

Renal arterial resistive index in Egyptian patients with lupus nephritis: Correlation with disease activity and biopsy parameters

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ABSTRACT

Lupus nephritis (LN) affects up to 60% of patients with systemic lupus erythematosus (SLE), either as the initial manifestation or during the disease course. Moreover, LN has a negative impact on survival of SLE patients. Accordingly, it is mandatory to identify specific and feasible markers able to guide clinicians towards the adequate therapeutic option in LN patients. The aim of this work was to evaluate the predictive value of renal resistance index (RRI), measured by Doppler Sonography in comparison with disease activity score, serologic and biopsy parameters in patients with LN. This study was carried out on forty three SLE patients, they were categorized into two groups: Group I included thirty three patients with LN and Group II included ten patients without LN and Group III included ten healthy subjects of matched age and sex as control group. All were subjected to history taking, clinical examination, assessment of disease activity by SLEDAI, laboratory investigations including FBG, blood urea, serum creatinine, serum albumin, CBC, ESR, CRP, complete urine analysis, 24 hour urine protein, eGFR, serum ANA, anti ds-DNA titre, C3, C4 and renal Doppler with measurement of RRI. Renal biopsy was done for those with LN. The mean value of RRI was statistically significantly higher in group I than that of group II and group III. Out of 33 cases of LN cases, 6 patients had RRI of 0.7 and above giving a percentage of 18.18%. LN patients with RRI higher than 0.7 had statistically significant higher age, mean serum creatinine and blood urea levels and a lower eGFR, higher chronicity index of renal biopsy. RRI is of clinical significance in predicting the chronicity index of renal biopsy which is a major determinant of renal outcome so it is useful as non invasive technique to evaluate chronicity in patients with LN, therefore justifying aggressive immune suppression but further follow-up studies are needed to evaluate its role in predicting response to treatment.

Keywords: Systemic lupus erythematosus, lupus nephritis, renal resistive index.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory multisystem disease mainly affecting women of childbearing age. It is characterized by a very large spectrum of clinical manifestations accompanied by prototypic abnormalities of the immune system with unpredictable flares and remissions (Lawrence et al., 1998). Many of its clinical manifestations are secondary to immune complex deposition in capillaries of visceral

structures or to autoantibody mediated destruction of host cells. The severity may vary from a mild episodic disorder to a rapidly fulminating life threatening illness (Edworthy, 2001).

The reported prevalence of SLE in the population is 20 to 150 cases per 100,000. Due to improved detection of mild disease, the incidence nearly tripled in the last 40 years of the 20th century (Uramoto et al., 1999) SLE is

usually a post pubertal disease, with onset of clinical symptoms between 20 and 30 yrs with a female to male ratio 9:1 (Uramoto et al., 1999).

The exact patho-etiology of SLE remains elusive. An extremely multi-factorial interaction among genetic and environmental components is probably involved (Moc and Lau, 2003). These factors lead to an irreversible break in immunological tolerance manifested by immune responses against endogenous nuclear antigens (Bertsias et al., 2012). According to the SLICC rule for the classification of SLE, the patient must satisfy at least 4 criteria, including at least one clinical criterion and one immunologic criterion OR the patient must have biopsy proven lupus nephritis in the presence of antinuclear antibodies or anti-double-stranded DNA antibodies (Petri et al., 2012).

The kidney is the most commonly involved visceral organ in SLE. Lupus nephritis (LN) is one of the most serious complications of SLE since it is associated with significant morbidity and mortality. In the United States, approximately 35% of adults with SLE have clinical evidence of nephritis at the time of diagnosis; with an estimated total of 50 to 60% developing nephritis during the first 10 years of disease (Lee et al., 2010; Hahn et al., 2012; Corapi et al., 2015).

Lupus nephritis is diagnosed by either the presence of proteinuria (>0.5 g/day), active urinary sediment (with red blood cell, granular, tubular and/or mixed casts), or an unexplained rise in serum creatinine. A kidney biopsy is the gold standard to diagnose LN as it provides information regarding the pattern and severity of renal involvement as well as the stage, activity and chronicity. These are all important considerations influencing treatment decisions (Corapi et al., 2015).

Renal resistive index (RRI) is commonly used as an index of intra-renal arterial resistance; it increases in various kidney diseases. It has been used in a variety of clinical settings such as the assessment of chronic renal allograft rejection, parenchymal nephropathies, acute kidney injury, detection and management of renal artery stenosis, evaluation of progression risk in chronic kidney disease (CKD), diabetic nephropathy, differential diagnosis in acute and chronic obstructive renal disease, cirrhosis and hepatorenal syndrome and as a predictor of renal and overall outcome in the critically ill patient (Radermacher et al., 2003; Crutchley et al., 2009; Radermacher et al., 2002; Granata et al., 2009; Viazzi et al., 2014; Lubas et al., 2014; Le Dorze et al., 2012).

Few studies have been carried out on patients affected by systemic vasculitis to evaluate the association between the anatomic-pathological findings and Doppler ultrasound parameters (Platt et al., 1990; Granata et al., 2014). Interestingly, the morphological changes of the Doppler waves found in these patients are similar to those of patients affected by renal microangiopathy related to haemolytic-uraemic syndrome (Patriquin et al., 1989).

Although Doppler sonography clearly does not

substitute for renal biopsy, several studies have suggested that Doppler sonography might aid in the management of established renal disease (Hanamura et al., 2012; Sugiura and Wada, 2011; Parolini et al., 2009). In a series published by Patriquin et al. (1989), Doppler sonography could predict renal recovery from hemolytic uremic syndrome before clinical improvement. Similarly, the RRI was thought to correlate well with renal involvement in patients with progressive systemic sclerosis (Mostbeck et al., 1991). Previous data have revealed a significant correlation between the RRI value and renal functional parameters (that is, creatinine and urea nitrogen blood levels) and/or histologic modifications, such as glomerulosclerosis, tubulo-interstitial damage and vascular lesions (Chen et al., 2014; Ikee et al., 2005; Aikimbaev et al., 2001).

Use of conventional ultrasound has been previously reported in the evaluation of lupus nephritis (Stanley et al., 1984). Abnormalities in renal size, cortical echogenicity have been reported as they have with many forms of renal disease (Platt et al., 1997).

Aim of study

The goal of our study is to evaluate the predictive value of RRI by Doppler US as compared to disease activity scores, serological and biopsy parameters in patients with lupus nephritis.

SUBJECTS AND METHODS

This study included forty three patients fulfilling Systematic Lupus International Collaborating Clinics (SLICC) Classification 2012 Criteria for diagnosing SLE disease (Petri et al., 2012). Patients were selected from the Nephrology ward and outpatient clinic in the Medical Research Institute, Alexandria University from March 2015 till March 2016.

Patients were categorized into three groups:

Group I: Thirty three patients with lupus nephritis diagnosed by the presence of proteinuria greater than 0.5 g/day or abnormal urinary casts (Jane and David, 2003).

Group II: Ten SLE patients without lupus nephritis.

Group III: Ten healthy subjects of matched age and sex as the patients as control group.

Patients with connective tissue diseases other than SLE, diabetes mellitus, hypertensive nephropathy, viral hepatitis B or C, active infections or malignancies, obstructive nephropathy, drug or toxic induced nephropathy and those with end stage renal disease were excluded from this study.

All patients were subjected to the following:

- i) Detailed history taking.
- ii) Thorough systemic physical examination.
- iii) Assessment of disease activity by applying the score of SLE disease activity index (SLEDAI) (Isenberg et al., 2005).
- iv) Lupus nephritis patients were assessed clinically with the renal SLE disease activity index [renal SLEDAI] (Chang et al., 2002).
- v) Laboratory investigations including:

- a) Fasting blood glucose (Burtis et al., 2006).

- b) Renal function tests: blood urea and serum creatinine (Burtis et al., 2006).
- c) Serum albumin (Burtis et al., 2006).
- d) Complete blood count (CBC) (Bain et al., 2006) and Erythrocyte sedimentation rate (ESR) (Sox and Liang, 1986).
- e) C-reactive protein (high sensitivity) (CRP) (Fouda et al., 2012).
- f) Complete urine analysis (Burtis et al., 2006), urinary albumin/creatinine ratio in spot urine sample (Cholongitas et al., 2007) and SLICC Renal Activity Score (SLICC RAS) (Petri et al., 2008) is calculated.
- vi) Ultrasound evaluation of kidneys and renal Doppler with measurement of renal resistance index (RRI) (Kalantarinia, 2009; Rauta et al., 2012).
- vii) Renal biopsy: it was done for patients of group I following an informed consent, the cores examined under light microscopy for staging of LN with estimation of chronicity and activity indices according to the scheme of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN (Korbet, 2002; Weening et al., 2004; Zappitelli et al., 2008).

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Alexandria University. After data was collected, it was revised, coded and entered to the statistical software SPSS version 21. Descriptive statistics were used for summarization of data, for quantitative variables, mean and standard deviations (SD) were calculated. Two tailed tests were used and P value of < 0.05 was considered significant. The Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the predictive value of RRI measured by Doppler Sonography in comparison with disease chronicity score in LN patients (Zweig and Campbell, 1993).

RESULTS

In this study, group I included 8 males (24.2%) and 25 females (75.8%) with mean age 30.48 ± 11.94 years, group II included 2 males (20%) and 8 females (80%) with mean age 27.50 ± 7.65 years and group III included 5 males (50%) and 5 females (50%) with mean age 27.8 ± 6.12 years with no statistical significant difference between the studied groups as regard age and sex (Table 1). The duration of the disease showed no statistically significant difference between the two groups (Table 2). No statistically significant difference between both groups as regard the presenting symptoms and signs of the studied cases but oedema were present in 7 patients (21.21%) of group I and none was found in group II (Table 3). Mean blood pressure (MBP) was within normal range in the studied groups with no statistically significant differences between these groups (Table 4).

The mean value of haemoglobin was statistically significant lower in group I than that of the other 2 groups with no statistically significant difference between group I and group II. White blood cells (WBCs) showed a statistically significant difference between group II and group III but no statistically significant difference between group I and other two groups. The mean value of lymphocytes and platelets had no statistically significant difference between groups (Table 5). The mean value of FBS was within normal in the study groups. It was statistically significant higher in group I than that of group

II and group III with no statistically significant difference between group II and group III. The mean value of serum creatinine was statistically significant higher in group I than that of the other 2 groups with no statistically significant difference between group II and group III. The mean value of blood urea was statistically significant different between the studied groups. The mean value of eGFR was statistically significant lower in group I than group II and group III but no statistically significant difference between group II and III. The mean value of serum albumin in Group I was statistically significant lower than group II and group III with no statistically significant difference between group II and group III. (Table 6)

As regard urine analysis among group I, 5 patients had (nil) proteins in urine and 3 patients had (1 plus) proteins in urine, 7 patients had (2 plus) proteins in urine, 15 patients had (3 plus) proteins and 3 patients had (4 plus) proteins in urine. Pus cells were ranged between 2 and 100 cells/HPF and RBCs were ranged between 2 and 57 cells/HPF in 9 patients of the LN cases (Table 7). The mean value of urinary albumin creatinine ratio showed statistically significant difference between the studied groups (Table 8)

ESR was statistically significant lower in first and second hour in group III than that of group I and group II with no statistically significant difference between these two groups. The mean value of CRP was statistically significant lower in group III than that of group II with no statistically significant difference between group I and group III or group II (Table 9).

In group I, 32 patients (96.97%) were positive for antinuclear antibodies while in group II, 9 patients (88.9%) were positive for antinuclear antibodies with no statistically significant difference between both groups (Table 10). The mean value of Anti ds-DNA in group I was statistically significant lower in group III than the other two groups but with no statistically significant differences observed between group I and group II. The mean value of C3 was statistically significant lower in group I than that of group II and III but no statistically significant difference between group II and III and the mean value of C4 was statistically significant lower in group I than that of group III but no statistically significant difference between it in group I and group II or between group II and group III (Table 11).

The mean value of SLEDAI score in group I was statistically significant higher in group I than group II (Table 12). In group I, the mean value of renal SLEDAI was 10.62 ± 3.14 and the mean value of SLICCRAS was 9.46 ± 3.91 (Table 13). As regard renal biopsy, no patient had class I, 3 patients had class II LN, 4 patients had class III LN, 20 patients had class IV LN, 5 patients had class V LN and only one patient had class VI LN. The mean value of activity index was 7.51 ± 4.06 while the mean value of chronicity index was 2.54 ± 2.07 (Table 14).

Table 1. Distribution of the studied groups by demographic data.

Parameter	Group I (n = 33)		Group II (n = 10)		Group III (n = 10)		Test of sig.	p
	No.	%	No.	%	No.	%		
Sex								
Male	8	24.2	2	20.0	5	50.0	$\chi^2 = 2.928$	$^{MC}p = 0.299$
Female	25	75.8	8	80.0	5	50.0		
Age (years)								
Min – Max	17.0 – 61.0		19.0 – 43.0		21.0 – 40.0		F = 0.489	p = 0.617
Mean ± SD	30.48 ± 11.94		27.50 ± 7.65		27.80 ± 6.12			
Median	27.0		24.0		26.5			

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group.

Table 2. Comparison between patients groups according to duration of the disease.

Duration of the disease (months)	Group I (n = 33)	Group II (n = 10)	T	P
Min – Max	0.25 - 96			
Mean ± SD	12.01 ± 25.826	4.37 ± 3.335	0.9255	0.360
Median	3.00	3.5		

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group.

Table 3. Presenting symptoms and signs of LN and SLE studied cases.

Presenting symptoms and signs	Group I (n = 33)	Group II (n = 10)	P
Arthritis	19 (57.6%)	5 (50%)	0.727
Alopecia	14 (42.42%)	8 (80%)	0.069
Rash	14 (42.42%)	2 (20%)	0.275
Oral ulcers	9 (27.27%)	3 (30%)	0.999
Fever	7 (21.21%)	1 (10%)	0.656
Oedema	7 (21.21%)	-	-

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group. *Fisher exact.

Table 4. Comparison between the different groups according to mean blood pressure.

MBP (mmHg)	Group I (n = 33)	Group II (n = 10)	Group III (n = 10)
Min – Max	80.00 - 150.00	90.0 - 120.0	85.00 - 110.00
Mean ± SD.	109.48 ± 18.58	101.87 ± 10.33	100.00 ± 7.07
Median	105.00	97.5	100.00
P	p = 0.124	p ₁ = 0.641	p ₂ = 0.225

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group.

MBP= Mean blood pressure

P: P value for comparing between group III with group I

p₁: P value for comparing between group III and group II

p₂: P value for comparing between group I and group II.

The mean value of RRI was statistically significant higher in group I than that of group II and group III but no statistically significant difference between group II and group III (Table 15). There was a statistically significant

difference between the mean values of creatinine among different lupus nephritis classes (Table 16). In addition serum creatinine and blood urea were statistically significant correlated with renal biopsy chronicity index

Table 5. Comparison between the different groups according to CBC.

Parameter	Group I (n = 33)	Group II (n = 10)	Group III (n = 10)
HGB (g/dl)			
Min – Max	5.2 -13.0	9.30 -13.0	11.0 -15.0
Mean ± SD	8.8±1.93	11.08±2.08	12.9 ±1.91
Median	8.58	10.5	13.0
P	p = 0.001*	p ₁ = 0.0554	p ₂ = 0.0005*
WBCs (cell/mm³)			
Min – Max	1.70–18.0	4.0 -9.50	4.1–7.0
Mean ± SD	6.57±4.30	6.92 ±1.60	5.21 ±1.10
Median	6.010	7.10	4.75
P	p = 0.331	p ₁ = 0.012*	p ₂ = 0.803
Lymphocytes (cell/mm³)			
Min – Max	400.00 -5000.00	500.00 – 5000	1400 -3500
Mean ± SD	2.437±1.34	2.487 ± 1.52	2.380 ± 6.62
Median	2300.00	2550	2550
P	p = 0.989	p ₁ = 0.839	p ₂ = 0.921
Platelets (cell/mm³)			
Min – Max	16.0-389.	5.0 –518.0	145.0–210.0
Mean ± SD	205.6±104.65	203.5 ± 147.0	174.7 ± 212.91
Median	188.50	208. 0	173.0
P	p = 0.532	p ₁ = 0.728	p ₂ = 0.960

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group.

CBC= Complete blood count

HGB= Haemoglobin WBCs= White blood cells

p: P value for comparing between group I with group III

p₁: P value for comparing between group II and group III

p₂: P value for comparing between group I and group II.

Table 6. Comparison between the different groups according to some laboratory parameters.

Parameter	Group I (n = 33)	Group II (n = 10)	Group III (n =10)
FBS (mg/dl)			
Min – Max	75 - 99	79 - 98	78 - 89
Mean ± SD	92.8 ± 5.45	85.12 ± 6.91	82.3 ± 3.68
Median	93	83.3	81.5
P	p = 0.0001*	p ₁ = 0.1004	p ₂ = 0.0007*
Serum creatinine (mg/dl)			
Min – Max	0.4 - 9.80	0.4 - 1.0	0.40 - 0.90
Mean ± SD	2.02 ± 2.03	0.71 ± 0.18	0.68 ± 0.147
Median	1.30	0.75	0.70
P	p = 0.045*	p ₁ = 0.687	p ₂ = 0.049*
Blood urea (mg/dl)			
Min – Max	20.00 - 180.00	16.00 - 47.00 g	14.00 - 27.00
Mean ± SD	66.58 ± 46.58	32.12±10.37	20.90 ± 3.84
Median	49.00	29.50	20.50
P	P = 0.0038*	p ₁ = 0.0049*	p ₂ = 0.0264*

Table 6. Continues.

eGFR (ml/min)			
Min – Max	5.0 - 120.0	68.0 - 120.0	100.0 - 117.0
Mean ± SD	55.85 ± 36.676	101.25 ± 19.717	107.40 ± 5.316
Median	45.5000	105.5000	107.50
P	p = 0.0001*	p ₁ = 0.3535	p ₂ = 0.0006*
Serum albumin (g/dl)			
Min – Max	1.10 - 4.1	2.40 - 4.50	2.0 - 4.0
Mean ± SD	2.46 ± 0.67	3.68 ± 0.762	3.68 ± 0.617
Median	2.50	4.00	3.8
P	p = 0.001*	p ₁ = 0.999	p ₂ = 0.0001*

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group

FBS = Fasting blood sugar.

eGFR = estimated glomerularfiltration rate

p: P value for comparing between group III with group I

p₁: P value for comparing between group III and group II

p₂: P value for comparing between group I and group II.

Table 7. Complete urine analysis in lupus nephritis patients.

Variable	Group I (n =33)	
	No.	%
Proteins		
Nil	5	15.2
1 plus	3	9.1
2 plus	7	21.2
3 plus	15	45.4
4 plus	3	9.1
Casts	9	22.27
Pus cells		
Min – Max	2.0 – 100	
Mean ± SD	11.08 ± 18.43	
Median	7.0	
Red cells		
Min – Max	2 – 57	
Mean ± SD	17.80 ± 16.30	
Median	10.0	

Group I: Lupus nephritis group.

(Table 17). Out of 33 LN cases, 6 patients had RRI of 0.7 and above giving a percentage of 18.18%.

The correlation of some demographic, clinical and laboratory variables with RRI showed that age, MBP, blood urea, serum creatinine, HB, urinary AC ratio, FBS, eGFR, ESR2, serum C3 and chronicity index in renal biopsy were statistically significant correlated with the RRI (Table 18). Multiple regression analysis showed that no variable was a significant predictor for Doppler-Based

RRI (Table 19).

The main demographic and clinical features of LN patients grouped with respect to the RRI value. Lupus nephritis patients with RRI ≥ 0.7 (n = 6) had statistically significant higher mean age, mean serum creatinine, blood urea level and higher chronicity index compared with patients with RRI in the normal range (Table 20). No statistically significant difference was observed between renal biopsy classes and RRI greater than 0.7 (Table 21).

In Figure 1, it appears that the Area under the ROC curve (AUC) was 0.769 (95% confidence interval 0.587 to 0.950, P = 0.019). The AUC was statistically significant different from 0.5 (null hypothesis area) and therefore there is evidence that Doppler-Based RRI has an ability to distinguish between the positive and negative groups.

DISCUSSION

Lupus nephritis (LN) affects up to 60% of patients with SLE, either as the initial manifestation or during the course of the disease (Boumpas et al., 1995). Moreover, LN has a negative impact on survival of patients with lupus (Cervera et al., 2003). It is extremely heterogenous both clinically and pathologically, flares and remissions of diseases are usually associated with therapy (Moc and Lau, 2003). Valesini and Conti (2011) considered that prognostic factors associated with poor outcome include: non-white ethnicity, male gender, uncontrolled hypertension, and high activity and chronicity indices on kidney biopsy. Accordingly, it is mandatory to identify markers of LN severity able to guide clinicians toward the adequate therapeutic option (Mok, 2010).

The most important survey of LN is histological assessment by renal biopsy. Clinicians usually select appropriate therapy according to the results of renal

Table 8. Comparison between the different groups according to urinary albumin creatinine ratio.

Urinary AC ratio (mg/g)	Group I (n =33)	Group II (n = 10)	Group III (n = 10)
Min – Max	788.00 - 17000.00	120.00 - 143.00	87.00 - 99.00
Mean ± SD	3578.42 ± 3546.13	132.62 ± 9.650	91.80 ± 4.13
Median	2661.50	131.0	92.00
P	p = 0.0038*	p ₁ = 0.0001*	p ₂ = 0.004*

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group
 Urinary AC ratio= Urinary albumin creatinine ratio
 p: P value for comparing between group III with group I
 p₁: P value for comparing between group III and group II
 p₂: P value for comparing between group I and group II.

Table 9. Comparison between the different groups according to ESR and CRP.

Variable	Group I (n =33)	Group II (n =10)	Group III (n =10)
ESR1 (mm/hour)			
Min – Max	10 - 137	43 - 120	15 - 24
Mean ± SD	55.27 ± 35.82	79.83 ± 32.10	20.08 ± 2.83
Median	45.0	77.5	20.5
P	P = 0.0037*	p ₁ = 0.0001*	p ₂ = 0.059
ESR2 (mm/hour)			
Min – Max	20 - 150	80 - 160	18 - 29
Mean ± SD	87.42 ± 42.09	114.0 ± 31.15	25.90 ± 3.63
Median	80	105	29
P	p = 0.0001*	p ₁ = 0.0001*	p ₂ = 0.0725
CRP (mg/L)			
Min – Max	2 - 131	3 - 29	1 - 5
Mean ± SD	18.57 ± 28.808	16.63 ± 11.045	2.6 ± 1.430
Median	5.00	21.50	2.5
P	p = 0.0898	p ₁ = 0.0009*	p ₂ = 0.8371

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group
 ESR= Erythrocyte sedimentation rate
 ESR1= Erythrocyte sedimentation rate in first hour
 ESR2= Erythrocyte sedimentation rate in second hour
 CRP = C-reactive protein
 p: P value for comparing between group III with group I
 p₁: P value for comparing between group III and group II
 p₂: P value for comparing between group I and group II.

Table 10. Comparison between patients groups according to antinuclear antibody.

Group	Antinuclear antibody		Total (%)
	Positive (%)	Negative (%)	
Group I	32 (96.97)	1 (3.03)	33 (100.0)
Group II	9 (88.9)	1 (11.1)	10 (100.0)

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group. Fisher exact P = 0.422.

biopsy. However, since renal biopsy is an invasive procedure, a non-invasive alternative would have clinical

benefits (Gao et al., 2013).

Conventional ultrasound does not provide any

Table 11. Comparison between the different groups according to immunological markers.

Variable	Group I (n =33)	Group II (n =10)	Group III (n =10)
Anti-ds DNA (IU/ml)			
Min – Max	24 -1200	30- 980	11- 29
Mean ± SD	217.38 ± 279.320	257.13 ± 342.24	17.60 ± 7.214
Median	78.00	118	14.5
P	p = 0.0311	p ₁ = 0.0045	p ₂ = 0.736
C3 (mg/dl)			
Min – Max	15 - 107	20 - 140	100 - 170
Mean ± SD	57.2 ± 27.62	98.13 ± 36.54	121.5 ± 23.34
Median	55.00	105.5	110
P	p = 0.0001*	p ₁ = 0.1004	p ₂ = 0.0004*
C4 (mg/dl)			
Min – Max	2 – 41	2 - 35	11 - 28
Mean ± SD	12.93 ± 9.81	15.7 ± 10.76	20.50 ± 5.25
Median	9.0	4.00	20.5
P	p = 0.0249*	p ₁ = 0.2211	p ₂ = 0.4485

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group

C3= Complement 3

C4= Complement 4

p: P value for comparing between group III with group I

p₁: P value for comparing between group III and group II

p₂: P value for comparing between group I and group II.

Table 12. Comparison between patients groups according to SLEDAI score.

SLEDAI score	Group I (n =33)	Group II (n =10)	t	P
Min – Max	4 - 30	6 - 14		
Mean ± SD	21.32 ± 6.28	10.75 ± 3.19	5.096	0.0001*
Median	24	11		

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group. SLEDAI = Systemic lupus erythematosus disease activity index.

Table 13. Renal SLEDAI and SLICCRAS scores in lupus nephritis patients.

Variable	Group I (n = 33)
Renal SLEDAI	
Min – Max	4.0 - 16.0
Mean ± SD	10.62 ± 3.14
Median	12.0
SLICCRAS	
Min – Max	3.0 - 15.0
Mean ± SD	9.46 ± 3.91
Median	9.0

Group I: Lupus nephritis group

Renal SLEDAI = Renal systemic lupus erythematosus disease activity index

SLICCRAS = Systemic lupus international collaborating clinics renal activity score.

additional predictive information over the traditional serological and biopsy parameters (Ozbek et al., 1995). Doppler analysis allows acquisition of information on renal macro-abnormalities and changes in renal blood flow. Renal resistive index (RRI) is commonly used as an index of intra-renal arterial resistance, and its use is proposed in the differential diagnosis of several nephropathies (Parolini et al., 2009; Rosato et al., 2012; Krumme, 2006).

The goal of our study was to evaluate the predictive value of RRI by Doppler US in LN as compared to disease activity scores, serological and biopsy parameters.

Group I included 25 females and 8 males with mean age 30.48 ± 11.94 years, and group II included 8 females and 2 males with a mean age 27.80 ± 6.12 years. Most reported data demonstrated that SLE occur in up to 10 times more common in women than men, and typically

Table 14. Distribution of the studied cases according to renal biopsy in lupus nephritis.

Variable	Group I (n = 33)	%
Class		
II Mesangial proliferative lupus nephritis	3	9.09
III Focal lupus nephritis	4	12.12
IV Diffuse lupus nephritis	20	60.60
V Membranous lupus nephritis	5	15.15
VI Advanced sclerotic lupus nephritis	1	3.03
Activity index		
Min – Max	1.0 – 15.0	
Mean ± SD	7.51 ± 4.06	
Median	8.0	
Chronicity index		
Min – Max	0 – 8.0	
Mean ± SD	2.54 ± 2.07	
Median	2.0	

Group I = Lupus nephritis group.

Table 15. Comparison between the different groups according to renal resistive index.

RRI	Group I (n = 33)	Group II (n = 10)	Group III (n = 10)
Min – Max	0.56 - 0.74	0.52- 0.61	0.54 - 0.57
Mean ± SD	0.65 ± 0.05	0.58 ± 0.03	0.55 ± 0.10
Median	0.65	0.58	0.55
P	p = 0.0001*	p ₁ = 0.3755	p ₂ = 0.0001*

Group I: Lupus nephritis group, Group II: Systemic lupus erythematosus group, Group III: Control group

RRI = Renal resistive index

P: P value for comparing between group III with group I

P1: P value for comparing between group III and group II

P2: P value for comparing between group I and group II.

Table 16. Distribution of renal biopsy classes by creatinine value in lupus nephritis patients.

Class (n = 33)	Mean	SD
II Mesangial proliferative lupus nephritis	0.7000	0.26458
III Focal lupus nephritis	1.9000	1.31149
IV Diffuse lupus nephritis	2.3409	2.58174
V Membranous lupus nephritis	1.9750	2.22017
VI Advanced sclerotic lupus nephritis	9.8000	-
Total	2.3333	2.64086

F = 2.866, P = 0.042.

Table 17. Correlation of both creatinine and blood urea values with renal biopsy chronicity index.

Variable		Renal biopsy chronicity index
Serum creatinine (mg/dl)	Pearson correlation	0.576*
	P	0.000
Blood urea (mg/dl)	Pearson correlation	0.449*
	P	0.009

Table 18. Correlation of some demographic, clinical and laboratory variables with RRI.

Variable		RRI
Age (years)	Pearson Correlation	0.314*
	P	0.032
HB (g/dl)	Pearson Correlation	-0.419*
	P	0.002
FBS (mg/dl)	Pearson Correlation	0.365*
	P	0.007
MBP (mmHg)	Pearson Correlation	0.482*
	P	0.000
eGFR (ml/min)	Pearson Correlation	-0.462*
	P	0.013
Creatinine (mg/dl)	Pearson Correlation	0.709*
	P	0.000
Blood urea (mg/dl)	Pearson Correlation	0.647*
	P	0.000
Serum albumin (g/dl)	Pearson Correlation	-0.057
	P	0.693
Urinary AC Ratio (mg/g)	Pearson Correlation	0.315*
	P	0.024
ESR2 (mm/hour)	Pearson Correlation	0.301*
	P	0.034
Anti ds DNA (IU/L)	Pearson Correlation	0.123
	P	0.381
Serum C3 (mg/dl)	Pearson Correlation	-0.438*
	P	0.001
Serum C4 (mg/dl)	Pearson Correlation	-0.175
	P	0.209
Activity index	Pearson Correlation	0.069
	P	0.704
Chronicity index	Pearson Correlation	*0.443
	P	0.010
Renal biopsy classes	Spearman correlation	0.243
	P	0.174
SLEDAI	Pearson Correlation	0.120
	P	0.450
SLICCRAS	Pearson Correlation	-0.100
	P	0.585

Table 18. Continues.

Renal SLEDAI	Pearson Correlation	-0.130
	P	0.477

RRI = Renal resistive index; HB = Haemoglobin; FBS = Fasting blood sugar; MBP = Mean blood pressure; eGFR = estimated glomerular filtration rate; Urinary AC ratio = Urinary albumin creatinine ratio; ESR2 = Erythrocyte sedimentation rate in second hour; Serum C3 = Serum Complement 3; Serum C4= Serum Complement 4; SLICCRAS = Systemic lupus international collaborating clinics renal activity score; Renal SLEDAI = Renal systemic lupus erythematosus disease activity index.

Table 19. Multiple regression analysis of Doppler-Based Renal Resistive index.

Variables	Standardized coefficients	t	Sig.	95.0% confidence interval for B	
	Beta			Lower bound	Upper bound
(Constant)		2.338	.037	0.054	1.519
Age	-.181	-.684	.507	-.003	0.002
HB	.134	.535	.602	-.010	0.016
FBS	-.211	-.750	.468	-.009	0.005
ESR	.039	.145	.887	-.001	0.001
MBP	.157	.460	.654	-.001	0.002
eGFR	.054	.122	.834	-.001	0.001
Creatinine	.632	1.253	.234	-.017	0.061
Blood urea	-.086	-.223	.827	-.001	0.001
Urinary AC ratio	-.192	-.698	.499	.000	0.000
Serum C3	-.104	-.354	.730	-.001	0.001
Renal biopsy chronicity index	.140	.495	.630	-.013	0.020

Hb = Haemoglobin; FBS = Fasting blood sugar; ESR= Erythrocyte sedimentation rate; MBP = Mean blood pressure; eGFR = Estimated glomerular filtration rate; Urinary AC ratio = Urinary albumin creatinine ratio; C3 = Complement 3.

has a predilection for women in their childbearing years (Uramoto et al., 1999).

The duration of the disease showed no statistically significant difference between the two groups (Ballow et al., 1996) stated that LN occurs early in the disease mostly during the 1st year, and it is uncommon to have the original onset of renal disease more than 10 years after the appearance of SLE.

The mean value of Hb was statistically significant lower in patients with group I than those of group II. This may be attributed to greater activity or prior use of aggressive immune suppression in group I. (Satirapoj et al., 2007) reported that Hb < 10 m is a major determinant of renal involvement in SLE patients. The mean value of WBCs count in group II was statistically significant higher than that of group III but the mean value of lymphocytes and platelets showed no statistically significant between the studied groups. However (Pitashny et al., 2007 and El-Shehaby et al., 2011) have found insignificant difference between groups regarding WBCs as well as platelets. This may reflect higher hematological activity in group I evidenced by both lower mean Hb and WBCs, also there were some patients in group I giving history of aggressive myelotoxic therapy prior to involving in the study.

That mean value of serum creatinine was statistically significant higher in group I than that of the other 2 groups with no statistically significant difference between group II and group III. The mean value of blood urea was statistically significant different between the studied groups. The mean value of eGFR was statistically significant lower in group I than that of group II and group III. This may be attributed to that more than 70% of group I belong to classes III and IV in renal biopsy and usually patients in these classes have impaired renal functions (Najafi et al., 2001).

The mean value of serum albumin in group I was statistically significant lower than in group II and group III. This might be explained by the fact that Group I with LN had significantly higher mean value of urinary albumin loss. These findings matched with those in Yip et al. (2010), where in 1078 patients with LN and SLE without nephritis, low serum albumin level is significantly associated with LN activity and higher SLEDAI scores. The mean value of uACR was statistically significant higher in group I than group II and III. The use of uACR was also used by Birmingham et al. (2008) were it was found that it is a better forecaster for proteinuric renal flare allowing early declaration of renal flare especially in

Table 20. Demographic and clinical features of lupus nephritis patients grouped according to RRI value.

Variable	R I < 0.7 (N = 27)	R I > 0.7 (N = 6)	p
Males/females	5/22	3/3	0.104
Age(years)	28.12 ± 9.465	41.80 ± 17.020	0.017*
Disease duration (months)	14.90 ± 29.129	2.41 ± 1.941	0.487
MBP (mmHg)	108.12 ± 18.285	116.00 ± 20.736	0.398
Renal function			
Serum creatinine (mg/dl)	1.46 ± 0.914	5.32 ± 3.016	0.000*
Blood urea(mg/dL)	57.50 ± 37.463	110.20 ± 65.155	0.018*
eGFR (mL/min)	60.65 ± 34.427	33.80 ± 42.669	0.141
Urine protein(g/24h)	1.62 ± 0.868	3.90 ± 3.726	0.241
Inflammatory markers			
ESR	59.54 ± 35.671	34.80 ± 32.151	0.164
CRP	19.79 ± 31.032	12.70 ± 14.848	0.625
Immunologic parameters			
Antinuclear Antibody	26 (96.3%)	6 (100%)	0.632
Anti ds DNA	240.08 ± 301.583	99.60 ± 78.951	0.317
Serum C3	55.57 ± 27.924	65.00 ± 27.650	0.497
Serum C4	12.79 ± 9.738	13.62 ± 11.324	0.867
SLEDAI	21.95 ± 5.520	17.50 ± 9.983	0.195
SLICCRAS	10.20 ± 4.010	6.25 ± 2.061	0.067
Renal SLEDAI	10.66 ± 3.472	11.00 ± 2.00	0.855
Histologic class			
Class II	3 (11.11%)	-	
Class III	3 (11.11%)	1 (16.67%)	0.202
Class IV	17 (62.96%)	3 (50%)	
Class V	4 (14.82%)	1 (16.67%)	
Class V1	-	1 (16.67%)	
Activity Index (range: 0 – 24)	7.87 ± 3.904	6.40 ± 2.966	0.434
Chronicity Index (range: 0 – 12)	2.16 ± 1.522	4.4000 ± 2.607	0.014*

RRI = renal resistive index; MBP = Mean blood pressure; eGFR = estimated glomerular filtration rate; ESR = Erythrocyte sedimentation rate; CRP = C- reactive protein; Serum C3 = Serum complement 3; Serum C4 = Serum complement 4; SLICCRAS = Systemic lupus international collaborating clinics renal activity score; SLEDAI = Systemic lupus erythematosus disease activity index.

normal range proteinuria avoiding greater nephrotoxicity of proteinuria when using higher threshold protein creatinine ratio.

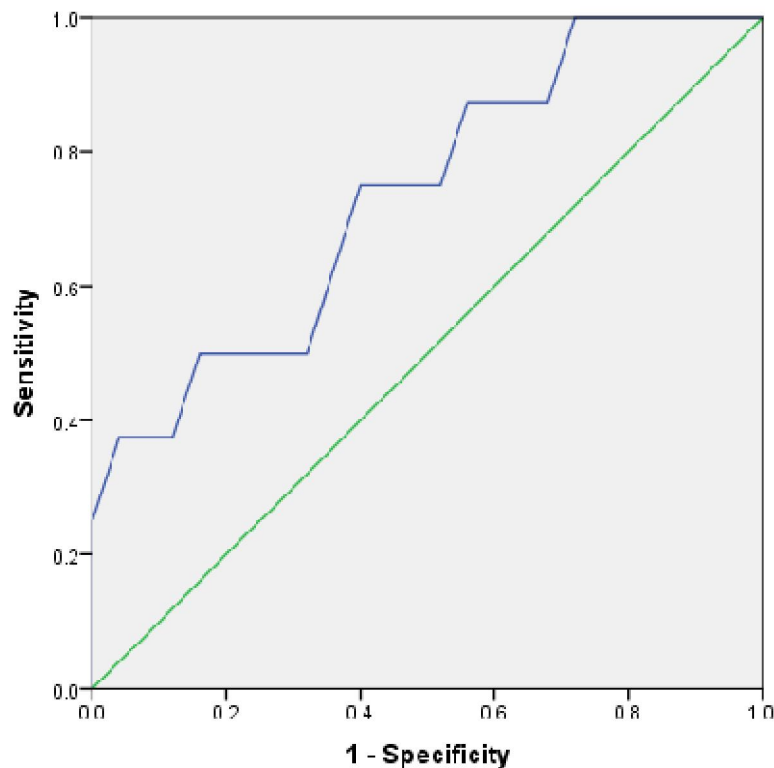
The mean value of ESR in group III was statistically significant lower than that of group I and group II in first and second hour, these findings matched with those of Stojan et al. (2013) where ESR is associated with disease activity in SLE and with organ-specific activity including serositis, rash, joint, renal and hematological affection. Also CRP was statistically significantly lower in group III than that of group II, this may be explained by that many patients in group II were known to suffer from infections (Mok et al., 2013) showed that CRP is detectable in 77% of lupus patients with active disease

and that CRP level correlate significantly with lupus disease activity, especially that involving the musculoskeletal system, hematological system, and serositis as in most of our patients in group II.

The majority (96.6%) of LN patients were positive for ANAs and (88.9%) among SLE patients with no statistical significant difference between both groups. This agrees with the data reporting ANAs are a highly sensitive screen for SLE, being found in more than 90% of untreated patients, but they are not specific for SLE and occur in many other rheumatologic and non-rheumatologic conditions (D'Agati, 1998). The mean value of Anti ds-DNA in group I and group II was statistically significant higher than that of group III with no significant

Table 21. Distribution of renal biopsy classes by renal resistive index.

Renal biopsy classes		RI		Total
		< 0.7	0.7+	
II	No.	3	-	3
	%	100.0%	-	100.0%
III	No.	3	1	4
	%	75.0%	25.5	100.0%
IV	No.	17	3	20
	%	85.0%	15.0%	100.0%
V	No.	4	1	5
	%	80.0%	20.0%	100.0%
VI	No.	-	1	1
	%	-	100.0%	100.0%

**Figure 1.** ROC curve of Doppler-Based RRI as a predictor of renal biopsy.

differences observed between group I and group II. Antids-DNA IgG antibodies of high avidity that fix complement have correlated best with the presence of renal disease (Rahman and Isenberg, 2008). Also, Farid et al. (2013) found that anti-ds-DNA was higher in the LN group compared with the non-LN group, showing that patients with active LN often have raised levels of anti-ds DNA antibodies. In addition

their titers correlate well with clinical activity as was studied by Linnik et al. (2005).

The mean value of C3 was statistically significant lower in group I than that of group II and group III with no statistical significant difference between group II and group III. While for C4; it was statistically significant lower in group I than group III while it did not differ significantly

between group I and group II nor group II and group III. Similarly (Narayanan et al., 2010) has found marked reduction in C3 and C4 levels in LN patients than in SLE patients without renal affection.

The mean value of the SLEDAI score in group I was statistically significant higher than that of group II. This matched with findings of (Zabaleta-Lans et al., 2006). Renal SLEDAI was ranged from 4 to 16 and SLICCRAS was ranged from 3 to 15. This denoting that most of the patients enrolled in the study are active proliferative LN cases. (Alharazy et al., 2015) found that there were significant differences between the active and inactive LN groups with regard to renal SLEDAI.

According to the WHO grading scheme for LN, most of our cases had class IV LN (60.60%) and only one (3.03%) had advanced sclerotic lupus nephritis with activity index ranged from 1 to 15 /24 and chronicity index ranged from 1 to 10 /12.

The mean value of RRI in group I was statistically significantly higher than that in group II and group III with no significant difference between group II and group III. Out of 33 cases of LN cases, 6 patients had RRI of 0.7 and above giving a percentage of 18.18%. This finding was matching the study carried by (Conti et al., 2014), where a higher mean value of RRI was calculated in LN patients than in SLE without renal affection than in normal subjects.

There was a statistically significant difference between the mean values of creatinine among different LN classes with higher levels in class IV LN, this was matching with most data (Appel and D'Agati, 2007; Markowitz and D'Agati, 2009). In addition serum creatinine and blood urea were significantly correlated with renal biopsy chronicity index. This matched with the study carried by Satirapoj et al. (2015).

Conti et al. (2014) also recorded RRI>0.7 only in patients with renal SLE suggesting a correlation of a pathologic RRI with glomerular lesions and histological classes. Platt et al. (1997) found RRI > 0.7 in 29% of 34 LN patients in a trial to correlate a pathologic RRI and chronicity index to poorer renal outcome after 1-y follow-up. Gao et al. (2013) retrospectively reviewed 24 LN patients and observed a significantly higher RRI in patients with moderate renal cortical fibrosis than in those with mild fibrosis.

In our study, we found that RRI significantly correlated with age, Hb, MBP, FBS, blood urea, serum creatinine, eGFR, uACR, ESR₂, C3 and chronicity index in renal biopsy. A significant correlation between RRI and renal function evaluated by urea, creatinine and eGFR in kidney diseases irrespective of etiologies has been demonstrated in many studies (Sugiura and Wada, 2011; Mostbeck et al., 1991; Ikee et al., 2005; Sugiura et al., 2004); others also significantly correlated RRI with age, systolic blood pressure and proteinuria in CKD. Hypertension and age are well-known parameters that influence renal resistance and vascular compliance

(Parolini et al., 2009; Sugiura and Wada, 2009).

While correlation with proteinuria may be due to the fact that almost all of the pathological RRI are detected in classes III, IV and V which are characterized by overt proteinuria, also proteinuria is both a marker for greater degree of renal damage as well as an independent risk factor for CKD progression. Moreover, the RRI has emerged as an independent risk factor for worsening of renal function in large follow-up studies on different renal diseases: renal survival rate was significantly lower in patients with a baseline RRI 0.7 (Sugiura and Wada, 2011; Sugiura and Wada, 2009).

On the other hand RRI did not significantly correlated with other parameters as serum albumin, anti-ds DNA, C4, SLEDAI scores, SLICCRAS score and activity index in renal biopsy, that in addition we could not find any significant correlation between RRI and any specific histological class although we could observe a lower mean of RRI in class II in comparison to other classes, which may aid in assessing the role of RRI in differentiating between different classes of LN with different outcomes and prognosis. The non-significance with SLEDAI score is not surprising. These are composite indices including items on involvement of different organs.

From our study we found that LN patients with RRI of 0.7 or more had higher age, higher mean blood urea and serum creatinine level and higher mean value of chronicity index of renal biopsy but no statistical significant difference was observed between renal biopsy classes and RRI of 0.7 or more.

Several studies evaluated the role of RRI in LN, the first one by Platt et al. (1997) who described a correlation between a pathologic RRI and creatinine level, histologic chronicity index and presence of interstitial disease only while there was an absent correlation between RRI and uACR, anti dsDNA, C3, C4, biopsy classes, activity index or total biopsy score. Moreover, a pathologic RRI and chronicity index were related to poorer renal outcome after 1 yr follow-up (doubling serum creatinine and/or need of RRT). Patients with an initial RRI of 0.70 or higher showed a worse outcome, independent of initial eGFR and they concluded that RRI and not the serum creatinine is significantly higher in those with poorer outcomes.

Later on, Wang et al. (2007) in his study on 44 patients with class IV LN, showed that the chronicity index of renal biopsy was significantly higher in patients with increased RRI. On the other hand when population study is divided according to immune suppression response, it was proven that increased RRI was significantly associated with an increased likelihood of poor response to treatment.

Gao et al. (2013) retrospectively reviewed 24 LN patients and observed a significantly higher RRI at the level of main renal artery (and not as in our study and other studies at level of interlobar arteries) in patients

with moderate renal cortical fibrosis than in those with mild fibrosis, with no marked difference at the level of interlobar arteries. It is worth saying there was a significant difference between both groups regarding serum creatinine. This study focused principally on the early stages of renal hemodynamic disturbances to grade renal cortical fibrosis. One of limitations of this study in addition to assessing patients retrospectively, the renal biopsy specimens when evaluating chronic irreversible changes only accounted on interstitial fibrosis and tubular atrophy while ignoring the other 2 parameters glomerulosclerosis and arteriosclerosis which are major determinants of intra-renal hemodynamic change (Bude and Rubin, 1999).

Conti (2014) as others have found that the RRI to be positively correlated only with creatinine and BUN and negatively correlated with eGFR, in addition out of 5 patients with pathological RRI > 0.7 in the 42 patients LN enrolled, 4 of them belong to class IV LN and 1 belonging to class III.

In addition, in controversy to other studies, Conti et al. (2014) found that SLE patients with RRI 0.7 had significantly higher mean activity index values with no significant correlation with the chronicity index. This may be in part due prevalence of severe glomerular histologic features (glomerular synechiae and glomerular cellular-fibrotic crescent formation), which are indicative of a worst prognosis in his studying sample, nevertheless the relatively low chronicity indices scores of his specimens. A similar observation was detected in our study where in both of the 2 patients having crescents (100%), RRI > 0.7 was calculated.

Study done by Gigante et al. (2016) on 100 biopsy proven GN including about 30 LN patients founded a significant correlation between RRI and age, serum creatinine, eGFR, % of glomerulosclerosis and of crescents and degree of arteriosclerosis .

From the study of ROC curve of Doppler-Based Renal Resistive index, we suggested that 0.70 threshold was better than 0.65 cut-off to predict renal biopsy chronicity index, although it has a higher sensitivity but with lower specificity and positive predictive value.

Chronicity index (CI) score had been found to be important predictor of long-term outcome in LN (Magil et al., 1988; Esdaile et al., 1991). It was demonstrated that tubulointerstitial lesions as the major locations of injury for determining prognosis in LN (Austin et al., 1994). The severity of interstitial disease correlated with the degree of renal insufficiency and was a valuable marker for progressive deterioration in renal function (Schwartz et al., 1992). Therefore, the predictive value of RRI is likely to result from the correlation of RRI with CI and tubulointerstitial changes.

Limitations of kidney biopsy are a result of its invasive nature, which prevents periodic sampling especially in the clinical setting of inactive lupus and renal symptoms, and its small sample size that might not reflect the disease in the entire kidney. As new technologies for the earlier

detection of kidney injury in LN such as biomarkers are emerging, renal sonography should provide complementary information (Manoharan and Madaio, 2010; Zhang et al., 2008).

Thus from the results of our study, we could conclude that renal Doppler is a useful non-invasive technique that can be used to evaluate chronicity of renal affection in SLE, and therefore justifying aggressive immune suppression, but further follow-up studies are needed to evaluate its role in predicting response to treatment. The strength of the present study is the homogeneity of the population evaluated and the inclusion of patients in different histologic classes of LN taking into account both glomerular and non-glomerular lesions.

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