Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founders:
- State Institution «Institute of Nephrology NAMS of Ukraine»
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352 **Journal homepage: https://ukrjnd.com.ua**

Research article

doi: 10.31450/ukrjnd.2(78).2023.08

O. Iaremenko[1], D. Koliadenko[1], K. Iaremenko[2], I. Matiyashchuk[3]

Lupus nephritis: clinical characteristics, serological associations, pattern of pro- and anti-inflammatory markers

[1]Bogomolets National Medical University, Kyiv, Ukraine
[2]Alexander Clinical Hospital, Kyiv, Ukraine
[3]Medical Center EmCell, Kyiv, Ukraine

Citation: Iaremenko O, Koliadenko D, Iaremenko K, Matiyashchuk I. Lupus nephritis: clinical characteristics, serological associations, pattern of pro- and anti-inflammatory markers. Ukr J Nephr Dial. 2023;2(78):69-80. doi: 10.31450/ukrjnd.2(78).2023.08.

Abstract. *The present study aimed to investigate the prevalence, clinical, and laboratory characteristics of renal involvement in a large cohort of Ukrainian patients with systemic lupus erythematosus (SLE).*

Methods. A total of 380 patients with SLE were enrolled in this cross-sectional study, including 176 with lupus nephritis (LN) and 204 with non-renal SLE. Patients were reviewed for demographic details, clinical SLE manifestations, SLE Disease Activity Index 2000 (SLEDAI-2K), and SLICC/ACR Damage Index. Laboratory evaluations included complete blood count with an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), anti-CRP antibodies, serum creatinine, complement C3 and C4 levels, urinalysis, 24-hour urine protein, specific autoantibodies, interleukin-6 (IL-6), IL-10.

Results. There was a significantly higher frequency of malar rash, lymphadenopathy, splenomegaly, serositis, pulmonitis, fever, necrotizing vasculitis, and a history of arterial/venous thrombosis in patients with LN; while Raynaud's phenomenon, Sjogren's syndrome, peripheral nervous system manifestations occurred more often in patients with non-renal SLE. Patients with LN were found to have higher ESR levels and lower IL-10 levels. Either frequency of anti-dsDNA positivity and its titer were higher in the LN group with no differences regarding other autoantibodies. C3 and C4, CRP, hs-CRP, anti-CRP, and IL-6 levels showed no significant difference between the groups.

Multivariate analysis demonstrated that LN was positively associated with pulmonitis (OR 5.34 (95% CI 1.88-15.10), p=0.002), arterial/venous thrombosis (OR 6.80 (95% CI 1.87-24.70), p=0.004), anti-dsDNA positivity (OR 6.22 (95% CI 1.89-20.50), p=0.003), higher SLEDAI-2K score (OR 1.15 (95% CI 1.08-1.23), p<0.001) and negatively associated with Raynaud's syndrome (OR 0.20 (95% CI 0.08-0.49), p<0.001) and younger age at disease onset (OR 0.96 (95% CI 0.93-0.99), p=0.003).

In the LN group, 27 patients (15.3%) had nephrotic syndrome. In multivariate logistic analysis, male sex (OR 5.21 (95% CI 1.77-15.30), p=0.003) and higher SLICC/ACR score (OR 2.12 (95% CI 1.45-3.09), p<0.001) were associated with increased risk of nephrotic syndrome, whereas lymphadenopathy (OR 0.31 (95% CI 0.12-0.80), p=0.02) was associated with decreased risk of nephrotic syndrome development.

Conclusions. Our cohort of Ukrainian LN patients showed different characteristics in demographic, clinical, and laboratory findings compared to patients with non-renal SLE. These features are mostly on par with LN patients of other nationalities around the world.

Keywords: *systemic lupus erythematosus, lupus nephritis, risk factor, biomarkers, autoantibodies, interleukins.*

Article history:
Received May 18, 2023
Received in revised form May 27, 2023
Accepted May 28, 2023

Conflict of interest. The authors declare no conflict of interest.

Correspondence should be addressed to Oleg Iaremenko: o.b.iaremenko@gmail.com

УДК 616.5-002.52-06-071(477)

О.Б. Яременко[1], Д.І. Коляденко[1], К.М. Яременко[2], І.Г. Матіящук[3]

Клініко-лабораторні особливості та патерн запальних і протизапальних маркерів у хворих з люпус-нефритом

[1]Національний медичний університет імені О.О. Богомольця, м. Київ, Україна
[2]Олександрівська клінічна лікарня, м. Київ, Україна
[3]Медичний центр EmCell, м. Київ, Україна

Резюме. *Мета роботи: вивчити поширеність, клінічні та лабораторні асоціації ураження нирок у великій когорті хворих на системний червоний вовчак (СЧВ) в Україні.*

Матеріал та методи. У крос-секційному дослідженні взяли участь 380 хворих на СЧВ, з них 176 із люпус-нефритом і 204 без ураження нирок. Проаналізовано демографічні та клінічні дані, індекс активності захворювання (SLEDAI-2K) і пошкодження (SLICC/ACR). Лабораторні дослідження включали загальний аналіз крові зі швидкістю осідання еритроцитів (ШОЕ), С-реактивний білок (СРБ), високочутливий СРБ (вч-СРБ), антитіла до СРБ, креатинін сироватки крові, рівні С3 і С4 комплементу, загальний аналіз сечі, добову протеїнурію, специфічні аутоантитіла, інтерлейкін-6 (ІЛ-6), ІЛ-10.

Результати. У хворих з люпус-нефритом спостерігалася значно більша частота еритематозного висипу на обличчі у вигляді метелика, лімфаденопатії, спленомегалії, серозитів, пульмоніту, лихоманки, некротичного васкуліту та артеріального/венозного тромбозу; тоді як феномен Рейно, синдром Шегрена, ураження периферичної нервової системи частіше виникали у хворих на СЧВ без ураження нирок. У хворих з люпус-нефритом спостерігався вищий рівень ШОЕ та нижчий рівень ІЛ-10 порівняно з пацієнтами без ниркових проявів. Частота виявлення та титр антитіл до двоспіральної ДНК були достовірно вищими у групі хворих на люпус-нефрит порівняно з пацієнтами без ураження нирок. Рівні С3 і С4, СРБ, вч-СРБ, антитіл до СРБ, ІЛ-6 суттєво не відрізнялись між групами.

При проведенні багатофакторного аналізу виявлено, що пульмоніт (ВШ 5,34 (95% ДІ 1,88-15,10), p=0,002), артеріальний/венозний тромбоз (ВШ 6,80 (95% ДІ 1,87-24,70), p=0,004), позитивні антитіла до двоспіральної ДНК (ВШ 6,22 (95% ДІ 1,89-20,50), p=0,003), вищий індекс SLEDAI-2K (ВШ 1,15 (95% ДІ 1,08-1,23), p<0,001), молодший вік на момент дебюту захворювання (ВШ 0,96 (95% ДІ 0,93-0,99), p=0,003) підвищують ризик люпус-нефриту, тоді як синдром Рейно (ВШ 0,20 (95% ДІ 0,08-0,49), p<0,001) пов'язаний зі зниженням ризику люпус-нефриту.

Серед хворих з люпус-нефритом 27 пацієнтів (15,3%) мали нефротичний синдром. У багатофакторному логістичному аналізі чоловіча стать (ВШ 5,21 (95% ДІ 1,77-15,30), p=0,003) і вищий індекс SLICC/ACR (ВШ 2,12 (95% ДІ 1,45-3,09), p<0,001) асоціювались з підвищеним ризиком нефротичного синдрому, тоді як лімфаденопатія (ВШ 0,31 (95% ДІ 0,12-0,80), p=0,02) пов'язана зі зниженим ризиком розвитку нефротичного синдрому.

Висновки. Наша когорта українських пацієнтів з люпус-нефритом демонструє певні відмінності в демографічних, клінічних і лабораторних показниках порівняно з хворими на СЧВ без ураження нирок. Ці відмінності здебільшого відповідають результатам міжнародних досліджень за участі пацієнтів інших національностей.

Ключові слова: *системний червоний вовчак, люпус-нефрит, фактор ризику, біомаркери, аутоантитіла, інтерлейкіни.*

Introduction. Immune complex mediated inflammation of the kidney, known as lupus nephritis (LN), is one of the most significant manifestations of systemic lupus erythematosus (SLE) [1]. LN develops in nearly 25-75% of SLE patients [2], usually at the onset of SLE or within the first five years of disease onset [3]. Data on the predictors of LN development among patients with SLE remain limited. However, male sex, younger age at the time of SLE diagnosis, and Hispanic or African American ethnicity are generally considered risk factors for LN [2, 4].

Олег Борисович Яременко
o.b.iaremenko@gmail.com

Although the dysregulated immune response in SLE is also responsible for the development of LN, recent research suggests that the role of autoantibodies may not be as direct as previously thought, with a greater emphasis on infiltrating innate cells causing local renal inflammation [5]. Factors such as ethnicities, human leukocyte antigen genotypes, specific autoantibodies and autoantigens have been linked to the development of LN [1]. However, the specific immunological mechanisms that determine why some individuals with SLE develop LN and others do not remain unclear. Aw Y.T. et al. hypothesized that intrinsic differences in the underlying peripheral immunophenotype of some individuals with SLE predispose to a proinflammatory response in renal tissue leading to the development of LN [1]. It was found that patients with LN had increased Th2 and T regulatory cells compared to both SLE patients with-

out nephritis and healthy donors. So SLE patients with and without LN have distinct immunologic differences that may reflect the unique pathophysiological processes contributing to disease manifestations [1].

LN may present with clinical manifestations (arterial hypertension, edema) [4] and/or laboratory changes (proteinuria, active urinary sediment, increased serum creatinine), and can progress to end-stage renal disease (ESRD) [3]. Kidney biopsy is the gold standard for diagnosing LN and determining the degree of renal inflammation [6]. Histologically LN is characterized by glomerular deposition of immune complexes with damage of mesangial, endothelial, and epithelial cells. Based on the glomerular location, extent, and pattern of injury LN can be classified into six histological classes established by the World Health Organization (WHO) and later updated by the International Society of Nephrology/Renal Pathology Society (ISN/RPS): minimal mesangial, mesangial proliferative, focal proliferative, diffuse proliferative, membranous, and advanced sclerosing LN [7]. Classes III-VI are associated with the greatest risk of long-term damage [4, 8]. Although kidney biopsy is considered the gold standard to accurately capture the degree of kidney inflammation, the renal domain score of the SLE disease activity index (rSLEDAI) is among the most commonly used routine clinical measures of LN activity [6].

LN has a greater impact on mortality than any other SLE manifestation. Despite the management options provided for patients with LN, 10% to 30% of cases progress to ESRD within 15 years after diagnosis [4]. A recent study suggests that simultaneous positivity for anti-dsDNA, -nucleosome, and -histone antibodies is related to severe LN with the rapid decline of renal function [9].

Despite the extensive international literature discussing LN, studies concerning clinical and laboratory associations of LN are limited in Ukraine. Data about the pattern of pro- and anti-inflammatory markers in patients with LN are still scarce and contradictory.

The aim of the study: to determine the prevalence of LN and to identify the demographic, clinical, and laboratory characteristics of LN in Ukrainian patients with SLE. In addition, we assessed and compared pro- and anti-inflammatory markers in SLE patients with and without renal involvement.

Materials and methods. This cross-sectional study was conducted at the Department of Internal Medicine #3 of Bogomolets National Medical University and included 391 patients 18 years and older who were diagnosed with SLE in the period from 1994 to 2023. All patients who had been initially monitored before 2019 were diagnosed in accordance with the American College of Rheumatology (ACR) criteria (1982, updated 1997) [10], in 2019, the diagnosis of SLE in these patients was reviewed for compliance with the European League Against Rheumatism (EULAR)/ACR classification criteria 2019 [11]. According to the results of this review, 11 patients were excluded from the primary pool of patients, and the data of 380 persons were included in the final analysis. All study procedures were in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of Bogomolets National Medical University.

Patients were reviewed for demographic details (sex, age), age at SLE onset, clinical manifestations of SLE (current and in medical history), SLE Disease Activity Index 2000 (SLEDAI-2K) [12], and SLICC/ACR Damage Index [13]. Laboratory evaluations included complete blood count with an erythrocyte sedimentation rate (ESR) measured by Westergren method, C-reactive protein (CRP) measured by latex turbidimetric method (Roche Diagnostics, Switzerland), high-sensitivity CRP (hs-CRP) measured by an enzyme-linked immunosorbent assay (ELISA) (DRG International Inc., USA), serum creatinine, complement C3 and C4 levels, urinalysis, 24-hour urine protein. The estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14]. Immunological markers, such as antinuclear antibodies detected by indirect immunofluorescence (EUROIMMUN, Germany; positive ≥1:80, in accordance with EULAR/ACR criteria 2019), anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm) antibodies, anti-Ro/SS-A, anti-La/SS-B, anti-ribonucleoprotein (anti-RNP), antiphospholipid antibodies, including immunoglobulin G (IgG) and immunoglobulin M (IgM) anticardiolipin antibodies, anti-β2-glycoproteins (all measured by a standardized ELISA, EUROIMMUN, Germany), and lupus anticoagulant (measured by coagulation assay, Siemens, Germany) were also documented. Serum levels of anti-CRP antibodies, interleukin-6 (IL-6), and IL-10 were assayed by ELISA (Wuhan Fine Biotech Co., Ltd., China; Demeditec Diagnostics GmbH, Germany).

LN was diagnosed by renal biopsy and/or according to renal SLEDAI criteria in the absence of other alternative causes. All pathology reports of patients who underwent kidney biopsies were reviewed to identify the ISN/RPS histological class of LN [7]. The presence of renal involvement due to renal SLEDAI criteria (score 4-16) was defined by the presence of at least one subcomponent of the following on urinalysis: hematuria (>5 RBC/HPF), proteinuria (>0.5 g/24 hours), pyuria (>5 WBC/HPF), urinary casts (hemegranular or red cell).

The use of the following medications at baseline was reviewed: hydroxychloroquine, glucocorticoids, cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, rituximab, belimumab. Adjustment of glucocorticoid dose or treatment regimen if needed was made after blood and urine collection.

For statistical analysis, EZR software (version 1.61) was used. Data were presented as means (± standard deviations) or medians (interquartile range) for normal distributing or non-normal distributing contin-

uous variables, respectively, and numbers (%) for categorical variables. For the comparisons between groups, Student's t-test or the Mann-Whitney test was used for continuous variables, and Fisher's exact test (or chi-square test when appropriate) was used for categorical variables. Stepwise multiple logistic regression analysis was performed to identify variables independently associated with renal involvement. The significance level was determined as $p<0.05$.

Results. A total of 380 patients with SLE were enrolled in the study, including 176 with LN and 204 with non-renal SLE. All study cohort participants were of Caucasian ethnicity. The median age of the patients was 37 (26-48) years and the majority of the patients were female (n=331; 86.6%). The age at disease onset was 27 (20-40) years and the disease duration was 59.5 (22-120) months. The median values of SLEDAI-2K and SLICC scores were 10 (6-16) and 1 (0-2), respectively. Hydroxychloroquine was used in 64.7% of the patients and glucocorticoids were used in 78.8% of patients. Regarding immunosuppressants, cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate, were used in 3.5%, 1.2%, 1.5%, and 2.3% of the patients, respectively. Belimumab was used in 5.0% of patients and rituximab was received by 0.3% of patients.

Overall, only 7 (4.0%) of our total LN patients had performed kidney biopsies. The most common ISN/RPS class of LN in our study was class IV, seen in 57.1% of biopsied cases. Class V was detected in 28.6% and class III in 14.3% for each. Two patients (1.1%) of the total LN cohort of our study required renal replacement (RRT) therapies; one was on RRT (hemodialysis) at the time of presentation.

Kidney involvement in SLE was associated with either younger age of patients and younger age at disease onset (Table 1).

Table 1

Clinical and laboratory manifestations of SLE patients depending on the presence of renal involvement

Variables	SLE patients with LN (n=176)	Non-renal SLE patients (n=204)	*p*
Demographic data			
Male sex, n (%)	28 (15.9)	23 (11.3)	0.243
Age, years	33 (24-42)	40 (29-50.5)	<0.001
Age at SLE onset, years	24 (18-35)	30 (21-44)	<0.001
Disease duration, months	56 (14-108)	59 (24-120)	0.162
SLE-specific indices			
SLEDAI-2K score	14 (8-19)	8 (4-14)	<0.001
SLICC/ACR score	1 (1-2)	1 (0-2)	0.013
Clinical manifestations, n (%)			
Skin manifestations	121 (69.5)	131 (64.5)	0.358
Malar rash	74 (43.0)	66 (32.5)	0.047
Alopecia	59 (33.9)	57 (27.9)	0.255
Sjogren's syndrome	5 (3.1)	16 (8.5)	0.048
Mucous membrane manifestations	62 (35.4)	66 (32.8)	0.675
Arthritis	104 (59.4)	114 (59.4)	0.632
Raynaud's syndrome	33 (19.0)	64 (31.8)	0.006
Arterial/venous thrombosis	17 (9.7)	5 (2.5)	0.005
Necrotizing vasculitis	16 (9.2)	4 (2.0)	0.003
Lymphadenopathy	107 (61.1)	89 (44.3)	0.002
Splenomegaly	19 (10.9)	6 (3.0)	0.004
Serositis	83 (47.4)	60 (29.7)	<0.001
Cardiac manifestations	114 (65.1)	114 (56.4)	0.106
Pulmonitis	57 (32.8)	27 (13.4)	<0.001
CNS involvement	36 (20.5)	41 (20.3)	0.928
PNS involvement	7 (4.0)	25 (12.4)	0.004
Antiphospholipid syndrome	13 (8.2)	13 (7.0)	0.842

Continuation of Table 1

Variables	SLE patients with LN (n=176)	Non-renal SLE patients (n=204)	*p*
Fever	63 (37.3)	47 (24.0)	0.008
Weight loss	24 (16.0)	30 (16.0)	0.889
Laboratory data			
Anemia, n (%)	43 (53.7)	29 (44.6)	0.354
Leukopenia, n (%)	41 (53.2)	37 (58.7)	0.632
Thrombocytopenia, n (%)	26 (33.8)	20 (31.3)	0.889
Serum creatinine, μmol/L	90 (64-110)	70 (61-80)	0.004
eGFR, ml/min/1.72m2	81.7±33.4	91.4±24.7	0.032
ESR, mm/hr	28 (13-48)	21 (10-35)	0.010
CRP, mg/L	6 (0-18)	8 (0-24)	0.153
hs-CRP, mg/L	7.19 (2.50-25.98)	6.79 (4.67-15.21)	0.795
IL-6, pg/ml	4.53 (2.40-10.40)	5.38 (2.30-23.51)	0.910
IL-10, pg/ml	3.21 (3.00-26.57)	14.58 (3.21-28.77)	0.042
C3, g/L	0.87 (0.65-1.03)	0.75 (0.61-1.06)	0.532
C4, g/L	0.15±0.09	0.14±0.06	0.634
Autoantibody positivity			
Anti-dsDNA, n (%)	84 (71.8)	93 (59.2)	0.042
Anti-dsDNA titer, IU/ml	23 (6-53)	13 (4-29)	0.002
Anti-Sm, n (%)	9 (14.5)	14 (29.2)	0.106
Anti-Ro, n (%)	28 (51.9)	29 (50.9)	0.928
Anti-La, n (%)	13 (25.0)	8 (17.8)	0.537
Anti-RNP, n (%)	12 (31.6)	19 (50.0)	0.163
APLA, n (%)	21 (61.8)	11 (42.3)	0.22
Anti-chromatin, n (%)	18 (72.0)	16 (53.3)	0.255
Anti-CRP, ng/ml	6.91 (4.79-10.89)	7.75 (4.78-12.29)	0.685
Medications			
Glucocorticoids, n (%)	139 (79.0)	159 (77.9)	0.905
Oral glucocorticoid dose, mg/d	10 (10-20)	10 (7.5-20)	0.248
Hydroxychloroquine, n (%)	102 (58.0)	144 (70.6)	0.014
Cyclophosphamide, n (%)	7 (5.1)	2 (1.7)	0.247
Mycophenolate mofetil, n (%)	2 (1.4)	1 (0.8)	0.889
Azathioprine, n (%)	4 (2.9)	0 (0.0)	0.132
Methotrexate, n (%)	1 (0.7)	5 (4.2)	0.143
Rituximab, n (%)	1 (0.6)	0 (0.0)	0.944
Belimumab, n (%)	11 (6.3)	8 (3.9)	0.424

Note: values are expressed as a median (QI-QIII), means (±standard deviations), or n (%).

Bolded p values indicate statistically significant group differences between SLE patients with lupus nephritis and non-renal SLE patients.

Abbreviations: SLE: systemic lupus erythematosus; LN: lupus nephritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CNS: central nervous system; PNS: peripheral nervous system; eGFR: estimated glomerular filtration rate using CKD-EPI; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; anti-dsDNA: anti-double-stranded DNA antibodies; anti-Sm: anti-Smith antibodies; anti-RNP: anti-ribonucleoprotein antibodies; APLA: antiphospholipid antibodies; anti-CRP: anti-C-reactive protein antibodies.

The proportion of male sex in patients with LN was higher than in non-renal SLE, however, the statistical significance was not reached. Malar rash (43.0% vs 32.5%), lymphadenopathy (61.1% vs 44.3%), splenomegaly (10.9% vs 3.0%), serositis (47.4 vs 29.7%), pulmonitis (32.8% vs 13.4%), fever (37.3% vs 24.0%) were more common in patients with LN; while Raynaud's phenomenon (19.0% vs 31.8%), Sjogren's syndrome (3.1% vs 8.5%), peripheral nervous system manifestations (4.0% vs 12.4%) occurred more often in patients with non-renal SLE. Besides, a higher proportion of LN patients had necrotizing vasculitis (9.2% vs 2.0%) and a history of arterial/venous thrombosis (9.7% vs 2.5%) compared to patients without kidney involvement. In addition, the SLEDAI score of LN patients was significantly higher (14 (8-19) points vs 8 (4-14) points, p<0.001) than in non-renal SLE patients. The frequency of anemia, leukopenia, and thrombocytopenia did not differ significantly between the groups. LN patients had significantly higher serum creatinine levels than those with non-renal SLE (90 (64-110) μmol/L vs 70 (61-80) μmol/L, p=0.004). Accordingly, eGFR in LN patients was lower compared to the non-renal SLE group (81.7±33.4 ml/min/1.72m2 vs 91.4±24.7 ml/min/1.72m2, p=0.035). Patients with LN were found to have higher ESR levels (28 (13-48) mm/hr vs 21 (10-35) mm/hr, p=0.01) and lower IL-10 level (3.21 (3.00-26.57) pg/ml vs 14.58 (3.21-28.77) pg/ml, p=0.042). Either frequency of anti-dsDNA positivity and its titer were higher in the LN group with no differences in regard to other autoantibodies. C3 and C4, CRP, hs-CRP, anti-CRP, and IL-6 levels showed no significant difference between the groups. It should be noted that the proportion of LN patients taking hydroxychloroquine (58.0%) was significantly lower than in the non-renal SLE group (70.6%, p=0.014). No differences were found in other medications used and oral glucocorticoid dose.

Based on the baseline comparisons above, risk factors were estimated by logistic regression analysis (Table 2).

Table 2

Logistic regression analysis of variables independently associated with LN

Variables	Univariate analysis			Multivariate analysis		
	Coefficient	Odds ratio (95% CI)	p	Coefficient	Odds ratio (95% CI)	*p*
Age	-0.04±0.01	0.96 (0.95-0.98)	<0.001			
Age at onset	-0.03±0.01	0.97 (0.95-0.99)	<0.001	-0.05±0.02	0.96 (0.93-0.99)	0.003
SLEDAI-2K score	0.11±0.02	1.12 (1.08-1.15)	<0.001	0.14±0.03	1.15 (1.08-1.23)	<0.001
SLICC/ACR score	0.24±0.09	1.27 (1.05-1.53)	0.012			
Malar rash	0.42±0.21	1.54 (1.01-2.34)	0.045			
Sjogren's syndrome	-1.04±0.52	0.35 (0.13-0.99)	0.047			
Raynaud's syndrome	-0.69±0.25	0.50 (0.31-0.81)	0.005	-1.63±0.47	0.20 (0.08-0.49)	<0.001
Arterial/venous thrombosis	1.59±0.53	4.93 (1.74-13.9)	0.003	1.92±0.66	6.80 (1.87-24.70)	0.004
Necrotizing vasculitis	1.61±0.57	4.99 (1.63-15.2)	0.005			
Lymphadenopathy	0.68±0.21	1.98 (1.31-2.99)	0.001			
Splenomegaly	1.38±0.48	3.96 (1.54-10.2)	0.004			
Serositis	0.76±0.22	2.14 (1.40-3.26)	<0.001			
Pulmonitis	1.14±0.26	3.14 (1.88-5.25)	<0.001	1.68±0.53	5.34 (1.88-15.10)	0.002
PNS involvement	-1.22±0.44	0.30 (0.12-0.70)	0.006			
Fever	0.63±0.23	1.87 (1.19-2.94)	0.007			
Hydroxychloroquine	-0.55±0.22	0.57 (0.38-0.88)	0.01			
ESR	0.01±0.01	1.01 (1.00-1.02)	0.005			
Anti-dsDNA positivity	0.53±0.26	1.70 (1.01-2.84)	0.044	1.83±0.61	6.22 (1.89-20.50)	0.003
Anti-dsDNA titer	0.06±0.002	1.01 (1.00-1.01)	0.004			
IL-10	-0.04±0.02	0.96 (0.93-0.99)	0.02			

Abbreviations: LN: lupus nephritis; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PNS: peripheral nervous system; ESR: erythrocyte sedimentation rate; IL: interleukin; anti-dsDNA: anti-double-stranded DNA antibodies.

In multivariate logistic analysis, LN was found to be positively associated with pulmonitis (OR 5.34 (95% CI 1.88-15.10), p=0.002), arterial/venous thrombosis (OR 6.80 (95% CI 1.87-24.70), p=0.004), anti-dsDNA positivity (OR 6.22 (95% CI 1.89-20.50), p=0.003), and higher SLEDAI score (OR 1.15 (95% CI 1.08-1.23),

p<0.001). However, renal involvement was negatively associated with Raynaud's syndrome (OR 0.20 (95% CI 0.08-0.49), p<0.001) and younger age at disease onset (OR 0.96 (95% CI 0.93-0.99), p=0.003). An area under the curve (AUC) of 0.856 was obtained in the receiver operating characteristic (ROC) curve (Fig. 1).

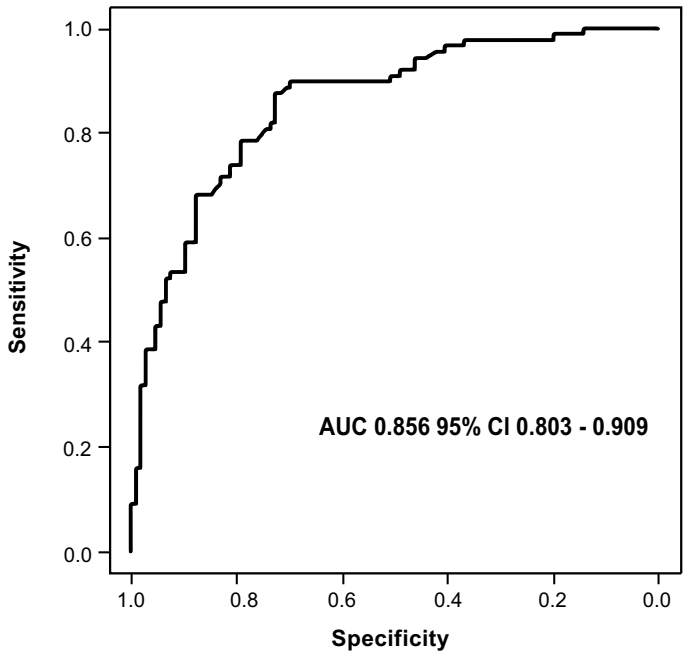

Fig. 1. ROC-curve for the multivariate logistic analysis of risk factors for renal involvement in patients with SLE. Variables included in the model: age at onset, SLEDAI-2K score, Raynaud's syndrome, arterial/venous thrombosis, pulmonitis, and anti-dsDNA positivity.

In the LN group, 27 patients (15.3%) had nephrotic syndrome and 149 patients (84.7%) had non-nephrotic range proteinuria (Table 3).

Table 3

Clinical and laboratory manifestations of LN patients depending on the presence of nephrotic syndrome

Variables	LN patients with nephrotic syndrome (n=27)	LN patients with non-nephrotic proteinuria (n=149)	*p*
Demographic data			
Male sex, n (%)	9 (33.3)	19 (12.8)	0.032
Age, years	30 (25-42)	33 (24-42)	0.998
Age at onset, years	24 (18-37)	24 (19-35)	0.933
Disease duration, months	48 (12-96)	60 (14-120)	0.633
SLE-specific indices			
SLEDAI-2K score	14 (8-18)	14 (8-19)	0.780
SLICC/ACR score	2 (1-4)	1 (0-2)	<0.001
Clinical manifestations, n (%)			
Skin manifestations	21 (77.8)	100 (68.0)	0.419
Malar rash	13 (48.1)	61 (41.5)	0.668
Alopecia	8 (29.6)	51 (34.7)	0.772
Sjogren's syndrome	1 (4.0)	4 (3.1)	0.682
Mucous membrane manifestations	13 (48.1)	49 (33.1)	0.209
Arthritis	16 (59.3)	88 (59.5)	0.850
Raynaud's syndrome	5 (18.5)	28 (19.0)	0.842
Arterial/venous thrombosis	8 (29.6)	9 (6.0)	0.005
Necrotizing vasculitis	0 (0.0)	16 (10.9)	0.065
Lymphadenopathy	11 (40.7)	96 (64.9)	0.035
Splenomegaly	4 (14.8)	15 (10.1)	0.712
Serositis	12 (44.4)	71 (48.0)	0.897

Continuation of Table 1

Variables	LN patients with nephrotic syndrome (n=27)	LN patients with non-nephrotic proteinuria (n=149)	*p*
Cardiac manifestations	13 (48.1)	101 (67.8)	0.091
Pulmonitis	7 (25.9)	50 (34.0)	0.543
CNS involvement	6 (22.2)	30 (20.1)	0.992
PNS involvement	1 (3.8)	6 (4.1)	0.646
Antiphospholipid syndrome	4 (16.7)	9 (6.6)	0.264
Fever	8 (30.8)	55 (38.5)	0.597
Weight loss	3 (12.0)	21 (16.8)	0.757
Laboratory data			
Anemia, n (%)	9 (52.9)	34 (54.0)	0.842
Leukopenia, n (%)	8 (50.0)	33 (54.1)	0.992
Thrombocytopenia, n (%)	4 (25.0)	22 (36.1)	0.584
Serum creatinine, μmol/L	111 (80-200)	82.9 (60-100)	0.001
eGFR, ml/min/1.72m2	62.3±36.3	86.3±31.2	0.004
ESR, mm/hour	36.5 (28-45)	24 (12-50)	0.223
CRP, mg/L	6.1 (0.5-12.0)	5.9 (0.0-24.0)	0.612
hs-CRP, mg/L	6.3 (1.6-7.2)	7.2 (5.2-27.8)	0.176
IL-6, pg/ml	5.4 (2.7-10.7)	4.3 (2.4-7.2)	0.375
IL-10, pg/ml	9.1 (3.0-30.9)	3.2 (3.0-26.6)	0.620
C3, g/L	0.825±0.146	0.908±0.295	0.524
C4, g/L	0.172±0.101	0.143±0.087	0.524
Autoantibody positivity			
Anti-dsDNA, n (%)	17 (77.3)	67 (70.5)	0.705
Anti-dsDNA titer, IU/ml	43 (23-54)	18 (6-46)	0.046
Anti-Sm, n (%)	2 (12.5)	7 (15.2)	0.889
Anti-Ro, n (%)	6 (46.2)	22 (53.7)	0.881
Anti-La, n (%)	2 (16.7)	11 (27.5)	0.698
Anti-RNP, n (%)	2 (18.2)	10 (37.0)	0.446
APLA, n (%)	5 (50.0)	16 (66.7)	0.607
Anti-chromatin, n (%)	3 (42.9)	15 (83.3)	0.152
Anti-CRP, ng/ml	6.4 (4.8-10.9)	7.4 (4.9-10.9)	0.596
Medications			
Glucocorticoids, n (%)	17 (63.0)	122 (81.9)	0.069
Oral glucocorticoid dose, mg/d	10 (10-15)	25 (10-30)	0.289
Hydroxychloroquine, n (%)	16 (59.3)	86 (57.7)	0.952
Cyclophosphamide, n (%)	2 (8.7)	5 (4.3)	0.742
Mycophenolate mofetil, n (%)	1 (4.3)	1 (0.9)	0.772
Azathioprine, n (%)	4 (17.4)	0 (0.0)	0.004
Methotrexate, n (%)	0 (0.0)	1 (0.9)	0.473
Rituximab, n (%)	0 (0.0)	1 (0.7)	0.454
Belimumab, n (%)	3 (11.1)	8 (5.4)	0.517

Note: values are expressed as a median (QI-QIII), means (±standard deviations), or n (%).

Bolded P values indicate statistically significant group differences between LN patients with nephrotic syndrome and LN patients without nephrotic syndrome.

Abbreviations: SLE: systemic lupus erythematosus; LN: lupus nephritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; CNS: central nervous system; PNS: peripheral nervous system; eGFR: estimated glomerular filtration rate using CKD-EPI; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; anti-dsDNA: anti-double-stranded DNA antibodies; anti-Sm: anti-Smith antibodies; anti-RNP: anti-ribonucleoprotein antibodies; APLA: antiphospholipid antibodies; anti-CRP: anti-C-reactive protein antibodies.

LN patients with nephrotic syndrome had a higher proportion of male sex than LN patients with non-nephrotic proteinuria (33.3% vs 12.8%, p=0.032). Evaluation of SLE clinical manifestations showed no difference between both groups except that LN patients with nephrotic syndrome had a significantly higher frequency of arterial/venous thrombosis (29.6% vs 6.0%, p = 0.005) and a lower frequency of lymphadenopathy (40.7% vs 64.9%, p=0.035). There was also a significantly higher SLICC/ACR damage index score in LN patients with nephrotic syndrome (2 (1-4) points vs. 1 (0-2) points, p<0.001). LN patients with nephrotic syndrome had higher levels of serum creatinine (111 (80-200) μmol/L vs 82.9 (60-100), p=0.001) and lower eGFR (62.3±36.3 ml/min/1.72m^2 vs 86.3±31.2 ml/min/1.72m^2, p=0.004) than those with non-nephrotic proteinuria. Types of autoantibodies were comparably expressed in both groups; however, the titer of anti-dsDNA was significantly higher in LN patients with nephrotic syndrome (43 (23-54) IU/ml vs 18 (6-46) IU/ml, p=0.046). There was no significant difference between the two groups regarding drug exposure, except for azathioprine, as LN patients with non-nephrotic proteinuria were less treated with this medication.

Risk factors for nephrotic syndrome in LN estimated by logistic regression analysis are displayed in Table 4.

Table 4.

Logistic regression analysis of variables independently associated with nephrotic syndrome in LN

Variables	Univariate analysis			Multivariate analysis		
	Coefficient	Odds ratio (95% CI)	*p*	Coefficient	Odds ratio (95% CI)	*p*
Male sex	1.23±0.48	3.42 (1.34-8.7)	0.01	1.65±0.55	5.21 (1.77-15.30)	0.003
SLICC/ACR score	0.69±0.18	1.99 (1.40-2.84)	<0.001	0.75±0.19	2.12 (1.45-3.09)	<0.001
Arterial/venous thrombosis	1.40±0.57	4.06 (1.33-12.4)	0.01			
Lymphadenopathy	-0.99±0.43	0.37 (0.16-0.86)	0.02	-1.19±0.49	0.31 (0.12-0.80)	0.02
eGFR	0.02±0.01	0.98 (0.96-0.99)	0.007			

Abbreviations: LN: lupus nephritis; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; eGFR: estimated glomerular filtration rate using CKD-EPI.

In multivariate logistic analysis, male sex (OR 5.21 (95% CI 1.77-15.30), p=0.003) and higher SLICC/ACR score (OR 2.12 (95% CI 1.45-3.09), p<0.001) were associated with increased risk of nephrotic syndrome, whereas lymphadenopathy (OR 0.31 (95% CI 0.12-0.80), p=0.02) was associated with decreased risk of nephrotic syndrome development. The AUC of the corresponding ROC curve was 0.798 (Fig. 2).

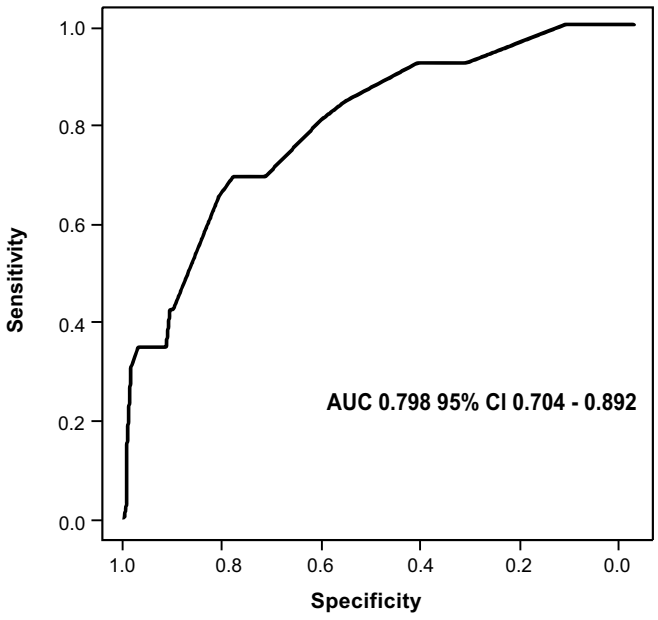

Fig. 2. ROC-curve for the multivariate logistic analysis of risk factors for nephrotic syndrome in LN patients. Variables included in the model: male sex, SLICC/ACR score, lymphadenopathy.

Discussion. To the best of our knowledge, this is one of the largest studies ever undertaken in a Ukrainian SLE cohort. Our results are generally consistent with the results of international studies. The prevalence of LN was 46.3%, a percentage that lies within the reported range of 25% to 75% from other studies [2]. Patients with renal involvement were younger than patients with non-renal SLE in our cohort. In agreement with previous reports [15], we also found younger age of SLE onset in LN patients than in those without kidney involvement. In opposition to most previous studies [16], there was no significant difference between men in women in LN and non-renal SLE groups. However, we have found a higher proportion of males in LN patients with nephrotic syndrome than in those with non-nephrotic proteinuria.

Our results were consistent with previous studies showing a higher prevalence of malar rash [17], serositis [18], pulmonitis [19], lymphadenopathy [20], necrotizing vasculitis [21], higher SLEDAI score [22], and lower prevalence of Raynaud's phenomenon [23], Sjogren's syndrome [24], and peripheral nervous system manifestations [25] in LN patients. SLE patients with LN had a higher frequency of arterial or venous thrombosis than non-renal SLE patients, while no differences were observed in regard to antiphospholipid syndrome and antiphospholipid antibodies positivity in line with literature data [26]. It is well-established that SLE itself carries a high risk for thrombotic and procoagulant status even if not associated with antiphospholipid syndrome [27]. So, we suggest that renal involvement may contribute to the intensified risk of thrombotic events in SLE patients. Associations of lupus nephritis with splenomegaly and fever were not confirmed by other studies. These relationships may be peculiar to the local ethnic background. A higher SLICC/ACR score was associated with nephrotic/range proteinuria in agreement with previous studies [28].

In relation to the laboratory findings, our LN patients had higher ESR levels compared to non-renal SLE patients, whereas no differences were found in regard to CRP and hs-CRP levels. This divergence between ESR and CRP levels in LN patients was already reported in other studies [29, 30]. Other authors have reported that LN patients have higher levels of anti-CRP antibodies [31], but our data were unable to confirm this. Despite previous studies reporting higher levels of IL-10 in LN patients [32], we have found the opposite association that supports the hypothesis that IL-10 can be either protective or pathologic at different stages of the disease [33]. In line with previously published data [34], there was no difference in the levels of IL-6 between the groups. Neither C3 nor C4 complement levels were found to be significant predictors of renal involvement in SLE which corresponds to some other studies [35].

In line with previous studies [32], we have as well shown that LN patients had a higher frequency of anti-dsDNA positivity than non-renal SLE patients. Furthermore, the titer of anti-dsDNA was significantly higher in LN patients with nephrotic syndrome compared to those with non-nephrotic range proteinuria. It corresponds to the results of Asif S. et al. [36] that reported a correlation between quantitative anti-dsDNA levels and the severity of proteinuria in SLE patients.

In our study, fewer SLE patients with LN received hydroxychloroquine compared to non-renal SLE patients and hydroxychloroquine showed a protective effect on decreasing the risk of renal involvement in univariate analysis. It should be noted that some LN patients in our cohort were monitored by nephrologists only and were referred to our department for SLE diagnosis confirmation or correction of the treatment algorithm. So, we recorded only baseline medication use and not the therapy that was adjusted after the visit to our department.

This article is subject to several limitations. The most prominent one is the absence of kidney biopsy results for confirmation of lupus nephritis diagnosis in the vast majority of patients. It generally reflects the biopsy rates in Ukraine as a very low percentage of patients agree to undergo this invasive and potentially hazardous procedure due to fear of possible complications, financial reasons, personal beliefs, etc. Another problem is the small number of specialized institutions in Ukraine capable of performing kidney biopsies. Accordingly, we could not assess the clinical characteristics of LN depending on the histological class.

Another limitation is the relatively small study sample and conduction at a single center over a period of many years. More close interaction with specialized nephrology centers is warranted for future research.

Conclusions. Our cohort of Ukrainian LN patients showed different characteristics in demographic, clinical, and laboratory findings compared to patients with non-renal SLE. These features are mostly on par with LN patients of other nationalities around the world.

Conflict of interest statement. The authors have no competing interests to declare.

Author contributions:

Oleg Iaremenko: conceptualization and study design, acquisition of clinical data, manuscript final editing;

Daria Koliadenko: acquisition of clinical samples and data, analysis and interpretation of data, writing the manuscript;

Kateryna Iaremenko: laboratory measurement;

Matiyashchuk Iryna: acquisition of clinical samples and data.

References:

1. *Aw YT, Whiley PJ, Lorenzo AM, Lea-Henry T, Shanmuganandam S, Stanley M, et al.* Immunophenotyping identifies distinct cellular signatures for systemic lupus erythematosus and lupus nephritis. Rheumatol & Autoimmun. 2022;3:15-25. doi: 10.1002/rai2.12060.
2. *Albirdisi MR, Al-Homood IA.* Characteristics of lupus nephritis in Saudi lupus patients: a retrospective observational study. Lupus. 2020 Oct;29(12):1638-43. doi:10.1177/0961203320947151.
3. *Kwon OC, Park JH, Lee SW, Song JJ, Park YB, Park MC.* Worse renal presentation and prognosis in initial-onset lupus nephritis than early-onset lupus nephritis. Yonsei Med J. 2020 Nov;61(11):951-7. doi: 10.3349/ymj.2020.61.11.951.
4. *Hasan MA, Alali L, Alsadah F, Alobud S, Alsaif J, Alali Z.* Prevalence and patterns of renal involvement among patients with systemic lupus erythematous at a tertiary center. J Clin Rheumatol. 2023 Mar 1;29(2):84-90. doi: 10.1097/RHU.0000000000001914.
5. *Lech M, Anders HJ.* The pathogenesis of lupus nephritis. J Am Soc Nephrol. 2013;24(9):1357 66. doi:10.1681/ASN.2013010026.
6. *Aljaberi N, Wenderfer SE, Mathur A, Qiu T, Jose S, Merritt A, et al.* Clinical measurement of lupus nephritis activity is inferior to biomarker-based activity assessment using the renal activity index for lupus nephritis in childhood-onset systemic lupus erythematosus. Lupus Sci Med. 2022 May;9(1):e000631. doi: 10.1136/lupus-2021-000631.
7. *Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004 Feb;65(2):521-30. doi:10.1111/j.1523-1755.2004.00443.x.
8. *Mahajan A, Amelio J, Gairy K, Kaur G, Levy RA, Roth D, et al.* Systemic lupus erythematosus, lupus nephritis and end-stage renal disease: a pragmatic review mapping disease severity and progression. Lupus. 2020 Aug;29(9):1011-20. doi:10.1177/0961203320932219.
9. *Choi SE, Park DJ, Kang JH, Lee SS.* Significance of co-positivity for anti-dsDNA, -nucleosome, and -histone antibodies in patients with lupus nephritis. Ann Med. 2023 Dec;55(1):1009-17. doi:10.1080/07853890.2023.2187076.
10. *Hochberg MC.* Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997 Sep;40(9):1725. doi:10.1002/art.1780400928.
11. *Aringer M.* EULAR/ACR classification criteria for SLE. Semin Arthritis Rheum. 2019 Dec;49(3S):S14-S17. doi:10.1016/j.semarthrit.2019.09.009.
12. *Gladman DD, Ibañez D, Urowitz MB.* Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002 Feb;29(2):288-91. URL: https://www.jrheum.org/content/29/2/288. (Last accessed 17.03.2023).
13. *Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al.* The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 1996 Mar;39(3):363-9. doi: 10.1002/art.1780390303.
14. *Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. doi:10.7326/0003-4819-150-9-200905050-00006.
15. *Luo W, Farinha F, Isenberg DA, Rahman A.* Survival analysis of mortality and development of lupus nephritis in patients with systemic lupus erythematosus up to 40 years of follow-up. Rheumatology (Oxford). 2022 Dec 23;62(1):200-8. doi:10.1093/rheumatology/keac218.
16. *Riveros FA, Casas I, Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J, Galindo M, et al.* Systemic lupus erythematosus in Spanish males: a study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. Lupus. 2017 Jun;26(7):698-706. doi:10.1177/0961203316673728.
17. *Somai M, Daoud F, Rachdi I, Zoubeidi H, Raies L, Aydi Z, et al.* Predictive factors of the lupus nephritis in a Tunisian cohort. Tunis Med. 2019 Dec;97(12):1399-406. URL: https://www.la-tunisiemedicale.com/article-medicale-tunisie.php?article=3643. (Last accessed 17.03.2023).
18. *Yuan F, Wei F, Wang J, You Y.* Clinical aspects and risk factors of lupus nephritis: a retrospective study of 156 adult patients. J Int Med Res. 2019 Oct;47(10):5070-81. doi:10.1177/0300060519871812.
19. *Aguilera-Pickens G, Abud-Mendoza C.* Pulmonary manifestations in systemic lupus erythematosus: pleural involvement, acute pneumonitis, chronic interstitial lung disease and diffuse alveolar hemorrhage. Reumatol Clin (Engl Ed). 2018 Sep-Oct;14(5):294-300. doi:10.1016/j.reuma.2018.03.012.

20. *Graef E, Magliulo D, Hollie N, Marcus C, Kyttaris V.* Clinical characteristics of lymphadenopathy in systemic lupus erythematous: a case control study from a tertiary care center [abstract]. Arthritis Rheumatol. 2019;71(10). Available from: https://acrabstracts.org/abstract/clinical-characteristics-of-lymphadenopathy-in-systemic-lupus-erythematous-a-case-control-study-from-a-tertiary-care-center/. (Last accessed 17.03.2023).

21. *Leone P, Prete M, Malerba E, Bray A, Susca N, Ingravallo G, et al.* Lupus vasculitis: an overview. Biomedicines. 2021 Nov 5;9(11):1626. doi: 10.3390/biomedicines9111626.

22. *Estévez DT, Varela CI, Chico CA, Kokuina E, Sánchez BY, Casas FN.* Predictive factors for the development of lupus nephritis after diagnosis of systemic lupus erythematosus. Reumatol Clin (Engl Ed). 2022 Nov;18(9):513-7. doi:10.1016/j.reumae.2021.08.003.

23. *Heimovski FE, Simioni JA, Skare TL.* Systemic lupus erythematosus and Raynaud's phenomenon. An Bras Dermatol. 2015 Nov-Dec;90(6):837-40. doi: 10.1590/abd1806-4841.20153881.

24. *Ruacho G, Kvarnström M, Zickert A, Oke V, Rönnelid J, Eketjäll S, et al.* Sjögren syndrome in systemic lupus erythematosus: a subset characterized by a systemic inflammatory state. J Rheumatol. 2020 Jun 1;47(6):865-75. doi:10.3899/jrheum.190250.

25. *Su YJ, Huang CR, Chang WN, Tsai NW, Kung CT, Lin WC, et al.* The association between autoantibodies and peripheral neuropathy in lupus nephritis. Biomed Res Int. 2014;2014:524940. doi:10.1155/2014/524940.

26. *İlgen U, Yayla ME, Ateş A, Okatan İE, Yurteri EU, Torgutalp M, et al.* Antiphospholipid antibodies and non-thrombotic manifestations of systemic lupus erythematosus. Lupus. 2018 Apr;27(4):665-9. doi: 10.1177/0961203317734924.

27. *Bazzan M, Vaccarino A, Marletto F.* Systemic lupus erythematosus and thrombosis. Thromb J. 2015 Apr 23;13:16. doi:10.1186/s12959-015-0043-3.

28. *Falaschi F, Ravelli A, Martignoni A, Migliavacca D, Sartori M, Pistorio A, et al.* Nephrotic-range proteinuria, the major risk factor for early atherosclerosis in juvenile-onset systemic lupus erythematosus. Arthritis Rheum. 2000 Jun;43(6):1405-9. doi:10.1002/1529-0131(200006)43:6<1405::AID-ANR26>3.0.CO;2-V.

29. *Smith EM, Jorgensen AL, Beresford MW.* Do classic blood biomarkers of JSLE identify active lupus nephritis? Evidence from the UK JSLE cohort study. Lupus. 2017;26(11):1212-7. doi: https://doi.org/10.1177/0961203317702253.

30. *Birmingham DJ, Irshaid F, Nagaraja HN, Zou X, Tsao BP, Wu H, et al.* The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus. 2010 Oct;19(11):1272-80. doi:10.1177/0961203310371154.

31. *Sjöwall C, Zickert A, Skogh T, Wetterö J, Gunnarsson I.* Serum levels of autoantibodies against C-reactive protein correlate with renal disease activity and response to therapy in lupus nephritis. Arthritis Res Ther. 2009;11(6):R188. doi:10.1186/ar2880.

32. *Palazzo L, Lindblom J, Mohan C, Parodis I.* Current insights on biomarkers in lupus nephritis: a systematic review of the literature. J Clin Med. 2022 Sep 28;11(19):5759. doi:10.3390/jcm11195759.

33. *Godsell J, Rudloff I, Kandane-Rathnayake R, Hoi A, Nold MF, Morand EF, et al.* Clinical associations of IL-10 and IL-37 in systemic lupus erythematosus. Sci Rep. 2016 Oct 6;6:34604. doi:10.1038/srep34604.

34. *Ripley BJ, Goncalves B, Isenberg DA, Latchman DS, Rahman A.* Raised levels of interleukin 6 in systemic lupus erythematosus correlate with anaemia. Ann Rheum Dis. 2005 Jun;64(6):849-53. doi:10.1136/ard.2004.022681.

35. *Rubinstein T, Pitashny M, Levine B, Schwartz N, Schwartzman J, Weinstein E, et al.* Urinary neutrophil gelatinase-associated lipocalin as a novel biomarker for disease activity in lupus nephritis. Rheumatology (Oxford). 2010 May;49(5):960-71. doi:10.1093/rheumatology/kep468.

36. *Asif S, Khan A, Zahoor S, Lashari N, Haroon M, Khanum A.* Correlation between quantitative anti-dsDNA levels with severity of proteinuria in systemic lupus erythematosus patients. Reumatol Clin (Engl Ed). 2022 Oct;18(8):464-8. doi:10.1016/j.reumae.2021.06.005.