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Serum progranulin: A potential marker of SLE activity

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Abstract

The assessment of systemic lupus erythematosus (SLE) disease activity is considered a challenge to patients and physicians. In the last few years, there was evidence that progranulin (PGRN) may be involved in the pathogenesis of SLE, so, it might be a suitable marker for the assessment of disease activity. In this study, we aimed to identify the role of PGRN in SLE pathogenesis and its association with disease activity and organ damage. This case-control study included 50 SLE patients, 20 patients with autoimmune diseases other than SLE, and 20 apparently healthy adults as a control group. The concentration of serum PGRN was assayed in all studied participants by using quantitative enzyme-linked immunosorbent assay. The results showed that serum PGRN levels were significantly higher among SLE patients when compared to the group of patients with autoimmune diseases other than SLE, as well as when compared to the control group. There was a significant positive correlation of serum PGRN levels of SLE patients with erythrocyte sedimentation rate, 24 hours urine protein, SLE disease activity index (SLEDAI)-2k score, and SLICC/ACR damage index (SDI) score; while there was a negative correlation with C3, C4 and hemoglobin concentrations. Thus, we concluded that serum PGRN could be a useful biomarker of SLE disease activity.

Keywords: PGRN; SLE; TLR9; ELISA.

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune and inflammatory disease characterized by the polyclonal activation of T and B lymphocytes, production of autoantibodies, and formation of immune complexes that result in tissue and organ damage.[1] Patients with active SLE have increased Toll-like receptor 9 (TLR9) expressions in peripheral blood memory and plasma B lymphocytes. This receptor recognizes unmethylated CpG oligodeoxynucleotides (CpG-ODNs), which are generally not present in mammalian cells. However, in SLE, nucleic acid-containing autoantigens can be released from apoptotic or necrotic cells because of increased apoptosis, reduced clearance of apoptotic cells, and hypomethylation of DNA.[2] Evidence showed that TLR9 signaling increased anti-DNA autoantibody production in murine and human lupus[3].

Progranulin (PGRN) is a protein composed of 593-amino-acids excreted by many cell types

including rapidly cycling epithelial cells, neurons, and cells of the immune system.[4] Progranulin can be subjected to cleavages by serine proteases resulting in release of individual polypeptides of ~6 kDa called granulins (GRN), sometimes also known as epithelins.[5] The GRN peptides not only acts as a reinforcing agent for a combination between CpG-ODNs and TLR9 by its binding to them both, but also heavily promotes CpG-ODNs delivery to the localization of TLR9 inside the vesicular wall of endosome and lysosome. In addition, PGRN is thought to play a proinflammatory role in the development of SLE partially through promoting the production of autoantibodies and enhancing Th1 and Th17 cell responses.[6]

Based on the aforementioned findings, it is hypothesized that serum PGRN might be a useful marker for prediction of SLE disease activity. In the present study, we aimed to investigate the clinical significance of PGRN in patients with SLE regarding its role in pathogenesis and its relation to clinical manifestations and SLE disease activity.

Materials and Methods

This case-control study was conducted at Ain Shams University Hospitals during the period from August 2022 to May 2023. The study included 90 participants who were divided into 3 main groups. Group I included 50 SLE patients fulfilling the scoring criteria of the 2019 European League against Rheumatism and the American College of Rheumatology (2019 EULAR/ACR)[7] and recruited from the Rheumatology Department of Ain Shams University Hospitals. This group was divided according to SLE Disease Activity Index (SLEDAI-2K) [8] score into 25 patients with no/low disease activity (Group Ia), and 25 patients with high disease activity (Group Ib). Group II included 20 patients having autoimmune diseases other than SLE [10 rheumatoid arthritis (RA) patients, 5 autoimmune thyroid diseases patients, 3 type I diabetes mellitus (T1DM) patients and 2 patients with psoriasis]. While group III included 20 apparently healthy adults as the control group. Individuals with infectious diseases, obesity, diabetes mellitus type II, or malignancy, were excluded from the study.

Full medical history was taken from all participants. The SLEDAI-2K[8] activity score and the Systemic lupus international collaborating clinics/American college of Rheumatology (SLICC/ACR) Damage Index (SDI) scoring[9] were performed for all studied SLE patients to assess SLE disease activity and organ damage. Laboratory investigations of SLE patients were retrieved from their hospital medical records. These included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 24 hours urinary protein (24hUP), serum urea, serum creatinine, glomerular filtration rate (GFR), and levels of complement proteins C3 and C4.

Sample collection and assay of serum PGRN

A whole venous blood sample (2 ml) was collected from each study subject under complete aseptic conditions, and added to sterile plain vacutainers. Serum was separated by centrifugation of the blood at 1500×g for 10 minutes and kept frozen (at -20°C). The assay for serum PGRN was performed at the Department of Clinical Pathology, Immunology unit, Ain Shams University by using commercial quantitative ELISA kits (supplied by SunRed Biotechnology Laboratory, Shanghai, China), according to the manufacturer instructions.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), (Version 26.0, IBM Corp., USA, 2019). Data are expressed as median and percentiles for quantitative non-parametric measures in addition to both number and percentage for categorized data. Wilcoxon Rank Sum test was used for comparison between two independent groups for non-parametric data. Ranked Spearman correlation test was used to study the possible association between each two variables among each group for non-parametric data. For categorized data the Chi-square test was used to study the association between each 2 variables or comparison between 2 independent groups. The receiver operating characteristic (ROC) curve was constructed to

obtain the most sensitive and specific cutoff for serum PGRN level discriminating high disease activity from no/low disease activity of SLE patients. The area under the curve (AUC) was calculated for the ROC curve. A value of $p \leq 0.05$ was considered statistically significant.

Results

This study was conducted on 90 participants, comprising 20 males and 70 females, and they were divided into three groups. Group I included 50 SLE patients fulfilling the 2019 EULAR/ACR criteria.[7] They comprised 40 (80%) females and 10 (20%) males, with median (range) of age that was 25.5 (18-48) years. The median (range) of the disease duration was 3(1-12) years. Group II included 20 age and sex matched patients with autoimmune diseases other than SLE. They were 17(85%) females and 3(15%) males, with median (range) of age that was 26 (17-50) years. The median (range) of the duration of their diseases was 5(2-9) years. Group III included 20 apparently healthy age-matched and sex-matched volunteers. They comprised 13(65%) females and 7 males (35%). The median (range) of their ages was 33.5 (10-51) years. There was no statistically significant difference between the three groups regarding age and sex (p value > 0.05), and there was no significant difference between group I of SLE and group II of autoimmune diseases other than SLE regarding the disease duration (p value > 0.05) (Table 1).

Table 1. Comparison between studied groups regarding demographic data (sex, age and duration of the disease).

Parameters		Group I (SLE group) n=50	Group II (Autoimmune diseases other than SLE group) n=20	Group III (control group) n=20	*p*-value
Sex	Female n (%)	40 (80.0%)	17 (85.0%)	13 (65.0%)	*NS
	Male n (%)	10 (20.0%)	3 (15.0%)	7 (35.0%)	
Age (years)	Median (25^{th}- 75^{th})	25.5 (22– 33)	26 (22 – 35)	33.5 (17.0–38.5)	≠NS
	Range	18 – 48	17 – 50	10 – 51	
Duration of the disease (years)	Median (25^{th}- 75^{th})	3 (2 – 5)	5 (3 – 5.5)	-	•NS
	Range	1 – 12	2 – 9	-	

*Chi-square test, ≠ Kruskal-Wallis test, • Mann-Whitney test. $p > 0.05$ is non-significant.

The most frequent clinical manifestations among patients with SLE were joint affection (100%), malar rash (94%), oral ulcers (82%), constitutional symptoms (76%) and photosensitivity (60%) (Figure 1).

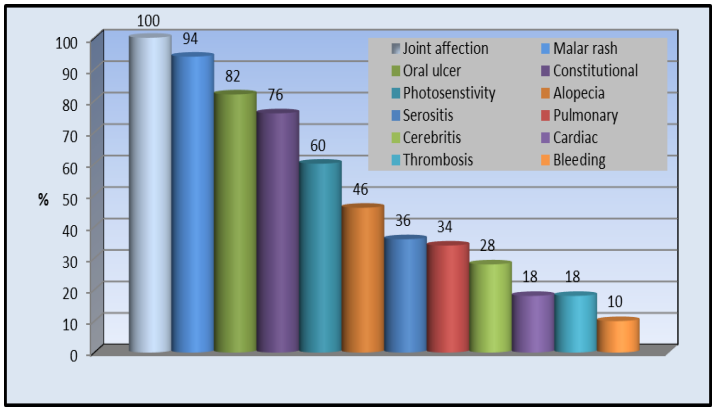

Figure 1. Frequency of clinical manifestations among group I of SLE.

At enrolment, patients with SLE (Group I) were subdivided into two subgroups according to disease activity using SLEDAI-2K score.[8] Group Ia included 25 SLE patients with no/low disease activity, while group Ib included 25 SLE patients with high disease activity. The demographic data, disease duration, SLEDAI-2k score, SDI and routine laboratory tests of both groups Ia and Ib are listed in (Table 2).

Table 2. Clinico-demographic and routine laboratory data of group Ia of SLE with no/low disease activity and group Ib of SLE with high disease activity.

Parameters	Group Ia (SLE with no/low disease activity) n=25	Group Ib (SLE with high disease activity) n=25
Age at enrollment (years):		
Median	25	26
Range	18-42	18-48
Sex:		
Male n (%)	2(8%)	8(32%)
Female n (%)	23(92%)	17(68%)
Duration of the disease (years):		
Median	3	4
Range	1-12	2-10
SLEDAI-2K:		
Median	0	11
Range	0-2	10-11
SDI:		
Median	0	1
Range	0-3	0-3
ESR (mm/hr) (male=0-10 mm/hr; female= 0-12 mm/hr):		
Median	25	55
Range	5-140	30-120
CRP (mg/ dl) (N: 0-6 mg/ dl):		
Median	6	12
Range	0.4-48	3-48
Albuminuria > 30 mg/ dl n(%)	1(4%)	22(88%)
24hUP(mg) (N:0-100 mg):		
Median	100	800
Range	100-300	100-6000

Table 2. Continued.

Parameters	Group Ia (SLE with no/low disease activity) n=25	Group Ib (SLE with high disease activity) n=25
BUN (mg/ dl) (N: 8-23 mg/ dl):		
Median	18	20
Range	18-22	12-75
s. Creatinine (mg/ dl) (N: male=0.7-1.2 mg/ dl, female= 0.5-0.9 mg/ dl):		
Median	0.6	0.6
Range	0.4-5	0.4-2.2
eGFR (mL/min/1.73m^2) (N:>90ml/min/1.73m^2):		
Median	93	93
Range	30-96	35-96
Positive ANA n (%)	24(96%)	25(100%)
Positive Anti-dsDNA n (%)	22(88%)	24(96%)
C3 (mg/ dl) (90-180mg/ dl):		
Median	120	62
Range	85-169	27-140
C4 (mg/ dl) (10-40mg/ dl):		
Median	20	8
Range	8-42	5-22
Positive LAC n (%)	6(24%)	2(18%)
Positive ACL (IgG and/or IgM)(> 20GPL and/ or > 20MPL): n(%)	2(8%)	1(4%)
Heamoglobin (Hb) (g/ dl) (N: male=13-17g/ dl; female=12-15g/ dl):		
Mean (SD)	11.38(1.31)	10.06(1.42)
Range	9-13.8	7.2-13
Total leucocyte count(TLC) (x10^9/l) (N: 4-10 x10^9/l g/ dl):		
Median (25th- 75th)	4.7 (4-6.8)	4.1 (3-5)
Range	2.8-13	2.6-12
Neutrophils (x10^9/l) (N:2-7 x10^9/l):		
Mean (SD)	4026 (1721.86)	4036 (1657.78)
Range	1500-7000	2000-7000
Lymphocytes (x10^9/l) (N: 1-3x10^9/l):		
Median (25th- 75th)	1300 (1200-2000)	950 (850-2000)
Range	800-3050	500-3000
Platelet(PLT) (x10^9/l) (N: 150-400x10^9/l):		
Mean (SD)	220 (84.55)	231.28 (68.77)
Range	25-347	120-369

Comparative statistics showed that patients with SLE had significant increase of serum PGRN levels when compared with the control group (p value < 0.05), as well as when compared to the group of patients with autoimmune diseases other than SLE (p value < 0.05). Similarly, serum PGRN of patients with autoimmune diseases other than SLE showed a significant increase compared to control group (p value < 0.05) (Table 3).

Table 3. Statistical comparison of serum PGRN level between the studied groups (group I SLE patients, group II autoimmune diseases other than SLE, and group III controls).

	Group I vs Group III		Group I vs Group II		Group II vs Group III	
	Group I (SLE) n=50	Group III (Controls) (n=20	Group I (SLE) n=50	Group II (Autoimmune diseases other than SLE) n=20	Group II (Autoimmune disease other than SLE) n=20	Group III (Controls) n=20
Median (25^{th}- 75^{th})	247.5 (185-395)	45 (38-50)	247.5 (185-395)	203.5 (124-306.25)	203.5 (124-306.25)	45 (38-50)
Range	95-760	30-55	95-750	100-430	100-430	30-55
^{Z}p value	<0.05		<0.05		<0.05	

^{z}Wilcoxon Rank sum test. $p \leq 0.05$ is significant.

Comparative statistics showed that Group Ib of SLE with high disease activity had significantly higher serum level of PGRN as compared to Group Ia of SLE with no/low disease activity (p<0.05) (Table 4).

Table 4. Comparison of serum progranulin (PGRN) level between Group Ia (no/low SLE disease activity) and Group Ib (high SLE disease activity).

PGRN (ng/ml)	Group Ia (SLE with no/low disease activity) n=25	Group Ib (SLE with high disease activity) n=25
Median (25^{th}- 75^{th})	185 (147.5-215)	385 (331.5-585)
Range	95-245	250-760
^{Z}p value	<0.05	

Z=Wilcoxon Rank sum test. $p \leq 0.05$ is significant.

Among SLE patients (Group I), serum PGRN level had significant positive correlation with SLICC/ACR damage index (SDI) (r=0.502, p<0.05) (Figure 2).

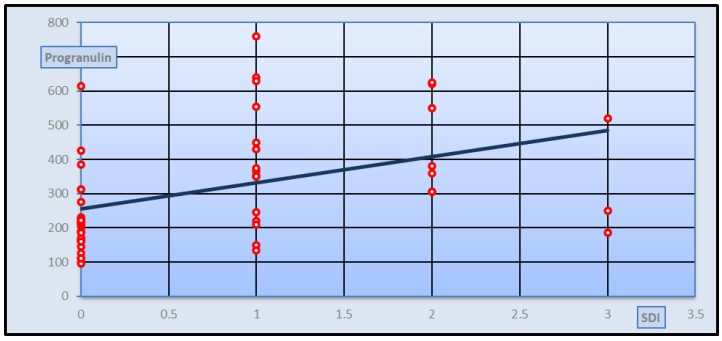

Figure 2. A significant positive correlation between serum progranulin (PGRN) level and Slicc damage index (SDI) score in the studied SLE patients (Group I).

The SLEDAI-2K score of SLE activity includes laboratory parameters which are urinary casts, heamaturia, proteinurea, pyuria, low complement level, increased DNA binding, thrombocytopenia, and leucopenia. In the present study, some of these activity markers were fulfilled in the patients' records such as 24hUP, C3, C4, total leukocyte count (TLC) and platelet (PLT) count. Study of the correlation of serum PGRN level in Group I of studied SLE patients with laboratory parameters revealed a significant positive correlation of serum PGRN level with SLEDAI-2k score and 24hUP (p value < 0.05) while there was a significant negative correlation of serum PGRN level with C3 and C4 levels (p value < 0.05). On the other hand, there was no significant correlation of serum PGRN level with TLC and PLT count with (p value > 0.05) (Table 5).

Table 5. Correlation of serum progranulin (PGRN) level with SLEDAI-2K and the studied laboratory activity parameters in the studied SLE patients.

	PGRN of SLE patients	
	r	*p* value*
SLEDAI-2K score	0.825	<0.05
24h.UP	0.727	<0.05
C3	-0.584	<0.05
C4	-0.633	<0.05
TLC	-0.208	NS
PLT count	-0.086	NS

SLEDAI-2K: The Systemic Lupus Erythematosus Disease Activity Index 2000; 24hUP: 24h urine protein, C3: complement 3, C4: complement 4, TLC: Total leukocyte count; PLT: platelet *Rank spearman correlation test. p > 0.05 is not significant (NS).

The ROC curve analysis revealed that the best cut-off point of serum PGRN level for differentiation between Group Ia of SLE with no/low disease activity and Group Ib of SLE with high disease activity was 250 ng/ dl, with a sensitivity and a specificity of 100%, positive and negative predictive values of 100%, at an area under the curve of 1 (Table 6) and (Figure 3).

Table 6. Receiver operating characteristic (ROC) curve analysis to discriminate Group Ia (no/low disease activity) from Group Ib (high disease activity) of SLE by serum PGRN level.

AUC	95% confidence interval	Cut off point (ng/ml)	Sensitivity %	Specificity %	PPV %	NPV %	*p* value
1	0.915-1.005	>250	100	100	100	100	<0.05

AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value. $p \leq 0.05$ is significant.

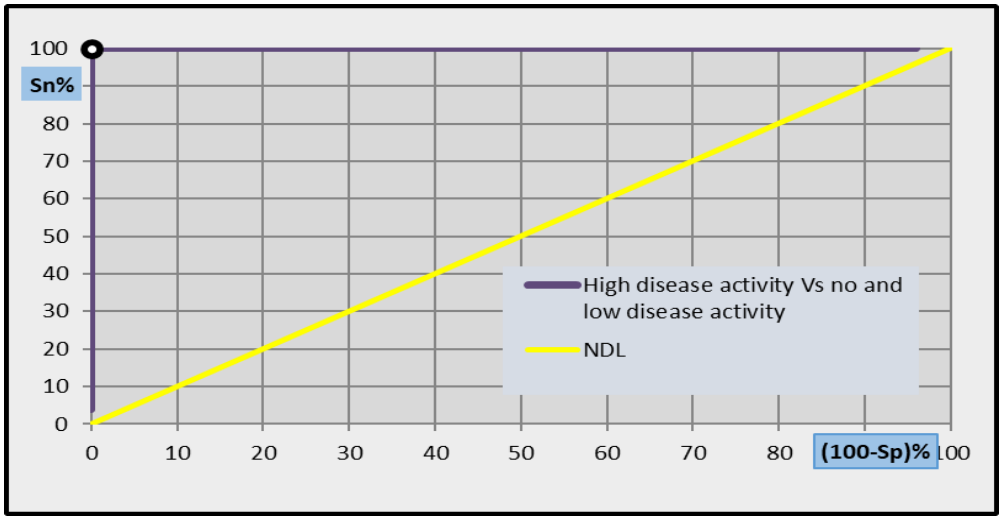

Figure 3. Receiver operating characteristic **(**ROC) curve to discriminate Group Ia from Group Ib of SLE by serum PGRN level.

Discussion

The current case control study was carried out to evaluate the clinical significance of serum PGRN in correlation to SLE activity. The level of serum PGRN was measured in all subjects included in our study and showed a significant increase in patients with SLE in comparison to controls. Our results agreed with those of the study by Tanaka et al., 2013,[1] Qiu et al., 2013,[10] and Ibrahim et al., 2020.[11] Using an animal model, the study conducted by Jing et al., 2020[6] observed that inflammatory cell infiltration, tissue edema, and necrosis were alleviated in PGRN-/- SLE mice and the levels of serum chemistry markers of tissue damage and the presence of anti-double-stranded DNA and anti-ribosomal antibodies were all significantly decreased compared with PGRN wild type SLE mice. These findings prove that PGRN plays a proinflammatory role in the development of SLE.

In the current work, a significant increase of median serum PGRN level was found in the SLE group as compared to the group of autoimmune diseases other than SLE. Our study included heterogeneous group of patients and the activity state of those patients was not assessed. To the best of our knowledge, no previous published literature with the same study design is available. However, Tanaka et al., 2013[12] found a significantly higher serum PGRN levels in the SLE patients when they were compared to rheumatoid arthritis patients.

In the present study, the group of patients with autoimmune diseases other than SLE had significantly elevated levels of serum PGRN levels in comparison to the control group. Chen et al., 2016,[13] Fouad et al., 2019[14] and Kong et al., 2020[15] found that serum PGRN levels in patients with RA were much higher than in the normal controls. The research work done by Abass et al., 2021[16] revealed a significant increase in serum PGRN levels in patients with thyroid illness causing whether hypo- or hyperthyoisdism compared with the normal control group. A study done by Rohoma et al., 2021[17] found higher levels of serum PGRN levels in subjects with T1DM when compared to controls. In addition, the research work by Abdel Gaber et al., 2020[18] showed significantly higher levels of serum PGRN levels in patients with psoriasis than in the controls. As mentioned by Huang et al., 2024[19] PGRN was identified as a crucial molecule in inflammation and developmental of disease processes, including autoimmune diseases, which supports our findings.

In the current study, serum PGRN levels were significantly higher in Group Ib of SLE patients with high disease activity compared to Group Ia of SLE patients with no/low disease activity. The

findings of studies by Tanaka et al., 2012,[1] Qiu et al., 2013,[10] Jian et al., 2013,[20] Wu et al., 2016[21] and Ibrahem et al., 2020[11] agreed with our results, and they all considered PGRN as a useful biomarker for SLE activity. This could be due to the proposed proinflammatory role of PGRN in SLE through promotion of autoantibody production and increasing proinflammatory cytokines by enhancing Th1 and Th17 cell responses.

A significant positive correlation was found between serum PGRN levels and SDI among the studied group of SLE patients indicating that serum PGRN could be used as a biomarker of internal organ damage. Progranulin has been shown to contribute to tissue damage in animal models of SLE, with PGRN-deficient mice exhibiting reduced inflammation and tissue damage compared to wild-type mice.[22] In the current research we conducted correlation for serum PGRN level with SLEDAI-2K and the studied laboratory activity parameters included in SLEDAI-2k among the group of SLE patients. Our data revealed a significant positive correlation between serum PGRN level with SLEDAI-2K and 24hUP. In addition, data showed a significant negative correlation between serum PGRN levels and levels of C3 and C4. Similar results were mentioned by Tanaka et al., 2013[12] as they indicated that serum PGRN levels had a significant positive correlation with SLEDAI, and were inversely correlated with C3, and C4 levels. Also, the research by Goma et al., 2017[23] found a significant negative correlation between serum levels of PGRN and serum levels of C3 and C4 in the studied SLE patients. Other studies done by Rong, 2019[24] and Ibrahem et al., 2020[11] found a positive correlation between serum PGRN levels and SLEDAI score within SLE patients.

However, we could not prove any significant correlation between serum PGRN and TLC or PLT count. On the contrary, the research by Tanaka et al., 2013[12] reported that the levels of serum PGRN were significantly related with the presence of thrombocytopenia and leucopenia. Also, Ibrahem et al., 2020[11] showed a statistically significant increase in the levels of PGRN in SLE patients with leukopenia compared to SLE patients with TLC within the reference range. The discrepancy may be due to the relatively smaller sample size in the current study. In addition, SLE activity was estimated by SLEDAI-2K score which included multiple clinical and laboratory parameters, and not by specific parameter alone. This increased the accuracy in diagnosing activity for better treatment and follow up. So, it is much more important for any suggested biomarker of SLE activity to correlate with SLEDAI-2k score rather than correlating with specific laboratory parameter, which was proved for serum PGRN, as shown in the current study.

By using the ROC curve analysis, calculation of serum PGRN level was able to discriminate between cases of SLE with no/low disease activity from those with high disease activity at a cutoff value of 250 ng/ml showed sensitivity and specificity of 100%, at AUC of 1.00. To our knowledge, no previous published studies performed this statistical analysis between SLE patients with no/low disease activity, and those with high disease activity. However, Wu et al., 2016,[21] analyzed a ROC curve for serum PGRN levels used in discriminating active lupus nephritis (LN) patients from stable LN or non-LN patients, and the used cutoff values were 159.4 ng/ml and 144.9 ng/ml, respectively. In their study, serum PGRN levels had a relatively weak performance in differentiating active LN from stable LN, which was evidenced by low sensitivity (52.6 %) and AUC (0.673).

In conclusion, the present study demonstrated that the serum levels of PGRN were elevated in patients with SLE and associated with the systemic disease activity. Patients with SLE with higher SLEDAI scores had higher serum PGRN levels, so PGRN level might play a role in pathogenesis of SLE and may have a potential value as a predictor of disease activity.

Author Contributions

DG, recruited patients, collected the samples, and performed the clinical assessment. MA, performed the laboratory work, statistical analysis and analyzed the data. NW and FM, drafted the paper. YZ and DS, revised the paper critically. All authors contributed significantly to the study's conception, design, and final approval of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (FMASU MS 447/2022).

Informed consent

An informed consent was obtained from every participant before being enrolled in this study.

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