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The Pattern of Soluble Urokinase Plasminogen Activator Receptor (suPAR) Levels in Lupus Nephritis and Its Correlation with Renal Biopsy

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is systemic autoimmune disease with variable clinical presentations. Lupus nephritis (LN) is type of glomerulonephritis that affect SLE patients and considers one of the most serious organ manifestations of SLE. SLE patients may develop LN within 5 years of SLE diagnosis and, in many cases, LN is the presenting manifestation.

Objective: Our study aimed to determine the value of suPAR levels in lupus nephritis patients and its correlation with renal biobsy.

Patients and Methods: This study was conducted in the Outpatient Clinics of Internal Medicine of Zagazig University Hospitals, Egypt, on 90 subjects both females and males. These participants were divided into three groups: Group (A): Comprised 30 SLE patients according to the 2019 EULAR/ACR classification criteria for SLE, without LN. Group (B): Included 30 SLE with LN patients. Group (C): Involved 30 healthy individuals were chosen with age and sex matching previous groups. Soluble urokinase plasminogen activator receptor (suPAR) was measured for all groups.

Results: Our study revealed there was statistically significant increase suPAR in LN and SLE patients compared to control participants and also in LN patients compared to SLE patients. There was a statistically significant positive correlation between suPAR and LN class in LN patients as suPAR level increased with increased degree of LN class. Our results show suPAR had sensitivity 93.3%, specificity 90% and accuracy 91.7% in diagnosis of LN.

Conclusion: Circulating suPAR can be considered a good marker to identify high risky patients with disease progression especially LN.

Keywords: Soluble Urokinase Plasminogen Activator Receptor, Lupus Nephritis, Inflammatory Biomarker, Immune Disease, Systemic Lupus Patients.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a worldwide autoimmune disease which causes significant morbidity and mortality rates. It is characterized by the loss of self-tolerance and formation of nuclear autoantigens and immune complexes, which results in systemic inflammation involves multiple organs such as skin, joints, kidneys and nervous system [(1)].

Lupus nephritis (LN) is a common sever organ manifestation of SLE which affects about 40% of SLE patients within 5 years of onset of the disease. Despite of ever-evolving diagnostic and therapeutic methods, LN still causes high rates of end-stage renal disease (ESRD) development and high mortality rates [(2)].

Soluble urokinase plasminogen activator receptor (suPAR) is an emerging inflammatory biomarker generated from shedding of urokinase plasminogen activator receptor (uPAR), which is a membrane-bound receptor acts as biological mediator of inflammation and host immunological response. Circulating suPAR is upregulated in cases of chronic inflammation and consequent immune response, and it is less likely to be affected by acute changes, unlike C-reactive-protein (CRP). Therefore, suPAR acts as a prognostic inflammatory marker which can predict the prognosis and mortality of several diseases [(3)].

Despite the improvement in diagnosis and treatment of SLE, still there is a need for new biomarkers in LN prediction, diagnosis and follow up, as the classic parameters such as GFR, urine sediment, proteinuria, anti-dsDNA and complements level are not sensitive or specific enough in detection and follow up of LN [(4)].

AIMS OF THE STUDY

This study aims to determine the value of suPAR levels in SLE patients and its role in prediction of LN.

PATIENTS AND METHODS

A prospective, comparative, case-control study was conducted in the outpatient clinics of Internal Medicine of Zagazig University Hospitals, Egypt (from 30/6/2021 to 30/3/2022).

Ethical consent:

Approval for performing the study was obtained from Internal Medicine Department and Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. All the procedures used in the present study were in keeping with the current revision of the Helsinki Declaration. All participants were informed of the various aspects of the study, and they were enrolled only after providing a signed consent form.

This study involved 90 subjects both females and males, their ages ranged from 18 to 58 years old. Sixty patients were diagnosed to have SLE according to

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the 2019 EULAR/ACR classification criteria for SLE, including positive ANA test at least once as obligatory entry criterion and a total score of ≥10 points of additive weighted criteria of SLE. These participants were divided into three groups:

Group (A): SLE patients without any SL manifestation:

This group comprised 30 SLE patients (28 females and 2 males with percentage of 93.3% and 6.7% respectively), their ages ranged from 18-55 years with mean ± SD: 32.7±10.63 years. They were sampled during routine visit in Internal Medicine Outpatient Clinic. At the baseline, SLICC/ACR Damage Index (SDI) was zero, proteinuria < 0.5 g/day, no hematuria or urinary casts sediment and all of them have normal kidney functions (S. creatinine <1.1 mg/dl in female or <1.2 mg/dl in male). These patients were followed up for 9 months, SDI was scored after 9 months of follow up.

Group (B): SLE patients with LN:

This group included 30 SLE with LN patients (28 females and 2 males with percentage of 93.3% and 6.7% respectively), their ages range from 18-49 years with mean ± SD: 31.37±7.42 years. They were sampled during routine visit to Internal Medicine Outpatient Clinic, all have evidenced clinical nephritis: proteinuria > 0.5 g/day and some patients have elevated serum creatinine level (> 1.1 mg/dl in female and > 1.2 mg/dl in males). All the patients in this group had a renal biopsy and were proved to have lupus nephritis. Renal biopsies were classified according to the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 classification and its modification published in 2018.

The renal disease was:

Class II in 2 patients (mesangial proliferative lupus nephritis) (6.7%). Class III in 9 patients (focal lupus nephritis) (30%). Class IV in 11 patients (diffuse lupus nephritis) (36.7%). Class V in 8 patients (membranous lupus nephritis) (26.7%).

Group (C): Control group:

This group comprised 30 healthy individuals (23 females and 7 males with percentage of 76.7 % and 23.3 % respectively) are chosen with age and sex matching previous groups. Their ages range from 20-58 years with mean ± SD: 36.63±9.54 years, they don`t have any immunological disease or other medical disorders.

All the patients participating in this study was chosen according to the following criteria:

Inclusion Criteria: All patients in both groups (A) and (B) are diagnosed to have SLE according to the 2019 EULAR/ACR classification criteria for SLE, including positive ANA test at least once as obligatory entry criterion and a total score of ≥10 points of additive weighted criteria of SLE, and all SLE patients and healthy participants aged 18-60 years old.

Exclusion Criteria: Patients with diabetes mellitus and other severe concomitant diseases. Patients with urinary tract infections, urinary stones or any urological problem, acute renal failure and dehydration. Advanced CKD patients. Patients with ESRD whether on hemodialysis or not. Patients with pregnancy, other autoimmune diseases, chronic inflammatory diseases or malignancies. Patients with cognitive dysfunction, not personally dependent based on assessment (unable to do their own activity), and patients unable to provide informed consent.

Methods: According to the inclusion and exclusion criteria set for this study, patients and healthy participants' selection were done as following: Full medical history and clinical examination was done to exclude any hidden medical problems especially undiscovered DM, chronic liver diseases or other causes of glomerulonephritis, and detection of any of the following: malar flush, photosensitivity, alopecia, oral ulcers, arthritis, Raynaud's phenomenon, pleurisy or pleural effusion, pericarditis or pericardial effusion, convulsions or cerebral accidents. The SLICC/ACR Damage Index (SDI) was measured for group (A) patients at time of sampling and after 9 months of follow-up.

The following laboratory investigations for all participants in the study were done after having written informed consent:

Random blood glucose. Kidney functions test (serum creatinine and blood urea). Estimated Glomerular Filtration Rate (GFR) by MDRD equation. Urine albumin/creatinine ratio (ACR). Urine analysis. Urine sediment. Erythrocyte sedimentation rate (ESR). C-reactive protein (CRP). Liver functions test (ALT, AST, serum albumin, total protein, direct bilirubin and total bilirubin). Complete blood count (CBC). Serum total calcium. Serum phosphorus. Serum parathyroid hormone (PTH). Antinuclear antibody (ANA). Anti-double stranded DNA antibodies (Anti-dsDNA). Complement c3. Complement c4. Soluble urokinase plasminogen activator receptor (suPAR) ELISA.

Estimated Glomerular Filtration Rate "GFR" Calculation: GFR was calculated for all participants in the study by using the MDRD equation of the National Kidney Foundation GFR mobile application.

"GFR (mL/min/1.73 m2) = 175 × (S.cr)-1.154 × (Age)-0.203 × (0.742 if female).

Albumin to creatinine ratio (ACR): Albumin-to-creatinine ratio (ACR) is the first method of preference to detect elevated protein. The recommended method to evaluate albuminuria is to measure urinary ACR in a spot urine sample. ACR is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams.

Assessment of renal disease pathology: After having written informed consent of the patients in group (B), sonar guided renal biopsy was taken by specialized

radiologist and classified according to the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 classification and its modification published in 2018.

Sampling:

Ten ml of venous blood were drowned under complete aseptic condition then divided into: Two ml for CBC (in EDTA solution) and shaken perfectly then examined immediately. Two ml for ESR (in Na citrate) shaken perfectly then examined immediately. Six ml for ANA, Anti ds-DNA, C3, C4, KFTs, LFTs, CRP, serum calcium, serum phosphorus, PTH and suPAR (in empty tube) were centrifuged at 1000 xg for 10 minutes, and sera were separated and were stored at -70◦C until use. Random urine sample is collected in sterile container and stored until use for urine sediment and ACR in urine measurement.

Laboratory Technique:

Soluble urokinase plasminogen activator receptor (suPAR): Was estimated by ELISA kits of (Shanghai Sunred Biological Technology Co., Ltd). Assay range: 5pg/ml→1000pg/ml.

Statistical Analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 27.0. Qualitative data were represented as frequencies and relative percentages, Chi square test was used to calculate difference between qualitative variables, as following: Quantitative data were expressed as mean ± SD (Standard deviation). Median: The mildest observation after arranging data into ascending or descending manner. Inter quartile range (IQR): Range between 25th percentile and 75th percentile of the observations. Independent T test was used to calculate difference between quantitative variables in two groups in normally distributed data. Mann Whiteny (MW) test was used to calculate difference between quantitative variables in two groups in not normally distributed data. ANOVA F-test test was used to calculate difference between quantitative variables in more than two groups in normally distributed data. Kruskal Wallis test was used to calculate difference between quantitative variables in more than two groups in not normally distributed data. Pearson's, spearman's correlation coefficient used to calculate correlation between quantitative variables. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of different parameters with maximum sensitivity and specificity for prediction of the outcome. P value < 0.05 was considered significant.

RESULTS

There were no statistically significant differences between the studied groups in age or sex distribution **Table (1)**.

Table (1): Demographic data of the studied groups:

Variable	Group A (SLE) (n=30)		Group B (LN) (n=30)		Group C (Control) (n=30)		F	P
Age: (years):								
Mean ± SD	32.7±10.63		31.37±7.42		36.63±9.54		2.6	0.08
Range	18-55		18-49		20-58			NS
Variable	**No**	**%**	**No**	**%**	**No**	**%**	**χ^2**	**p**
Sex:								
Female	28	93.3	28	93.3	23	76.7	5.18	0.08
Male	2	6.7	2	6.7	7	23.3		NS

SD: Stander deviation, F: ANOVA test, χ2: Chai square test, NS: Nonsignificant (P>0.05).

There was a statistically significant difference between the studied groups in suPAR level. Post hook test showed that there was a statistically significant increase suPAR in LN and SLE group compared to Control group and also in LN group compared to SLE group **Table (2)**.

Table (2): suPAR level among the studied groups:

Variable	Group A (SLE) (n=30)	Group B (LN) (n=30)	Group C (Control) (n=30)	F	P	Post hook
suPAR (pg/ml): Mean ± SD	101.23±15	168.34±31.53	58.37±6.43	184.53	<0.001 **	**<0.001**^{**1} **<0.001**^{**2} **<0.001**^{**3}

SD: Stander deviation, F: ANOVA test, **: Highly significant (p<0.001),
Post Hook: P1: Group A versus B, P2: Group A versus C, P3: Group B versus C.

That 6.7% of group B were grade II, 30% were grade III, 36.7% were grade IV and 26.7% were grade V **Table (3)**.

Table (3): LN classes results among LN group:

Variable	Group B (LN) (n=30)	
	No	%
LN class:		
II (mesangial proliferative LN)	2	6.7
III (focal LN)	9	30
IV (difuse LN)	11	36.7
V (membranus LN)	8	26.7

There was a statistically significant increase in suPAR level with increase stage of renal biopsy among Group B (LN) **Table (4)**.

Table (4): Relation between suPAR level and LN classes among Group B (LN):

Variable	No	suPAR			F	P
		Mean	SD	Range		
LN class:						
II(mesangial proliferative LN)	2	113.45	5.73	111.5-119		
III (focal LN)	9	152.34	24.81	128.4-181.2	**7.33**	**0.001***
IV (difuse LN)	11	174.13	29.85	109-205.4		
V (membranus LN)	8	192.09	18.85	152-234		

SD: Standard deviation, F: ANOVA test, *: Significant (p<0.05).

There was a statistically significant –ve correlation between suPAR and C3, C4, GFR, albumin and protein level among the studied cases groups. Also, there was a statistically significant +ve correlation between suPAR and SDI score, biopsy degree, Ph, PTH, creatinine, urea, ACR and ESR 2nd h among the studied cases groups **Table (5)**.

Table (5): Correlation between suPAR and age & Laboratory parameters among the studied cases groups:

Variable	suPAR (n=60)	
	r	P
Age (years)	0.02	0.87 NS
LN Class	**0.32**	**0.02***
C3: (mg/dl)	**-0.38**	**0.002***
C4: (mg/dl)	**-0.39**	**0.002***
Ca: (mg/dl)	-0.08	0.53 NS
Ph: (mg/dl)	**0.34**	**0.008***
PTH: (pg/ml)	**0.46**	**<0.001****
S. creatinine (mg/dl)	**0.57**	**<0.001****
Bl. Urea (mg/dl)	**0.54**	**<0.001****
GFR (ml/min/1.73m)	**-0.36**	**0.005***
ACR (mg/g)	**0.93**	**<0.001****
AST (U/L)	0.09	0.50 NS
ALT (U/L)	0.02	0.90 NS
S. Albumin (g/dl)	**-0.39**	**0.002***
Total Protein (g/dl)	**-0.45**	**<0.001****
Direct Bilirubin (mg/dl)	-0.25	0.05 NS
Total Bilirubin (mg/dl)	0.17	0.19 NS
Hb (gm/dl)	0.06	0.63 NS
TLC ($x10^9$/L)	0.24	0.06 NS
Lymphocytes ($x10^3$/uL)	0.13	0.33 NS
Platelets ($x10^9$/L)	0.07	0.62 NS
RBS (mg/dl)	0.07	0.57 NS
ESR 1st H. (mm/hr)	0.21	0.11 NS
ESR 2nd H. (mm/hr)	**0.26**	**0.04***
CRP (mg/L)	0.17	0.20 NS

r: Pearson's and Spearman's correlation coefficient, NS: Non significant (P>0.05),
*: Significant (P<0.05), **: Highly significant (P<0.001).

That suPAR at cut off 115.2 pg/ml had sensitivity 93.3%, specificity 90% and accuracy 91.7% in diagnosis of LN **Table (6) & figure (1).**

Table (6): Validity of suPAR in diagnosis of LN among the studied cases groups:

Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
>115.2pg/ml	0.96 0.94-1	93.3%	90%	90.3%	93.1%	91.7%	**<0.001****

AUC: Area under curve, CI: Confidante interval, PPV: +ve predicted value, NPV: -ve predicted value, **: Highly significant (P<0.001).

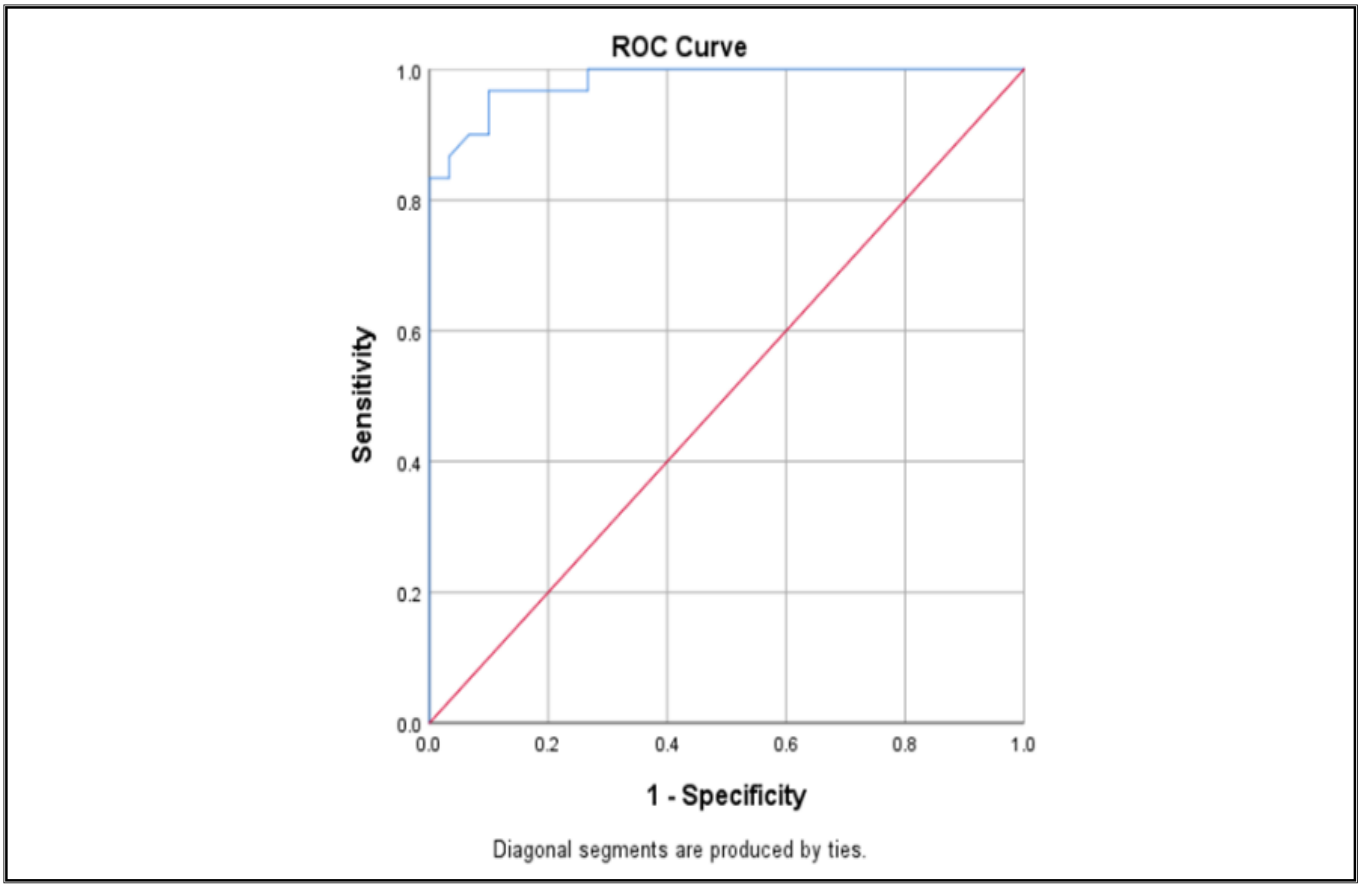

Fig. (1): Roc curve for Validity of suPAR in diagnosis of LN among the studied cases groups.

DISCUSSION

Systemic lupus erythematosus (SLE) is a chronic multisystemic inflammatory disease of autoimmune etiology which predominantly affects young women. In United States of America, 20 to 150 cases per 100,000 have SLE. Despite a marked improvement in 10-year survival for SLE patients over the past five decades, mortality rates from SLE remain high compared to those in the general population [(5)].

Lupus nephritis (LN) is a severe organic manifestation of SLE, characterized by subendothelial and/or subepithelial immune complex depositions in kidney, resulting in extensive injury and nephron loss and eventually chronic irreversible damage and renal function impairment if not treated effectively. There are increasing needs for early predictors of renal function impairment as it is known that early response to treatment is coupled with favorable renal outcomes [(6)].

Soluble urokinase plasminogen activator receptor (suPAR) is a novel inflammatory biomarker which is considered as a prognostic marker in several diseases as it seems to be more correlated with chronic rather than acute inflammation. Circulating suPAR has been proved as a valuable inflammatory marker in kidney diseases as focal segmental glomerulosclerosis (FSGS), minimal change disease, diabetic nephropathy (DN) and immunoglobulin A nephropathy [(7)]. However, available data on value of suPAR as a prognostic biomarker in SLE and LN patients are limited [(8)]. Regarding demographic data in this research, there was no statistically significant differences between the studied groups in age or sex distribution.

Our results come in line with **Elsayed and Mohafez** [(9)] results as they found no difference between cases with SLE and LN in age or sex with female patients' percentage in SLE and LN groups of 91.18% and 92.05% respectively.

The marked predominance of females among patients with SLE has long suggested a pathogenic role for female hormones, as there are evidences has been obtained that estrogens directly influence the survival, development, or function of immune cells strongly involved in SLE, such as B cells and dendritic cells (DCs), which are the main sources of type 1 IFNs, which in turn had been proved to be involved in SLE pathogenesis in several studies. However, sex hormones are not the only factor involved. The X chromosome carries many genes that are directly or indirectly involved in immunity. Among them, TLR7, which is located on the short arm of the X chromosome and encodes toll-like receptor 7, has been linked in many studies in development of SLE [(10)].

Regarding suPAR, our results show that there is a statistically significant increase suPAR in LN and SLE group compared to control group and also in LN group compared to SLE group.

Our results go in harmony with **Toldi *et al.*** [(11)] who proved that suPAR level is higher in SLE patients than controls and correlated with disease activity. **Zaitoon *et al.*** [(12)] had found that suPAR levels are higher in LN patients than SLE patients, also suPAR was proved to be a valuable biomarker for disease activity in SLE according to their study.

As plasma suPAR is an inflammatory biomarker closely linked to organ damage and immune activation in many diseases. Recently, researches had been focused on suPAR value in SLE, it has shown a valuable role as an indicator for disease activity and organ damage in most of studies [(13)].

Regarding correlation between suPAR and laboratory parameters in the studied groups, our results shows that there was no correlation between suPAR and age, calcium, AST, ALT, bilirubin, TLC, hemoglobin, platelets, random blood sugar and CRP. There was a statistically significant negative correlation between suPAR and GFR, C3, C4, albumin and total protein level among the studied cases groups. Also, there was a statistically significant positive correlation between suPAR and S. creatinine, Bl. urea, ACR, phosphorus, PTH and ESR 2nd H among the studied cases groups. Our results come in harmony with **Enocsson *et al.*** [(14)] results as they found no statistically significant correlation between CRP and suPAR and negative correlation between suPAR and GFR. However, they were against our results as they didn't find statistically significant correlation between suPAR and ESR, C3 and C4 levels, also found a significant correlation between age and suPAR levels, it is may be due to sample size or patient's ethnicity.

Regarding correlation between suPAR and LN class in LN patients, our results show a statistically significant positive correlation between suPAR and LN class in LN patients, as suPAR level increase with increase degree of LN class.

Our results are supported by study done by **Qin *et al.*** [(15)] whom found that suPAR level is negatively correlated with GFR in LN patients, higher in nephrotic syndrome patients and shows a significant association with different histopathological classes of LN as it was the highest in proliferative LN especially class IV.

LN is generally caused by immune-complex deposition and complement activation which result eventually in glomerular damage. Podocytes injury had been observed in different classes of LN histologically, as there are strong evidences that podocytes are targets for immune-complex deposition either directly or indirectly. As podocytes genetics play an important role in podocytes injury in LN pathogenesis, **Hayek *et al.*** [(16)] had found that suPAR considers as a potential injury molecule in LN contributing podocytes damage by direct interaction with pathogenic variants of apolipoprotein L1 (ApoL1) shown to be associated with integrin activation and podocyte detachment [(17)].

CONCLUSION

Circulating suPAR can be considered a good marker to predict early organ damage and follow up SLE patients especially LN.

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