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Research Article

The Patient with Lupus Nephritis: Comprehensive Assessment and Potential Risks

N.F. Soroka*, K.A. Chyzh, A.K. Tushina

Belarusian State Medical University Department of Internal Diseases, Cardiology and Rheumatology with a course of advanced training and retraining Minsk, Belarus.

***Corresponding Author:** Nikolay Soroka., Belarusian State Medical University Department of Internal Diseases, Cardiology and Rheumatology with a course of advanced training and retraining Minsk, Belarus.

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Abstract:

Systemic lupus erythematosus is a potentially fatal, chronic, multisystem autoimmune condition. Kidney damage plays a special role in the course and prognosis of SLE, being associated with the greatest number of complications and high mortality. The main type of renal damage in lupus is the development of secondary glomerulonephritis - lupus nephritis. Therefore, it's of great importance to establish so-called "risk factors" that would make it possible to predict the development of LN in patients with SLE, its exacerbations, features of the course and possible outcomes. It is noteworthy that at the onset of the disease, kidney damage was noted in almost half of the patients with SLE (48.2%), and in many cases, the first clinical and laboratory manifestations of LN were only changes in urine tests.

Key words: systemic lupus erythematosus; lupus nephritis; risk factors

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology, based on a genetically determined disorder of immune regulation, which determines the formation of organ-nonspecific antibodies to antigens of cell nuclei and immune complexes with the development of immune inflammation in the tissues of many organs [1]. It is a potentially fatal, chronic, multisystem autoimmune condition that primarily affects women of reproductive age. Its pathogenesis involves multiple components of the immune cascade, resulting in a striking heterogeneity of clinical manifestations. Almost any organ or system of the body can be involved in the pathological process - skin, joints, heart, lungs, serous membranes, nervous system, hematopoietic system, etc. It is obvious that late diagnosis of SLE is associated with an increased risk of damage to vital body systems. The severity and clinical course of SLE are extremely variable - from very mild with arthralgia and skin rashes to life-threatening when there is severe impairment of renal or central nervous system function. Kidney damage plays a special role in the course and prognosis of SLE, being associated with the greatest number of complications and high mortality. The main type of renal damage in lupus is the development of secondary glomerulonephritis - lupus nephritis. Lupus nephritis (LN), one of the most serious manifestations of SLE, occurs in up to two-thirds of patients, depending largely on ethnicity and race. It is much more common in African-American and Hispanic patients, less common in Asians, and even less common in Caucasian patients. The presence of LN predicts worse survival compared to patients without kidney disease, with the cause of death being due to both disease-related and treatment-related factors [2, 3, 4]. The 10- and 20-year survival rates (renal and/or overall) are approximately 70% and 60%, respectively. LN is associated with a twofold increase in complications and mortality compared with individuals without renal pathology and a fourfold increase in individuals receiving renal replacement therapy [5, 6]. More severe course of SLE in the presence of LN also requires more intensive treatment (high doses of glucocorticosteroids, immunosuppressive drugs), which, in turn, leads to a significant increase in the number of complications [4]. Despite significant improvements in survival (both renal and patient) over the past decades associated with the advent of new treatment strategies, a significant proportion of patients (10 to 30%) continue to steadily progress to end-stage chronic kidney disease (CKD) within 10 to 15 years from diagnosis of LN. For example, 44% of people with proliferative forms of LN (morphological classes III and IV) after 15 years are forced to resort to methods of renal replacement therapy (hemodialysis, peritoneal dialysis, kidney transplantation). [5,6] Clinical and laboratory manifestations of LN almost the same as the symptoms of primary chronic glomerulonephritis. Clinical signs of kidney involvement in the pathological process are observed in 40-80% of patients with SLE,

most often occurring in childhood [7]. They range from minimal changes in urinary sediment to frank nephritic or nephrotic syndrome, as well as rapidly progressive glomerulonephritis or acute kidney injury (AKI). In the absence of adequate therapy (and in some cases, despite its presence), over time, LN ends with the development of the end stage of CKD. In the early stages of the disease in lupus patients, changes in urine tests or impaired renal function are observed approximately in 25-50% of cases. Kidney damage often manifests as proteinuria, microhematuria, decreased glomerular filtration rate (GFR), increased blood creatinine levels, or the presence of casts in the urine (approximately in 50% of cases). In most cases, kidney damage is accompanied by extrarenal clinical manifestations and changes in laboratory parameters, which ultimately makes it possible to suspect the likelihood of lupus kidney damage. An essential part of renal involvement in lupus is proteinuria, which is detected in 100% of patients with lupus nephritis, and in 45-65% of cases it can reach the nephrotic level. Hematuria (in the vast majority of cases, microhematuria), as well as the presence of red blood cell casts, are found approximately in 80% of patients during the course of the disease. The presence of LN should be considered in any lupus patient with renal impairment, proteinuria, arterial hypertension or active urinary sediment. Active sediment includes the detection of hematuria, especially acanthocytes, indicating the glomerular origin of erythrocytes in the urine, leukocyturia when excluding its infectious genesis (especially lymphocyturia), as well as erythrocyte, leukocyte and other casts. The great diagnostic importance in verifying the diagnosis of LN has intravital puncture biopsy of the kidney. The histological data obtained through this manipulation serve as the basis for establishing the morphological class of LN, assessing the activity of inflammatory and chronic changes in the renal tissue, recommendations for developing treatment tactics, as well as prognosis of the disease. LN is often asymptomatic and requires active screening to detect it. Clinical and laboratory features reflect the type of renal histological lesions present in a given patient. Proteinuria, microhematuria, casts and hypertension (in some cases severe) are often found in individuals with proliferative LN, and may be accompanied by the development of renal failure. Patients with membranous or proliferative LN often develop nephrotic syndrome with the presence of peripheral edema, serous effusions, cachexia and hypercoagulation. LN can also manifest itself as AKI or have a rapidly progressive nature associated with severe glomerular inflammation (the presence of cellular crescents and fibrinoid necrosis of capillary loops in the glomeruli of the kidneys), which is observed relatively rarely. Most patients with LN have a relapsing course, with treatment-induced remissions and spontaneous relapses of renal tissue inflammation being quite common. At the same time, the course of LN is extremely variable. In some cases, a long-term stable chronic course is observed, accompanied by the presence of minimal or no urinary syndrome, with preserved renal function. In another situation, a rapidly progressive course is observed, accompanied by nephrotic or nephritic syndrome, severe hypertension and a steady decline in the functional state of the kidneys, leading within several years to the end stage of CKD with the necessity of renal replacement therapy. Most patients have a wave-like course, in which exacerbations of nephritis are replaced by more or less long periods of complete or partial remission, with gradual progression of existing CKD to later stages. The presence of different variants of the course of LN is associated with the complexity of the pathogenesis of both SLE and LN. Many researchers believe that the term “systemic lupus erythematosus” includes various diseases that meet the classification criteria of SLE. This polymorphism of clinical and laboratory manifestations, as well as the rarity of SLE in general, makes difficulties in providing multicenter clinical trials for novel treatment. The most important risk factor for progression of LN is the frequency, nature and degree of its exacerbation. After an exacerbation of LN, irreversible structural changes are formed in the renal tissue, leading to the formation of sclerosis and the progression of CKD. Therefore, it is extremely important to predict such exacerbations, which would allow the use of adequate therapeutic agents to prevent them, stop them and control the course of the disease while minimizing the side effects of the drugs used [8]. Therefore, it’s of great importance to establish so-called “risk factors” that would make it possible to predict the development of LN in patients with SLE, its exacerbations, features of the course and possible outcomes. A variety of genetic, demographic, clinical and laboratory parameters have been attempted. Patient age, gender, ethnicity, disease duration, presence of hypertension, anemia, elevated serum creatinine, rapid decline in GFR, and many others parameters have been studied as possible prognostic factors. Potential risk factors include any parameters (modifiable and non-modifiable) that contribute to the progression of CKD. More specific indicators that influence the nature of the course of LN were also studied, such as SLE activity (determined by the indices SLEDAI, SELENA-SLEDAI, BILAG, etc.), the influence of damage to other organs and systems in lupus (SLICC/ACR Damage Index), immunological indicators (C1q, C3 and C4 complement components in the blood and urine, the level of antinuclear antibodies and antibodies to double-stranded DNA (dsDNA) in the blood). In various studies, many of the mentioned parameters had a certain impact on the activity and progression of LN, but to date, a universal predictor of exacerbation of nephritis in SLE has not been established. The most significant factors were the level of proteinuria (especially daily), the presence of impaired renal function at the onset of LN, high titers of anti-dsDNA antibodies in the blood, and low levels of the complement component C1q. LN has been found to be more aggressive and have a worse prognosis in people of African-American ethnicity, especially males. And, of course, many studies have noted lack of adherence to treatment in patients with LN as a poor prognostic sign. A key role in diagnosis of lupus nephritis plays kidney biopsy. Indications for its implementation are proteinuria (in a general urine test, in the daily amount of urine, when calculating the protein/creatinine ratio in a single portion of urine), especially above 0.5 g/day (g/l), the presence of changes in the urinary sediment (hematuria, casts, leukocyturia, not associated with an infectious process in the urinary tract), an otherwise unexplained impairment of the functional state of the kidneys, manifested by signs azotemia and a decrease in GFR, or one or another combination of these signs. Performing a nephrobiopsy followed by morphological examination using light, immunofluorescence, and in some cases electron microscopy makes it possible to clarify the histological class of LN according to the 2003 ISN/RPS classification (modified 2018), develop a suitable therapeutic regimen and assess the prognosis [9]. Also, this invasive diagnostic procedure helps in differential diagnosis - excluding kidney damage due to secondary or primary antiphospholipid syndrome (APS), hypertension, primary glomerulonephritis, tubulointerstitial nephritis, diabetic nephropathy, renal amyloidosis, etc. To assess morphological changes in LN, the 2003 International Society of Nephrology/Society of Renal Pathologists (ISN/RPS) classification, which includes 6 classes of the disease, is currently used. This classification subdivides LN according to the location of immune complex deposition in the glomeruli, the presence or absence of mesangial or endocapillary proliferation, the overall degree of glomerular involvement (focal or diffuse) and glomerular damage

(global or segmental), as well as active (inflammatory) or chronic (sclerotic) glomerular damage.

- I class. Minimal mesangial LN. Light microscopy (LM): normal glomeruli. Immunofluorescence (IF): mesangial immune complexes (IC)
- II class. Mesangial proliferative LN. LM: mesangial hypercellularity and/or expansion of the mesangial matrix. IF: mesangial IR
- III class. Focal LN. LM: segmental or global endo- or extracapillary GN affecting <50% of the glomeruli. IF: subendothelial ± mesangial IF. There are active (A) - proliferative, chronic (C) - sclerosing, and a combination of active and chronic (A+C) focal LN
- IV class. Diffuse LN. LM: segmental or global endo- or extracapillary GN affecting ≥50% of the glomeruli. IF: subendothelial ± mesangial IF. A, C or A+C diffuse LN is distinguished
- V class. Membranous LN. LM: thickening of the wall of glomerular capillaries. FI: many subepithelial ICs, >50% glomerular capillaries. Membranous changes can be isolated or combined with proliferative ones. Their combination is designated as class V+ III or class V+ IV.
- VI class. Sclerosing LN. LM: sclerosis >90% of glomeruli.

Although immunocoplex-mediated glomerulonephritis is the most common cause of renal damage in SLE, there are other mechanisms that can only be diagnosed by biopsy and require a different treatment approach than immune-complex LN. For example, thrombotic microangiopathy and podocytopathy, can be observed in 24% and 1.3% of patients with LN, respectively. The finding of isolated tubulointerstitial nephritis is rare.In general, the morphological class of LN according to ISN/RPS determines decisions on further treatment tactics. Patients whose glomerular involvement is limited to the mesangium (Class II) generally do not require specific therapy, but immunosuppression may be required to treat extrarenal manifestations of SLE. With the predominance of chronic damage (any morphological class) or with the total development of glomerulosclerosis (class VI), there is also no need for immunosuppressive treatment of LN, and a positive therapeutic effect can be obtained with the help of antiproteinuric, renoprotective measures. Proliferative classes of LN (III and IV) usually require active immunosuppression, whereas nonproliferative, membranous LN (class V) can be treated conservatively (antiproteinuric therapy) if patients have subnephrotic proteinuria, or with immunosuppression if patients have nephrotic syndrome. The role of repeat renal biopsy in LN remains controversial, but emerging evidence suggests that serial biopsies may influence ongoing treatment decisions and long-term renal prognosis. Repeat nrphrobiopsies showed significant discrepancy between clinical and histological disease activity. 6-8 months after completion of immunosuppressive therapy, 20-50% of patients with complete clinical remission of LN still had histological evidence of active inflammation, and 40-60% of patients without histological evidence of disease activity had persistent proteinuria. Even after several years of immunosuppressive treatment, histological activity occurred in almost 20% of patients with long-term clinical remission. Conversely, 40% of patients with complete histological remission remained persistently clinical after long-term treatment. These results indicate the need for repeated nephrobiopsies when deciding whether to discontinue maintenance immunosuppressive therapy [10]. There are currently no recommendations regarding the duration of maintenance therapy for LN.

Statistical analysis

The structure of the prepared database is represented by numeric, categorical and binary data types. Mathematical processing of the material was carried out using the statistical software package Statistica 10.0 for Windows (StatSoft Inc., USA) and the MedCalc software package version 15.8, more adapted for medical data. To check the normality of the distribution of the original numerical data, the coefficients of skewness and kurtosis, as well as the Kolmogorov–Smirnov test (for small samples) were used. Since databases with numerical indicators for patients suffering from SLE with and without LN had samples with a large number of observations, almost all numerical indicators had a normal distribution, and therefore the following statistical indicators were calculated: mean (M), dispersion (σ^2), mean error (SE), minimum and maximum value, coefficient of variation (CV). If the data were normally distributed, the mean (M), standard deviation (σ), error of the mean (SE), t-test and P-value (to assess the significance of the difference between means and variances) were determined. For data that were not normally distributed, the median (Me), interquartile range (IQR) (Me, [25th; 75th percentiles]) and nonparametric statistical methods (Wilcoxon test for comparisons) were used. When comparing quantitative indicators, the Pearson χ^2 test, the Mann–Whitney U test, and the Kruskal–Wallis test were used.

Materials and methods

Medical documentation (medical histories, outpatient records, etc.) of 574 patients with SLE treated in the rheumatology department of the 9th city hospital in Minsk (since 2018, Minsk Scientific and Practical Center for Surgery, Transplantology and Hematology) for the period from 1990 to 2024 was studied. In addition, some of the patients were observed on an outpatient basis by staff of the Republic Rheumatology Center. The diagnosis of SLE was established based on the classification criteria of the American College of Rheumatology (ACR, 1997) and the International Society of Systemic Lupus Erythematosus Clinics (SLICC, 2012) [11, 12]. 284 patients were observed prospectively, and in 290 cases a retrospective analysis of the available data was performed. All patients were divided into two groups depending on the presence (397) or absence (177) of LN. Diagnosis of LN was based on the ACR classification criteria (2012), including persistent daily proteinuria of at least 0.5 grams and/or erythrocyturia (5 or more red blood cells in the microscopic field), leukocyturia (5 or more white blood cells in the microscopic field) not associated with a urinary tract infection, and casts. In almost half of the cases (195 patients - 49% of all cases of LN), the diagnosis was confirmed by the results of histomorphological examination of renal biopsies.

Results and discussion

Among the examined patients, female patients predictably predominated - 537 (93.6%), the number of males - 37 (6.4%). The average age of the subjects was 35.3±0.5 years. The age of onset of the disease was 28.6±0.5 years. The average duration of SLE at the time of observation was 6.5±0.3 years. The first group consisted of patients with an established diagnosis of LN- 397 patients (69.2% of all examined), among whom there were 30 men (7.6%). The average age in this group was 34.9±0.6 years. The age of onset of the disease in the presence of LN is 28.0±0.6 years. The average duration of SLE at the time of observation was 6.9±0.3 years. The

age of onset of LN was 28.9±0.7 years. The duration of LN at the time the patient was taken under observation was 5.9±0.6 years. Clinical and laboratory signs of kidney damage at the onset of the disease were noted in 47.2% of all cases of LN. The comparison group consisted of 177 patients with SLE without signs of LN. The groups of patients with or without LN did not differ significantly in gender, age, or age at diagnosis of SLE. However, the duration of the disease at the time of the initial examination of the patient was higher in the group of people with LN. (Tables 1 and 2)

Parameter		LN+	LN-	χ^2	P
Gender, n (%)	M	30 (7,6)	7 (4,0)	-1,624	>0,05
	F	367 (92,4)	170 (96,0)		

Table 1: Proportion of patients by gender in the study groups.

Parameter	Number of observations		LN+	LN-	t -criteria	P
	LN+	LN-				
Age, years	397	177	34,9±0,6	36,1±1,0	-1,019	>0,05
SLE duration, years	391	160	6,9±0,3	5,4±0,5	2,344	<0,05
Patient's age on onset of SLE, years	391	160	28,0±0,6	30,1±0,9	-1,928	>0,05
Observation duration, monthes	283	62	48,6±3,0	25,3±4,3	3,425	<0,001

Table 2: Age of patients at the time of inclusion in the study and at the onset of the disease, as well as the duration of SLE in the study groups.

In most cases of LN, a subacute course of the disease was observed (81.7%), while in the absence of kidney damage, the overwhelming majority of patients with SLE had a chronic course (68.9%). (Table 3)

Course	Number of observations		LN+	LN-	χ^2	P
	LN+	LN-				
Acute, %	397	177	6,2	0,0	9,881	<0,005
Subacute, %	397	177	81,7	31,1	140,957	<0,001
Chronic, %	397	177	12,1	68,9	191,497	<0,001

Table 3: The nature of the course of SLE in the study groups.

Similarly, in the group with LN, a significantly higher degree of disease activity was naturally observed - high activity was detected in almost every third patient (30.4%), compared with patients without kidney damage (19.4%). This is also evidenced by the higher SELENA-SLEDAI disease activity index – 14.2±0.4 versus 6.9±0.3 points (p<0.001).

Predictably, in patients with LN, the estimated GFR was much lower than in individuals without kidney damage (71.4 and 92.5 ml/min, respectively). In the presence of chronic kidney disease, stage 1 prevailed in persons without LN (other causes of CKD), and late stages (3-5) were observed predominantly in LN and accounted for more than a third of cases (36.4%) (Table 4).

CKD stage	Number of observations		LN+	LN-	χ^2	P
	LN+	LN-				
I, %	389	142	38,4	69,0	39,158	<0,001
II, %	389	142	25,2	21,8	0,637	>0,05
III, %	389	142	22,4	7,8	14,725	<0,001
IV, %	389	142	9,5	1,4	9,962	<0,01
V, %	389	142	4,5	0,0	6,566	<0,05

Table 4: CKD stages in the study groups.

In the group of people with LN, as expected, the presence of proteinuria was more often noted (97.7% versus 8.5% in the group without LN), and its level both in a single portion and when calculating the daily amount was significantly higher. In LN, hematuria (56.9% and 2.3%, respectively), leukocyturia (51.8% and 9.5%, respectively), and casts (31.8% and 1.1%, respectively) were significantly more common (Tables 5 and 6).In the biochemical analysis of blood in LN, there were significantly higher levels of creatinine (136.4 versus 78.3 μmol/l, respectively), total cholesterol (6.64 versus 5.24 mmol/l) and low-density lipoproteins (4.25 versus 2.89 mmol/l) with lower blood concentrations of total protein (65.5 versus 77.2 g/l) and albumin (41.7 and 48.9 g/l).

In the general blood test, the average hemoglobin level was significantly lower in the group with LN (109.7 versus 117.5 g/L), as was the percentage of lymphocytes (25.7 versus 28.7%), with a higher level of leukocytes (6.7 x 109/L and 5.7 x 109/L).

Immunological blood parameters showed no significant differences in the study groups, except for a higher frequency of detection of

antiphospholipid antibodies in the group of patients without lupus nephritis (p <0.05).

Parameter	Number of observations		LN+	LN-	t -criteria	P
	LN+	LN-				
GFR, ml/min	314	96	71,4±2,1	92,5±2,7	-5,199	<0,001
Urine protein, g/l	379	148	1,76±0,13	0,02±0,004	8,692	<0,001
Daily proteinuria, g	209	20	2,31±0,21	0,06±0,01	3,246	<0,001
Serum creatinine, μmol/l	312	96	136,4±7,6	78,3±2,8	4,233	<0,001
Total serum protein, g|l	385	156	65,5±0,6	77,2±0,8	-10,379	<0,001
Serum albumin, g/l	369	92	41,7±0,7	48,4±0,8	-5,563	<0,001
Total cholesterol, mmol/l	253	55	6,64±0,13	5,24±0,16	4,695	<0,001
Low-density lipoprotein cholesterol, mmol/l	125	22	4,25±0,15	2,89±0,20	3,783	<0,001
Hemoglobin, g/l	397	179	109,7±1,1	117,5±1,4	-4,041	<0,001
Leukocytes, 10^9/l	393	180	6,7±0,18	5,7±0,2	3,319	<0,001
Lymphocytes, %	292	90	25,7±0,7	28,7±1,1	-2,282	<0,05
Platelets, 10^9/l	278	101	247,3±5,7	251,3±9,1	-0,365	>0,05
ESR, mm|h	390	175	30,2±1,0	27,8±1,4	1,38	>0,05
Antibodies to C1q, U/ml	42	42	201,3±40,0	149,6±34,6	0,977	>0,05

Table 5: Comparison of laboratory parameters in groups of patients with LN and without LN.

Parameter	Number of observations		LN+	LN-	t -criteria	P
	LN+	LN-				
Hematuria, %	397	177	56,9	2,3	14,376	<0,001
Leukocyturia, %	392	169	51,8	9,5	10,257	<0,001
Casta, %	390	177	31,8	1,1	8,645	<0,001
C3, %	165	35	68,5	68,6	0,0001	>0,05
C4, %	162	35	55,6	60,0	0,231	>0,05
CH50, %	86	67	77,9	74,6	0,225	>0,05
Anti-dsDNA antibodies, %	346	166	77,5	72,9	1,367	>0,05
ANA, %	248	93	84,3	91,4	2,888	>0,05
Antibodies to phospholipids, %	114	38	47,4	65,8	3,874	<0,05

Table 6: Comparison of laboratory parameters in groups of patients with LN and without LN.

Patients with LN had hypertension significantly more often (49.9% versus 21.1%), but secondary APS was detected less frequently (Table 7).

Parameter	Number of observations		LN+	LN-	χ^2	P
	LN+	LN-				
Patients with arterial hypertension, %	397	177	49,9	21,1	42,446	<0,001
Patients with APS, %	397	177	8,6	9,4	32,393	<0,001

Table 7: Comorbid conditions in patients with SLE.

LN was more often accompanied by such extrarenal manifestations of SLE as anemia (49.8% versus 28.3%), lymphopenia (18.1% versus 6.1%), and stomatitis (4.0% versus 1.1%). At the same time, the absence of LN was significantly more often accompanied by skin manifestations (51.7% versus 37.2%), photosensitivity phenomena (7.8% versus 2.0%), signs of arthritis (37.8% versus 21.9%) and arthralgia (45.6% versus 36.9%), Raynaud's syndrome (19.4% versus 11.6%) (Table 8).

Parameter	Number of observations		LN+	LN-	χ^2	P
	LN+	LN-				
Arthritis, %	397	177	21,9	37,8	16,009	<0,001
Arthralgia, %	397	177	36,9	45,6	3,851	<0,05
Body temperature increasement, %	397	177	23,4	29,4	2,425	>0,05
Myalgia, %	397	177	2,0	1,1	0,589	>0,05
APS, %	397	177	8,6	9,4	32,394	<0,001
Central nervous system involvement, %	397	177	5,3	6,1	0,165	>0,05
Lymphadenopathy, %	397	177	14,3	18,3	1,517	>0,05
Pneumonitis, %	397	177	7,8	5,6	0,938	>0,05
Photosensitivity, %	397	177	2,0	7,8	11,261	<0,001

Erythema, %	397	177	37,2	51,7	10,691	<0,001
Alopecia, %	397	177	14,3	18,3	1,517	>0,05
Lupus-carditis, %	397	177	20,6	22,8	0,35	>0,05
Stomatitis, %	397	177	4,0	1,1	3,476	<0,05
Weight loss, %	397	177	14,3	18,3	1,517	>0,05
Gastrointestinal tract involvement, %	397	177	3,0	2,8	0,024	>0,05
Serositis, %	397	177	9,6	6,1	1,887	>0,05
Capillaritis, %	397	177	4,8	5,0	0,014	>0,05
Raynaud's syndrome, %	397	177	11,6	19,4	6,398	<0,05
Sjögren's syndrome, %	397	177	2,3	1,1	0,878	>0,05
Anemia, %	397	177	49,8	28,3	23,181	<0,001
Leukopenia, %	397	177	23,4	25,6	0,325	>0,05
Lymphopenia, %	397	177	18,1	6,1	14,927	<0,001
Thrombocytopenia, %	397	177	9,8	8,3	0,314	>0,05

Table 8: Frequency of clinical manifestations of SLE in the study groups.

At the onset of SLE, the picture of extrarenal lesions that accompanied LN or preceded its development was somewhat different: signs of arthritis (45.3% versus 33.6%), lymphadenopathy (11.8% versus 4.8%), and anemia (17.8% versus 4.9%) prevailed. Differences between groups in other clinical manifestations were not statistically significant (Table 9).

Parameter	Number of observations		LN+	LN-	χ^2	P
	LN+	LN-				
Arthritis, %	338	125	45,3	33,6	5,095	<0,05
Arthralgia, %	338	125	13,9	15,2	0,125	>0,05
Body temperature increasement, %	338	125	41,4	32,8	2,848	>0,05
Myalgia, %	338	125	3,9	3,2	0,107	>0,05
APS, %	338	125	3,3	5,6	1,343	>0,05
Central nervous system involvement, %	338	125	2,7	2,4	0,025	>0,05
Lymphadenopathy, %	338	125	11,8	4,8	5,046	<0,05
Photosensitivity, %	338	125	1,5	2,4	0,456	>0,05
Erythema, %	338	125	33,4	30,4	0,382	>0,05
Alopecia, %	338	125	11,8	8,0	1,393	>0,05
Lupus-carditis, %	338	125	5,4	2,4	0,0089	>0,05
Weight loss, %	338	125	8,9	5,6	1,332	>0,05
Gastrointestinal tract involvement, %	338	125	1,5	1,6	0,009	>0,05
Serositis, %	338	125	4,7	3,2	0,519	>0,05
Raynaud's syndrome, %	338	125	6,5	5,6	0,134	>0,05
Anemia, %	338	125	13,9	1,6	14,602	<0,0001
Leukopenia, %	338	125	10,7	4,8	3,787	>0,05
Lymphopenia, %	338	125	4,4	0,8	3,619	>0,05
Thrombocytopenia, %	338	125	8,6	4,0	2,813	>0,05

Table 9: Frequency of clinical manifestations of SLE in the study groups at the onset of the disease.

At the time of the patient's initial examination, the duration of LN averaged 5.9±0.6 years. At the onset of the disease, kidney damage was noted in almost every second person (47.2%). In a number of patients, the first clinical and laboratory manifestations of LN were only changes in urine tests (hematuria, leukocyturia, casts and slight proteinuria - no more than 0.5 g/day). Isolated urinary syndrome (IUS) was observed in 33.5% of cases. In another 11%, isolated proteinuria was detected, not exceeding 3.0 g/day. Thus, in 44.5% of patients (almost half!) the first manifestations of LN concerned only abnormal urine tests, i.e. latent course of nephritis without extrarenal manifestations, which indicates the need for a careful study of urinary tests (general analysis, Nechiporenko test, daily proteinuria) at the initial diagnosis of SLE. In a third of patients (32.1%), LN debuted with the classic nephritic (acute nephritic) syndrome, manifested in most cases by hematuria, casts, moderate or slight proteinuria (usually no more than 1.5 g/day), increased blood pressure and periodically decreased GFR. Almost one in ten (9.2%) had signs of nephrotic syndrome, and in 5% of cases a diagnosis of acute kidney injury (AKI, 1.3%) and rapidly progressive glomerulonephritis (RPGN, 3.7%) was established. Finally, a combination of nephrotic syndrome and RPGN (5.5%), as well as nephrotic and acute nephritic syndromes (3.7%) was found in a number of individuals (Table 10).

Clinical and laboratory syndrome	Number of patients	Number of cases	Frequency, %
UTI	218	73	33,5
Proteinuria	218	24	11,0
Acute nephritic syndrome	218	70	32,1
Nephrotic syndrome	218	20	9,2
RPGN	218	8	3,7
AKI	218	3	1,3
Nephrotic syndrome + RPGN	218	12	5,5
Nephrotic syndrome + acute nephritic syndrome	218	8	3,7
Total		218	100

Table 10: Variants of the onset of LN and their frequency.

Based on histomorphological data obtained after nephrobiopsies in patients with SLE, the most common types of LN are IV (50.3%) and III (25.6%). In 14.1%, “pure” class V was diagnosed. The remaining options were found much less frequently (Table 11).

LN morphological class	Number of nephrobiopsies, n (total 199)	Frequency, %
II	10	5
III	51	25,6
IV	100	50,3
V	28	14,1
VI	3	1,5
III+V	2	1,0
IV+V	1	0,5
Not informative	4	2

Table 11: Morphological types of kidney damage in patients with SLE according to the ISN/RPS classification (2003).

A total of 317 cases of exacerbation of LN were recorded during observation in patients with SLE. The table below shows the types of exacerbations and their frequency. (Table 12)

Type of exacerbation	Number of patients	Number of cases	Frequency, %
UTI	203	43	19,3
Proteinuria	203	66	18,5
Acute nephritic syndrome	203	94	25,2
Nephrotic syndrome	203	25	7,0
RPGN	203	22	7,6
AKI	203	6	1,1
Nephrotic syndrome + RPGN	203	32	8,7
Nephrotic syndrome + acute nephritic syndrome	203	25	1,4
Nephrotic syndrome +AKI	203	4	11,2
Total	203	317	100

Table 12: Variants of exacerbations of LN and its frequency.

Just as in the onset of LN, a significant portion of exacerbations are represented by latent changes (IUS and proteinuria), accounting for 37.8% of all exacerbations. In these cases, there were no extrarenal signs (increased blood pressure and edema), and exacerbation was established by the increase (appearance) and persistent (at least three tests) persistence of proteinuria and changes in urinary sediment. Acute nephritic syndrome was observed in a quarter of cases. However, in contrast to the debut manifestations of LN, more severe variants were much more common - RPGN (7.6%) and combinations of nephrotic syndrome with RPGN (8.7%) and AKI (11.2%), amounting to a total of 27.5% (i.e., in every fourth patient with LN). These types of exacerbations, according to the literature, are serious predictors of adverse outcomes (development of late stages of CKD, initiation of renal replacement therapy, deaths).In the treatment of patients in both groups, almost 100% used glucocorticosteroids (GCS), the average dosage of which in patients with LN was 20.3 mg/day, and in the other group - 12.9 mg/day ($p < 0.001$) (Table 13).

Parameter	Number of observations		LN+	LN-	t -criteria	P
	LN+	LN-				
GCS per os, mg/daily	332	125	20,3±0,7	12,9±0,7	6,210	<0,001

Table 13: Average dosage of prescribed corticosteroids in the study groups.

There was a more frequent use of GCS pulse therapy in the group of patients with LN (26.1% compared to 12.8%). In more than half (53.1%) of patients with LN, immunosuppressive therapy was added to the treatment – azathioprine (27.6%) and cyclophosphamide (17.1%). In the group of patients without LN, cytostatics agents were prescribed much less frequently (azathioprine - 16.0%). Angiotensin-converting enzyme inhibitors (ACEIs) (58.1% vs. 26.0%) and angiotensin II receptor blockers (ARBs) (7.3% vs. 0.0%) were used significantly more often in LN, taking into account their antihypertensive and renoprotective effects. However, in the absence of immune complex kidney damage, hydroxychloroquine (HCQ) was more widely used (54.4% versus 44.1%), although without significant differences. Antiplatelet drugs (36.0% vs. 22.4%) were also more often prescribed to patients with LN; no significant differences could be detected with regard to anticoagulant therapy (16.2% vs. 10.4%). However, plasmapheresis sessions were more often performed in the group without lupus nephritis (in 20.3% and 4.7% of cases, respectively). In 3.7% of patients with LN, methods of renal replacement therapy were used (sessions of hemodialysis, hemodiafiltration, peritoneal dialysis and kidney transplantation) (Table 14).

Parameter	Number of observations		LN+	LN-	χ^2	P
	LN+	LN-				
GCS pulse therapy, %	333	125	26,1	12,8	9,259	<0,005
Hydroxychloroquine, %	333	125	44,1	54,4	3,838	>0,05
Cyclophosphamide,%	333	125	17,1	0,0	24,438	<0,001
Azathioprine, %	333	125	27,6	16,0	6,651	<0,05
Mycophenolate mofetil, %	254	50	11,5	0,0	6,375	<0,05
ACEIs, %	254	50	58,1	26,0	17,042	<0,001
BRA, %	254	50	7,3	0,0	3,864	<0,05
Heparin, %	333	125	16,2	10,4	2,462	>0,05
Antiplatelet agents, %	333	125	36,0	22,4	7,726	<0,05
Plasmapheresis, %	234	79	4,7	20,3	18,124	<0,001
Hemodialysis, %	333	125	3,3	0,0	4,231	<0,05
Kidney transplantation, %	234	50	0,4	0,0	0,214	>0,05

Table 14: Frequency of use of various therapeutic agents in the study groups.

Among patients under dynamic observation (from 1 month to 20 years), the development of complications associated with both the underlying disease and the therapy was studied. A total of 49 such complications (19.3%) were identified, 36 in the group with LN and 13 without kidney damage. The most common changes (8 cases) were changes in the musculoskeletal system (aseptic necrosis of bone tissue), which were observed only in the group of patients with LN and were probably associated with a higher dose of corticosteroids used. Infectious complications come in second place in frequency (7 cases in the LN group and 5 cases in people without LN). This is followed by a complication in the form of osteoporosis with symptoms of vertebral compression fractures (6 cases in the LN group and 4 cases in the absence of LN). Five cases of Cushing syndrome have been described (all in individuals with LN). Complications from the cardiovascular system in the form of myocardial infarction and acute cerebrovascular accident were noted in 5 cases (3 and 2, respectively). In 4 cases, patients developed glaucoma (2 and 2, respectively), in 2 - a steroid gastric ulcer, in one - drug-induced stomatitis, etc. (all in the LN group). One patient from the group without kidney damage was diagnosed with ovarian cancer. Apparently, the vast majority of the described complications are associated with the drug therapy and, above all, with the prescription of GCS. When studying disease outcomes, the end points were patient death and "renal" death, i.e. development of end-stage chronic renal failure and/or transfer of the patient to renal replacement therapy. According to the data obtained, the presence of LN is an extremely unfavorable factor. If in the group of patients without kidney damage the rate of adverse outcomes was 1.7%, then in the presence of LN this figure reached 20.7%. Mortality in the group of people with LN was 9.9%, while the death of patients associated specifically with the presence of nephritis (end-stage CKD) occurred almost 2 times more often than deaths associated with other causes (cardiovascular and infectious complications, gastrointestinal bleeding, etc.). In addition to these cases, end-stage CKD was noted in 7.8% of cases, and taking into account deaths - in almost 15% (14.1%). An important end point in assessing the outcome of renal pathology is a persistent (at least 3 months) doubling of blood creatinine levels compared to the initial level, indicating the steady progression of CKD. In the study group of patients, this figure was 3.3%; these individuals are potential candidates for the use of renal replacement therapy methods in the near future. 12.7% were treated with program hemodialysis, 7% of patients underwent kidney transplantation. (Table 15)

Parameter	LN+	LN-
Number of patients, n	396	172
Doubling of serum creatinine level, n (%)	13 (3,3)	0
End-stage CKD (including those receiving RRT), n (%)	31 (7,8)	0
LN-associated death, n (%)	25 (6,3)	0
Death from other causes, n (%)	13 (3,3)	3 (1,7)
Total number of adverse outcomes, n (%)	82 (20,7)	3 (1,7)
Duration of observation, months	48,6±3,0	25,3±4,3

Table 15: Adverse outcomes in patients with and without LN.

Finally, the number of hospitalizations appears to be an important socioeconomic indicator. It turned out that during the observation period in the presence of LN it averaged 2.09±0.3, and in the absence of kidney damage - 1.43±0.3 (p=0.0033). (Table 16)

Parameter	Number of observations		LN+	LN-	t -criteria*	P
	LN+	LN-				
Number of hospitalizations,n	237	39	2,09	1,43	2,999	=0,0033

Table 16: Comparison of normalized number of hospitalizations per year between patients with and without LN.

Discussion and conclusions

Systemic lupus erythematosus is a fairly rare disease. Its highest incidence and prevalence are reported in North America, with rates of 23.2 and 241 per 100,000 population, respectively. In the United States, there are more than 250,000 patients suffering from SLE [13]. However, worldwide, the overall incidence of SLE varies widely, ranging from 4 to 250 cases per 100,000 population [14]. According to our earlier study, in Minsk the incidence of SLE was 4-5, and the prevalence was 18-20 patients per 100,000 urban adult population [15]. The clinical forms and course of SLE are diverse and often become severe, accompanied by serious complications and even deaths. In such situations, there is a need to prescribe active therapy using high doses of GCS and immunosuppressive drugs, the administration of which may be accompanied by severe side effects. LN, along with damage to the central nervous system, is the cause of complications and unfavorable outcomes of SLE, but is much more common than neurolupus. For the first time, using a large material, we tried to give a comprehensive (clinical, laboratory and morphological) assessment of patients with LN, to analyze the features of the course of nephritis and its outcomes. A retrospective and prospective analysis of 574 cases of SLE over a more than 30-year period revealed a high incidence of lupus nephritis (69.2%), probably associated with the predominance of inpatients in whom exacerbation of LN was one of the indications for hospitalization. The study showed an increase in cases of LN as the duration of the underlying disease increased. Accordingly, the observation time for patients with LN turned out to be significantly longer than for persons without kidney damage, due to the need for more careful and frequent monitoring of the course of the disease. Among patients with LN, the acute and subacute course of the disease was significantly more common, while in patients without lupus nephritis, a chronic course of SLE was mainly observed. Disease activity, including that calculated using the SELENA-SLEDAI index, was also significantly higher in the group of patients with LN. Interestingly, the immunological activity of SLE in patients with and without LN did not have significant differences, which is at odds with a number of literature data [5, 7]. In the presence of LN, hypertension was more often observed, which is partly explained by the presence of more advanced stages of CKD. At the same time, patients with LN are significantly less likely to have secondary APS. In addition, patients with SLE without LN were significantly more likely to have symptoms such as skin manifestations, photosensitivity, arthritis and arthralgia, and Raynaud's syndrome. It is noteworthy that at the onset of the disease, kidney damage was noted in almost half of the patients with SLE (48.2%), and in many cases, the first clinical and laboratory manifestations of LN were only changes in urine tests. In more than 10% of cases, lupus nephritis debuted with manifestations of RPGN or AKI, including in combination with nephrotic syndrome. Obviously, taking into account the unfavorable prognosis and more intense immunosuppression already at the time of diagnosis of SLE, to improve patient survival, a careful analysis of available clinical and laboratory data is required: general urine analysis, analysis for daily proteinuria, determination of GFR, as well as monitoring these parameters over time. Such therapeutic tactics as nephrobiopsy makes possible early identification of lupus nephritis, as well as choosing the most rational immunosuppression, which will ultimately reduce the number of exacerbations of LN, especially in combination of RPGN and AKI or acute nephritic syndrome. In this way, it is possible to achieve a reduction in the number of hospitalizations, as well as prolongation of the patient's "renal" and general life. The vast majority (75%) of patients with LN have proliferative forms according to histological examination. The presence of lupus nephritis in a patient with SLE is associated with a higher incidence of complications and deaths, as well as more hospitalizations.

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