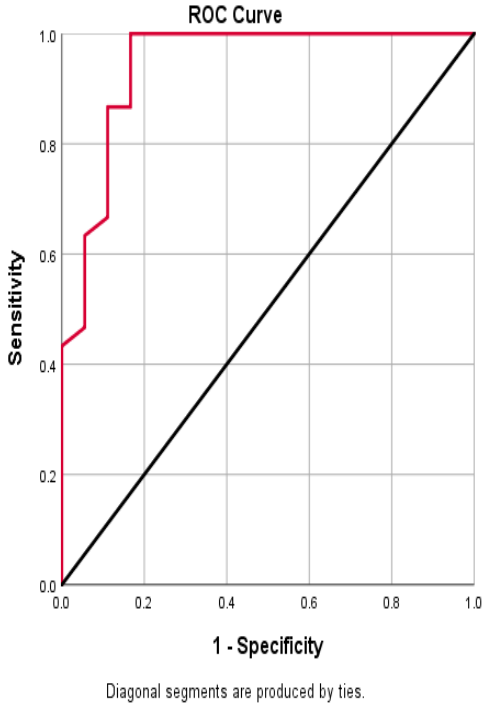

Figure (2): Roc curve of FC gamma receptor and for severity of SLE to discern moderate/severe from mild

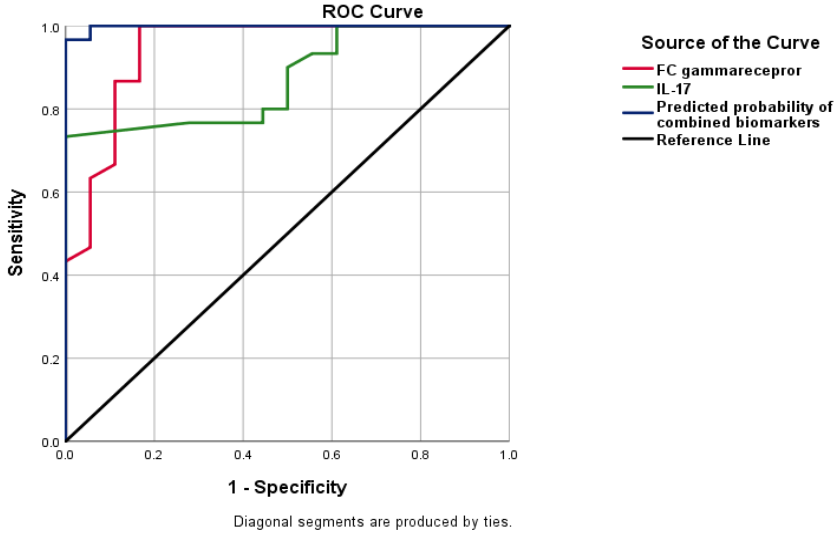

Figure (3): Roc curve of Predicted probability of combined biomarkers and for severity of SLE to discern moderate/severe from mild.

Discussion:

The chronic multi-organ systemic autoimmune disease known as systemic lupus erythematosus (SLE) damages and inflames several organs, most notably the kidneys, by producing autoantibodies to nuclear antigen. It manifests in those who are genetically predisposed to it and is brought on by unidentified environmental circumstances. Autoantibody deposition typically occurs in susceptible vascular beds in the skin, joints, and renal glomeruli, resulting in local tissue damage and inflammation that may intensify the autoimmune response.[7]

A pro-inflammatory cytokine called interleukin (IL)-17A is implicated in the pathophysiology of

several autoimmune and inflammatory disorders. The primary cellular source of IL-17A was first identified as T helper (Th) 17 cells, as opposed to the more traditional Th1 and Th2 subsets. With licensure for psoriasis, rheumatoid arthritis, and ankylosing spondylitis, numerous treatment options are now approved that target the IL-17 pathway and Th17 production.[8]

Fc receptors (FcRs), which are found on many hematopoietic cells, are crucial for the regulation of the immune system through effector pathways mediated by immune complexes. They are crucial for the modulation of the immune system because they provide communication between cellular and humoral immune responses. The activating FcR, which upon interaction with IgG begins phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), transcription of cytokines genes, and release of inflammatory mediators, aids in both the opsonization of antigens and the process of antigen presentation.[9]

This prospective study included 100 SLE patients divided into three groups according to severity by SLEDAI score into 36 mild cases (36%), 28 moderate cases (28%), and 36 severe cases (36%) and aimed at studying the serum level interleukin-17 (IL-17) and Fc gamma receptor (FcγR) levels in lupus erythematosus patients and to evaluate the association with different clinical presentation, disease activity and laboratory findings.

The mean age of systemic lupus erythematous was 31.5±6.9 years ranging from 21 to 53 years with higher percentage of females (87%) among patients in this study. In accordance with our results, Boghdadi & Elewa (2014).[10] studied 40 Egyptian patients with SLE, mean age for lupus patients was 31.1 ± 9.95 years (range 17–50 years); there were 38 females and 2 males.

In the same line, in China a study by Tang et al (2019).[11] studied 140 patients complained from SLE with the mean age of 36.75± 11.42 years. A higher percentage of females (80.7%) than males as reported in our results. The female gender was predominant among previous studies this due to the role of estrogen which may give rise to SLE especially during the pubertal state. This may explain the unmatched female to male ratio.

In the present study, regarding clinical presentation, severe cases were significantly associated with fever (88.9%), oral ulcer (83.3%), pleural effusion (69.4%), and NPSLE(52.8%), while mild cases were significantly associated with arthralgia (77.8%) (P.<0.05) comparing to our results, an gyptian study by Boghdadi & Elewa.[10] found that 55% of SLE patients had fever, 60% had arthritis, 27.5% had NPSLE .

Chen (2012) .[12] reported that arthritis (33% to 67%), malar rash (33% to 100%) and serositis (29 to 50%) were common among SLE patients.

While Karimifar (2021) .[13] described that the most frequent clinical manifestations among 80 SLE patients were rash, arthritis, and leucopenia. This discrepancy was due to the wide spectrum of manifestations of SLE which also influenced by ethnicity, duration of disease and its severity. The previous studies conducted in different locations among patients with different ethnicity. The genetic factors may also play a role in the presentation of disease together with variation in climate.

In this study, within all groups, IL17 had significant positive correlation with ESR, alb/creat ratio, FC gamma receptor (R +ve, P.<0.05). Results of our study disagreed by Galil (2015).[14] who found no significant correlation between IL-17 and ESR. This may due to the variation in the measurement tests of the biological markers.

In the current study, within all group, IL17 had significant positive correlation with SLEDAI score (R +ve, P.<0.05). Significant positive correlation between IL17 and SLEDAI score in all group, as correlation coefficient (r) was positive and P. value <0.05. Severe cases were significantly associated with higher SLEDAI score in comparison to mild and moderate cases (P.<0.05). IL-17 was significantly different between mild, moderate and severe SLE (217.48±49.35, 243.98±12.81 and 339.07±331.58 respectively p <0.05). In a meta-analysis by Lee & Song (2020).[15] IL-17 levels were significantly higher in SLE than healthy controls (standardized mean difference was1.045, 95% confidence interval 0.521-1.568, p＜0.001).

Also, Yin (2021).[16] And Shahin (2017).[17] demonstrated significantly higher median values of IL-17 (48; 25–198 vs. 24.6; 8–42 pg/ml) in SLE patients vs. controls (p < 0.0001).

In contrast to our results, Raymond (2017) .[18] in Australia found that IL-17 did not correlate with SLEDAI among SLE patients. This may be explained by the different age group (49± 16 years) and American nationality of the partic-ipated group.

Unlike our results, Talaat (2015).[19] found no difference in IL-17 level among Egyptian SLE patients in activity as compared to those in remission.

Other explanation may be the sensitivity of tools used as ELISA tests. The confounders were not controlled in all studies as the treatment of SLE as immunosuppressive medications which affect the concentration of serum cytokines. Different disease duration among the studies may contribute to these diversities. More localized production of IL-17 in the affected tissues than in plasma may influence in the variation also.

Also, Elewa (2014).[10] agreed that IL-17 predicted SLE with sensitivity of 77.5% and specificity of 83.3%. The positive predictive value was 86.1 while the negative predictive value was 73.5 with area under the curve of 81.1% at cut off value ≥ 11.5.

In this study, significant positive correlation between FC gamma receptor and SLEDAI score in all group, as correlation coefficient (r) was positive and P. value <0.05.

In accordance with our results, Karimifar (2021).[13] showed that the frequencies of some genotype and allele of FcγR played significant roles in determining SLEDAI. Similar to FcγR, our results indicated that some genotype and allele frequencies of FcγR were significantly correlated to SLEDAI (P<0.001–0.05).

The results of this study by ROC curve showing that the IL17 level in discerning moderate/severe from mild cases of SLE are highly significant and indicative of a strong discriminatory power. The AUC of 0.880 suggests that the IL17 biomarker has a high level of accuracy in distinguishing between these two groups. The sensitivity and specificity values of 73.33% and 100% respectively, further reinforce this conclusion. The cut-off value of 240 is found to be the point of differentiation between mild and moderate/severe cases, with the latter having higher levels of IL17.

The results of this study by ROC curve showing that the FC gamma receptor in discerning moderate/severe from mild cases of SLE are highly significant, suggesting a strong discriminatory power. The AUC of 0.943 indicates that the FC gamma receptor biomarker has a high level of accuracy in distinguishing between these two groups. The sensitivity value of 100% suggests that all patients with moderate/severe SLE have elevated levels of FC gamma receptor, while the specificity value of 83.38%.

The results of the ROC curve analysis for the predicted probability of combined biomarkers in discerning moderate/severe from mild cases of SLE are highly significant, The AUC of 0.998, with a standard error of 0.003, indicates that the combined biomarkers have a very high level of accuracy in distinguishing between these two groups. Also, Elewa.[10] agreed that IL-17 predicted SLE with sensitivity of 77.5% and specificity of 83.3%. The positive predictive value was 86.1 while the negative predictive value was 73.5 with area under the curve of 81.1% at cut off value ≥ 11.5.

Similarly, Galil.[14] agreed that the optimal cutoff level of IL-17 was19.7 pg/ml, with 93.3% sensitivity, 92.9% specificity, 90.3 PPV and AUC 0.95 (95% CI of 0.90–1).

Conclusion:

The study found association between IL-17 and Fc gamma receptor and SLE which suggests that they have a role in the SLE pathogenesis.

Also, IL17 and FC gamma receptor had significant positive correlation with SLE activity indicating their role in activity of SLE.

Recommendations:

Based on the results of our study, We recommend using IL17 and FC gamma receptor in assessment of SLE activity and follow up treatment for proper and early management

Limitations:

This study had limitation which is the absence of control group to compare with SLE patients. Further studies should be done to investigate the role of IL-17 in the pathogenesis and diagnosis of SLE.

Also, another point regarding no recorded cases of antiphospholipid antibody syndrome due to financial aspect

Ethical approval

The Sohag Faculty of Medicine's Ethics Committee gave its approval to the study protocol. All participants gave their informed permission.

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