Facteurs prédictifs de la néphropathie lupique dans une population tunisienne

Predictive factors of the lupus nephritis in a Tunisian cohort

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RÉSUMÉ

Introduction : L'atteinte rénale est une manifestation fréquente et grave du lupus érythémateux systémique (LES) et elle met en jeu le prognostic vital.
Objectif : Identifier les facteurs prédictifs de la néphrite lupique (LN).
Méthodes ; Il s'agit d'une étude descriptive, analytique et rétrospective de 115 patients atteints de LES (ACR, 1997) menée dans un service de médecine interne sur une durée de 20 ans, de 1997 à 2017. Le LN a été diagnostiqué devant une protéinurie de 0,5 g/24 h et/ou une anomalie des sediments urinaires. Quatre-vingts patients n'ont pas eu de lésions rénales pendant le suivi et trente-cinq ont développé une atteinte rénale après le diagnostic du LES.
Résultats : L'analyse univariée a retenu plusieurs paramètres de corrélation épidémiologiques, cliniques et biologiques, selon le développement de la néphropathie lupique, statistiquement significatifs. Il s'agit du sexe masculin, de l'âge du diagnostic de LES inférieur ou égal à 34 ans, de la présence d'éruption cutanée au moment du diagnostic de LES, d'ulcérations naso/pharyngées, de leucopoénie, de positivité de l'anticorps anti-Sm et du complément C3 consommé.
L'analyse multivariée a révélé que l'âge inférieur ou égal à 34 ans au moment du diagnostic du LES était le seul facteur prédictif de l'apparition de LN (OR=5,1 et HR=3,4).
Conclusions : Compte tenu de la gravité de la pathologie et de la complexité de sa prise en charge, le LN devrait être détecté le plus tôt possible et doit être traité de façon appropriée en sélectionnant la population de lupique à risque de développer une LN grave.

Mots-clés
Lupus érythémateux systémique, néphropathie lupique, facteurs de risque

SUMMARY

Introduction: Renal involvement is a common and serious manifestation of systemic lupus erythematosus (SLE) and it is life-threatening.
Aim: To identify the predictive factors of the lupus nephritis (LN).
Methods: A descriptive, analytical, single-centre, retrospective study of 115 patients with SLE (ACR 1997) was carried out in an internal medicine department for a period of 20 years from 1997 until 2017. LN was diagnosed by proteinuria ≥ 0.5 g /24h and / or urine sediment abnormality. Eighty patients did not have kidney damage during the follow-up and thirty-five developed renal involvement after SLE diagnosis
Results: The univariate analysis retained several epidemiological, clinical and biological correlation parameters, according to the development of lupus nephritis, statistically significant. They are as follows, the male gender, the age of diagnosis of SLE less than or equal to 34 years, the presence of malar rash by the time of SLE diagnosis, naso/pharyngeal ulcerations, leucopoenia, positivity of anti-Sm antibody and low C3 complement.
The multivariate analysis had found that age less than or equal to 34 years at the diagnosis of the SLE was the only predictive factor of the onset of LN (OR=5.1 and HR=3.4).
Conclusion: Given the seriousness of the pathology and the complexity of its management, LN should be detected as soon as possible and must be treated appropriately by selecting the lupus population at risk for developing a serious LN.

Key-words
Systemic lupus erythematosus, lupus nephritis, risk factor

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide variety of clinical expression. It has a clear predominance of women, nearly six women for one man [1]. Its incidence varies widely between countries: 23.2/100000 person-years in North America and 0.3/100000 person-years in respectively Africa and Ukraine [2].

During the evolution of lupus disease according to ethnicity, between 40and 60% of patients will develop a renal disease of SLE [3-7]. This prevalence varies according to published studies and series. It would be more frequent in men than in women.

Lupus nephritis (LN) conditions to a large extent of functional and vital prognosis of the lupus disease. Despite adequate and early medical care, the frequency of progression to chronic kidney disease remains significant. Early detection of LN is important for patients before irreversible damage occurs. The identification of LN predictive factors improves management, by selecting Lupus patients who may develop LN.

The aim of our study was to identify the predictive factors for the development of LN.

METHODS

Patients and study design

It was a retrospective and an analytical study that was conducted in the internal medicine department of Habib Thameur University Hospital Centre over a period of 20 years from July 1997 to June 2017.

We reviewed all medical records of SLE patients according to the inclusion and exclusion criteria of our study.

We included, in this study, patients who were followed in our department for a SLE. The positive diagnosis was retained according to the revised criteria of the American College of Rheumatology (ACR) of 1997 [8,9]. Systematic Lupus International Collaborating Clinic criteria were calculated for all patients [10].

LN was defined according to the consensus conferences by ACR and EULAR (EUropean League Against Rheumatism) in other words proteinuria greater than or equal to 0.5 g per 24 hours and / or urine sediment abnormality, such as glomerular haematuria or aseptic leukocyturia, confirmed at least on a second sample of a cytobacteriological examination of urine [11,12]. Patients with these urinary abnormalities explained by other pathologies were excluded.

To define the predictive factors of the onset of renal impairment during SLE evolution, after excluding patients presenting an inaugural LN, we subdivided the other patients into two groups:

• Group 1 (G1) included patients who had renal impairment during the progression of SLE.

• Group 2 (G2) included patients who never had renal impairment during the progression of SLE during the study time.

We also excluded SLE patients with a follow-up duration of less than six months with the exception of patients who died during this follow-up period.

Data

Data was collected from patient records on a pre-established form. This sheet specified for each patient the following characteristics of the SLE:

Epidemiological data: Sex, smoking and SLE diagnosis age.

Clinical data: It specified the different systemic manifestations presented throughout their follow-up. The activity score of lupus disease at the time of diagnosis of SLE by the SLEDAI-2k score (Systemic Lupus Erythematosus Disease Activity Index 2000) was calculated [13].

Para-clinical data: Complementary biological examinations were performed during the diagnosis of SLE, such as renal function, 24-hour proteinuria, blood count, electrophoresis of serum proteins, erythrocyte sedimentation rate, C-reactive protein, fibrinogenaemia, cytobacteriological examination of urine, assay of serum complements and immunoassay.

Statistical analysis

We performed a comparative study between the two groups based on clinical, biological and immunological parameters and lupus disease activity scores at SLE diagnosis.

All data was analysed using the software Statistical Package for Social Sciences (SPSS) version 23.0.

Statistical analysis consisted of absolute frequency and relative frequency (percent) calculations for qualitative variables. Mean, median and standard deviation were calculated and extreme values were determined for the quantitative variables.

For the analytical study, the comparison of two independent

series means was performed using the Student's t-test for the independent series, and the non-parametric Mann-Whitney test for small numbers. Comparisons of percentages on independent series were made by the Pearson chi-square test. In the case of significance in the chi-square test and invalidity of this test, the comparison of the two percentages was made by Fisher's exact bilateral test. In all statistical tests, the materiality threshold was set at 0.05.

• To transform quantitative variables into qualitative variables, we proceeded with two modalities. To determine the threshold at which the quantitative variable had to be cut, we developed Receiver Operating Characteristics (ROC) curves. After verifying that the area under the curve was significant (>0.500), we chose the value of the variable that corresponds to the best "sensitivity-specificity" pair as a threshold.

• Factors associated with the occurrence of LN ($p<0.05$) in univariate analysis were introduced in a multivariate analysis independent of time in a binary logistic regression, by calculating the Odds Ratio (OR). If the follow-up of patients was uneven, then we talked about censored data. The link between the two variables the occurrence of an event (LN onset) during the follow-up of a patient with SLE and the factor related to this event had to take into account the time. The study of the binding was carried out by the Kaplan Meier method (event-free survival according to a factor). Survival data without LN onset were studied by establishing survival curves according to the Kaplan Meier method. The search for the predictive factors was performed in a univariate analysis (factor-by-factor) by comparing the survival curves using the Log rank test. Then a multivariate analysis with a Cox regression model was carried out to identify the factors predicting the occurrence of the LN taking into consideration the time, by calculating the Hazard Ratio (HR).

RESULTS

During the period of the study, we collected 150 patients with SLE, seventy (46.6%) had developed renal involvement. Of these 70 patients, 35 had developed LN prior to or at SLE diagnosis and 35 developed renal involvement after SLE diagnosis (Figure 1).

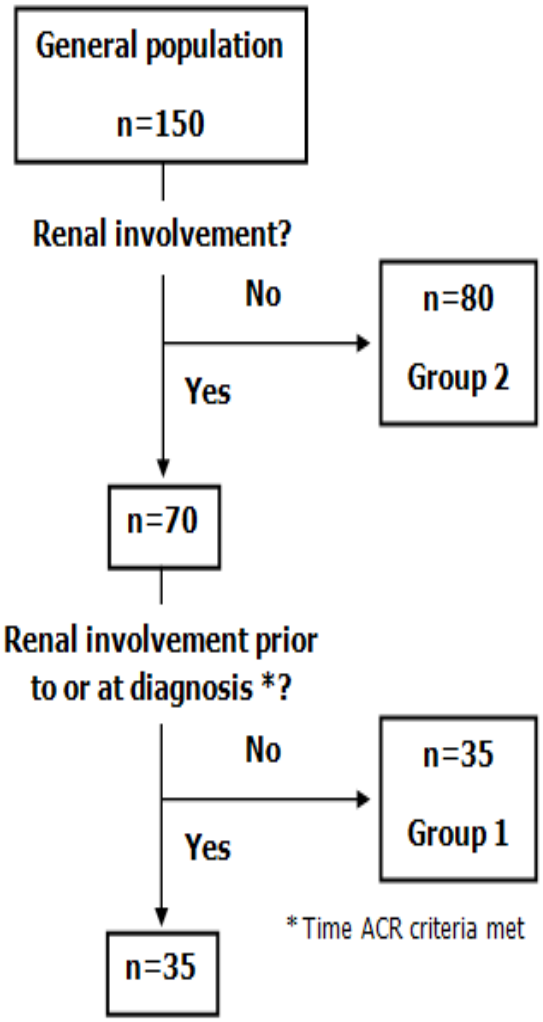

Figure 1 Flow diagram of general population included in analyses of the renal involvement

To define the predictive factors of onset of renal impairment during SLE evolution, after excluding patients presenting an inaugural LN, we subdivided the other patients into two groups:

Group 1 (N = 35) included patients who had renal involvement during the evolution of SLE.

Group 2 (N = 80) included patients who never had renal involvement during the progression of SLE during the study period.

Mean duration of LN-free follow-up of the patients (n=115) was 89 months (7.4 years).

We performed a comparative study between the two

groups based on clinical, biological and immunological parameters and a lupus disease activity score at SLE diagnosis.

By comparing the two groups, independently of time, the univariate analysis retained several parameters, epidemiological, clinical and biological correlation according to the developing of LN, statistically significant, which are: the male gender (p=0.027), age of diagnosis of SLE less than or equal to 34 years (p<0.001), presence at the time of SLE diagnosis of malar rash (p=0.005), naso/pharyngeal ulcerations (p=0.016), leucopoenia (p=0.011), positivity of anti-Sm antibodies (p=0.005) and low C3 complement (p=0.01). This data is depicted in Table 1.

The multivariate study by binary logistic regression retained, as predictive factors of the LN, an age at SLE diagnosis ≤ 34 years (p=0.038, OR=5.1 (1.09-24.11)). Table 2 showed the results of the logistic regression for the LN predictive factors.

Table 2 : Estimates of relative rate of onset of lupus nephritis for independent prognostic factors according to logistic regression model

Variable	p-Value	Odds Ratio	95% Confidence intervals
Age ≤ 34 years at SLE diagnosis	0.038	5.128	1.091 - 24.112
Male sex	0.214	6.311	0.344 - 115.694
Malar rash	0.163	3.192	0.625 - 16.302
Naso/pharyngeal ulcerations	NS	0.931	0.120 - 6.966
Leucopoenia	NS	1.877	0.419 - 8.416
Anti-Sm antibodies	NS	2.094	0.465 - 9.424
Low C3 complement	NS	1.688	0.370 - 7.694

NS: not significant

Table 1 : Baseline socioeconomic–clinical and biological features of patients as a function of renal involvement

Variable	G1 (n=35)	(%)	G2 (n=80)	(%)	P-Value
Male sex	5	14	2	3	0.015
Age * (Mean±SD) years	29±10.7		41±14.6		<0.001
Age ≤ 34 years*	26	74	25	31	<0.001
Smoking	4	11	4	5	NS
Caucasian ethnicity	35	100	80	100	NS
Malar rash	24	69	32	40	0.005
Discoid lupus	4	11	10	13	NS
Photosensitivity	27	77	54	68	NS
Nsao/pharyngeal ulcerations	11	31	10	13	0.016
Non erosive oligoarthritis	18	51	45	56	NS
Serositis	5	14	19	24	NS
Autoimmune haemolytic anaemia	2	6	10	13	NS
Hemoglobinemia rate (Mean±SD) g/dL	11.4±1.8		10.7±2		0.085
Leucopoenia	23	66	32	40	0.011
Lymphopenia	29	83	61	76	NS
Hypoalbuminemia	20/26	77	57/72	79	NS
Albuminemia rate (Mean±SD) g/L	34.5±4.8		34.6±5.8		NS
Low C3 complement	14/25	56	20/73	27	0.010
Low C4 complement	19/25	76	40/72	56	0.071
Erythrocyte sedimentation rate (Mean±SD)	63±31		62±36		NS
Anti-nuclear antibodies	35/35	100	77/79	98	NS
Anti-dsDNA antibodies	27/30	90	59/73	81	NS
Anti-Sm antibodies	11/20	55	11/52	21	0.005
Median number ACR criteria* (IQR)	5 (4-6)		5 (4-6)		0.009
Median number SLICC criteria* (IQR)	6 (5-7)		5 (4-6)		<0.001
Median SLEDAI* (IQR)	10 (8-16)		8 (5-14)		0.002

G1: included patients who had renal impairment during the progression of SLE, G2: included patients who never had renal impairment during the progression of SLE during the study period,* at SLE diagnosis, NS: not significant, SLE: systemic lupus erythematosus, ACR: American College of Rheumatology, SLICC: Systematic Lupus International Collaborating Clinic, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index 2000, SD: Standard Deviation, IQR: inter-quartile range

The search for prognostic factors for survival without renal impairment was performed using univariate analysis (factor-by-factor) by comparing survival curves using the Kaplan-Meier method.

This analysis did not show any significant difference in cutaneous impairment, articular involvement, serous, anaemia, anti-DNA antibody positivity and low C4 complement. Male gender (p<0.001), age at SLE diagnosis ≤ 34 years (p<0.001), leucopoenia (p=0.002), low C3 complement (p=0.020) and anti-Sm antibodies positivity (p=0.006) were the prognostic factors associated with LN-free survival (Figure 2).

As shown in table 3, the Cox proportional hazard regression, for the identification of predictive factors of LN by time, found only one predictive factor that was an age at SLE diagnosis ≤ 34 years (p=0.039, HR=3.4 (1.06-11.22)).

Table 3 : Estimates of relative rate of onset of lupus nephritis for independent prognostic factors according to Cox regression model

Variable	p-Value	Hazard Ratio	95% Confidence intervals
Age ≤ 34 years at SLE diagnosis	0,039	3.458	1.066-11.220
Male sex	0,054	3.849	0.977-15.157
Leucopoenia	0.092	2.544	0.858-7.537
Anti-Sm antibodies	0.135	2.170	0.786-5.990
Low C3 complement	NS	1,686	0.611-4.648

NS: not significant

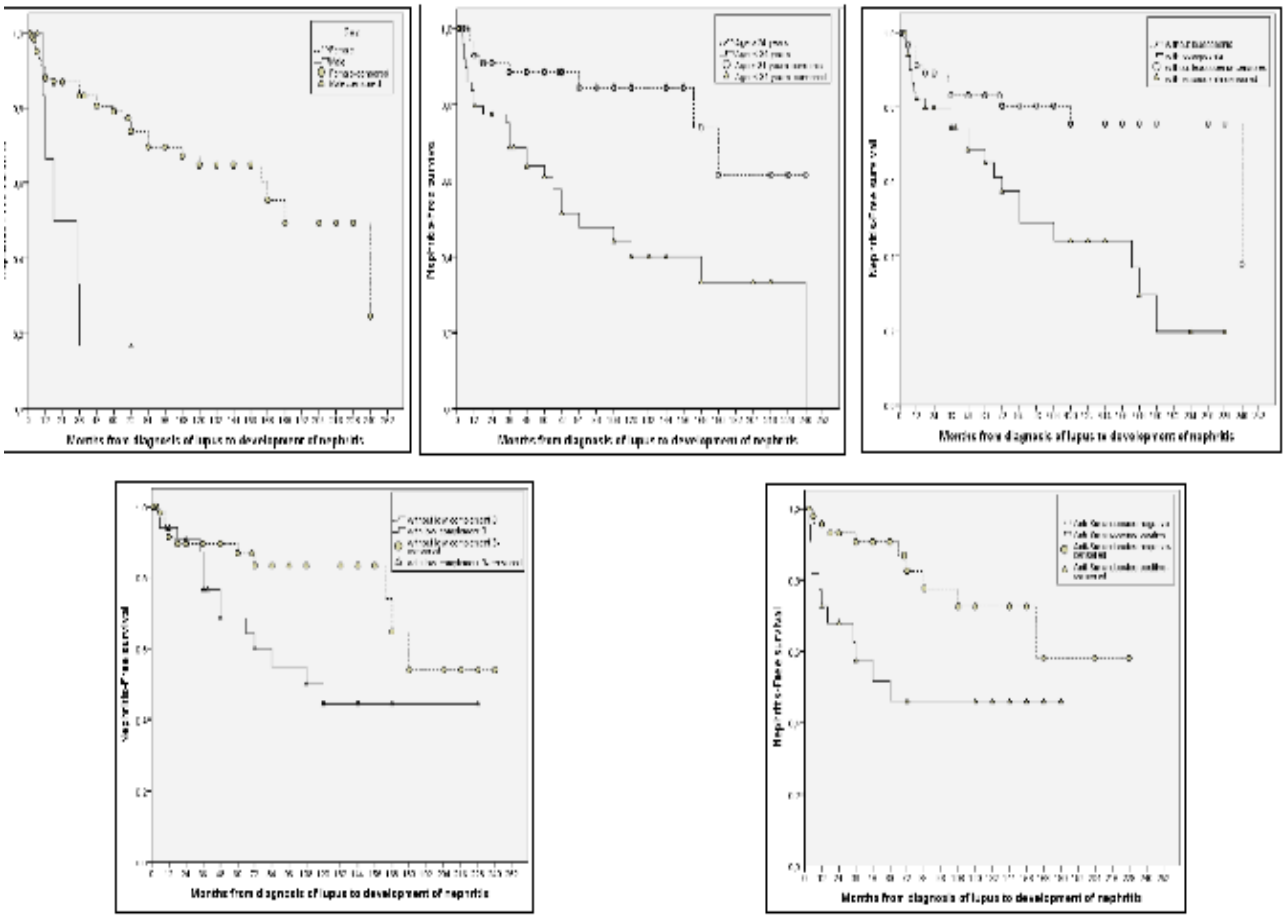

Figure 2. Survival comparison curves without renal impairment (Kaplan-Meier)

DISCUSSION

Predictive factors of the development of the LN, time dependent and independent in univariate analysis, were: males, an age at SLE diagnosis less than or equal to 34 years, leucopoenia, the positivity of the anti-Sm antibody and the low C3 complement. In the time-dependent univariate analysis, predictive factors were malar rash and naso/pharyngeal ulcerations. The multivariate analysis found an age at SLE diagnosis less than or equal to 34 years as the only predictive factor of the onset of LN (OR=5.1 and HR=3.4).

We excluded patients who already had LN at the SLE diagnosis as there was no way to provide comparison, assess predictive factors or give proper follow up in those cases. We also felt that this method was the most appropriate to examine our data in a Cox regression model.

Few studies, with a design study similar to ours, have been interested in identifying factors that can predict the onset of LN, absent at the SLE diagnosis and excluding patients with LN prior to or at SLE diagnosis. These rare series are interested in the American, Asian, Scandinavian or English population, certainly diverse from the ethnic point of view, but having no or few patients of the Maghreb, Mediterranean or Arab origin [14-20].

In these studies predictive factors of LN onset were at a younger age [14,15,20], male gender [14,15], African-American [14-16], Hispanic ethnicity [14-16], Asian American [15], Afro-Caribbean [17], not married[16], smoking and hypertension [15], high SLE activity and high ACR criteria number [15,16], anaemia and low serum complement (> 6 months) [18], lymphopenia [19], low albumin-globine ratio [20] and the positivity of anti-DNA [16,19,20], anti RNP antibodies [16], anti-cardiolipin antibodies [17] and anti-Sm antibodies [20] (Table 4).

Table 4 : Different studies presenting the predictive factors of the onset of lupus nephritis according to multivariate analysis

Studies [references]	Country, Year of study	Number LN/no LN	Predictive factors	Hazard / Odds rate ratio	95% Confidence intervals
Hopkinson ND [17]	UK, 2000	28 / 161	Afro-Caribbean race	HR=4.4	1.9-10.2
			Presence of IgG anti-cardiolipin antibodies	HR=2.6	1.2-5.7
Seligman VA [14]	USA, 2002	91 / 561	Age < 33 years at lupus diagnosis	HR=1.9	1.7-2.1
			Male Sex	HR=1.7	1.5-1.9
			African American	HR=1.5	1.3-1.7
			Hispanic American	HR=1.5	1.4-1.7
			Asian American	HR=1.8	1.6-1.9
Bastian HM [16]	USA, 2002	88 / 161	African-American ethnicity	OR=3.1	1.2-8
			Hispanic ethnicity	OR=2.7	1-6.8
			Not married / living together	OR=3.4	1.6-7.6
			Higher Systemic Lupus Activity Measure Score	OR=1.1	1-1.1
			Anti-dsDNA antibodies	OR=3.1	1.5-6.5
			Anti-RNP antibodies	OR=4.2	1.9-9
Alarcon GC [15]	USA, 2006	229 / 570	Younger age	HR=0.97	0.96-0.98
			African-American ethnicity	HR=3.23	2.13-4.9
			Texan Hispanic ethnicity	HR=2.8	1.55-5.06
			ACR criteria number	HR=1.41	1.28-1.55
Burling F [18]	NZ, 2007	32 / 114	Anaemia	HR=3.2	1.4-7.1
			Low complement > 6 months	HR=3.4	1.4-8.7
Tanha N [19]	Dk, 2018	184/420	Lymphopenia	HR=1.49	1.08-2.06
			Anti-dsDNA	HR=1.38	1.01-1.87
			High number of antibodies	HR=1.49	1.06-1.48
Kwon OC [20]	KR, 2018	37/241	Age	aHR=0.989	0.895-0.961
			C3	aHR=0.977	0.966-0.928
			Anti-dsDNA titre	aHR=1.004	1.000-1.007
			Anti-Sm	aHr=2.097	1.040-4.229
			Low albumin-globine ratio	aHR=6.866	3.452-13.654
Our study	**Tn, 2019**	**35/80**	**Age ≤ 34 at SLE diagnosis**	**HR=3,4 OR=5,1**	**1-24,1 1-11,2**

UK: United Kingdom; USA: United States of America; NZ: New Zealand; Tn: Tunisia; Dk: Denmark; KR: South Korea; LN: lupus nephritis

We have noted in our work as limits the retrospective nature since this type of study has limits concerning the lack of information and the lost of sight, the monocentric nature and the bias of selection as the patients hospitalized in an internal medicine department often have more severe forms of SLE, with multi-systemic involvement. Moreover, our sample was homogeneous from an anthropological and ethnical point of view, which did not allow a comparison of the ethnic variable between the two groups of our study. Sex hormones have already shown their role in the pathogenesis of lupus and its kidney involvement. Wen C et al. demonstrated that the increment of plasma estradiol E2 is associated with lupus activity in both male and female patients and the decrement of plasma testosterone was only in female ones is also related to lupus activity [21]. The plasma level of oestrogens increases physiologically after puberty, which corresponds to the risk period for renal involvement during SLE. Several studies, with human or mice models, have demonstrated the role of oestrogens and essentially the alpha receptors of oestrogens in the pathogenesis of lupus or as an inducer [22,23]. The deficiency of this oestrogen's receptor attenuates lupus nephritis and increases survival [24,25]. This period of post-pubertal hormonal upheaval is favorable for the development of SLE and LN.

In summary, in this retrospective study, we observed epidemiological differences in the development of lupus nephritis in a cohort of patients from Tunisia. This prognostic information can be important for doctors who treat patients with SLE throughout, knowing those at risk and deciding how often they should monitor patients to diagnose LN and to take care of it in the spirit of avoiding progression towards chronic kidney disease.

Competing interests: none declared.

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