



## Determination of nutrition indices and their correlation with activity of lupus nephritis

### Određivanje nutricionih indeksa i njihova korelacija sa aktivnošću *lupus nephritis*-a

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#### Abstract

**Background/Aim.** Lupus nephritis (LN), as an immunoinflammatory kidney lesion and the most severe manifestation of systemic lupus erythematosus (SLE), is accompanied by a disorder of nutritional status of patients. The aim of our study was to determine the importance of parameters of nutritional status [nutritional risk index (NRI), prognostic nutritional index (PNI), and Controlling Nutritional Status (CONUT)] and their association with standard parameters of LN activity. **Methods.** The clinical study included a group of 92 participants: 67 patients with LN (34 patients had LN active disease – the LNa group, and 33 patients were in LN remission – the LNr group) and 25 healthy subjects in the control group. In addition to standard laboratory parameters and LN activity parameters, derived parameters were also determined:  $PNI = 10 \times \text{serum albumin value (g/dL)} + 0.005 \times \text{total lymphocyte count/mm}^3$ ;  $NRI = 1.519 \times \text{serum albumin value (g/dL)} + 41.7 \times \text{present weight (kg)/usual body weight (defined as stable body weight for last six months) (kg)}$ ;  $CONUT \text{ score} = \text{serum albumin value (g/dL)} + \text{total lymphocyte count/mm}^3 + \text{total cholesterol level (mmol/L)}$ . **Results.** A statistically significant difference

between all three groups was observed for the PNI ( $p = 0.001$ ) and the CONUT score ( $p = 0.000$ ), while there was no significant difference for NRI. In the LNa group, a statistically significant correlation was found for PNI in relation to albumin, complement C3 and C4, and a statistically significant negative correlation with the level of anti-double stranded (ds) DNA antibodies (Abs). NRI had a statistically significant correlation only with proteinuria in the LNa group. CONUT showed significant correlations with most of the parameters of disease activity: negative correlation with albumin and complement C3 ( $p = 0.000$ ), and positive correlation with anti-dsDNA Abs ( $p = 0.002$ ), Systemic Lupus Erythematosus Disease Activity Index/renal (SLEDAI/r), and proteinuria g/24 hrs ( $p = 0.000$ ). **Conclusion.** A statistically significant difference was observed between the groups for the nutrition score CONUT and the PNI. Their correlation with standard parameters of active disease was significant for most parameters in the group of patients with LNa.

#### Key words:

autoimmune diseases; lupus erythematosus, systemic; lupus nephritis; nutritional status.

#### Apstrakt

**Uvod/Cilj.** Lupus nefritis (LN), kao imuno-inflamacijsko oštećenje bubrega i najteža manifestacija sistemskog eritemskog lupusa (SLE), praćen je i poremećajem nutritivnog statusa bolesnika. Cilj rada bio je da utvrdimo značaj određivanja parametara nutritivnog statusa [indeksa nutritivnog rizika (*nutritional risk index* – NRI), prognostičkog nutritivnog indeksa (*prognostic nutritional index* – PNI) i kontrolnog nutritivnog statusa (*Control Nutritional Status* – CONUT)] i njihovu povezanost sa standardnim parametrima aktivnosti LN. **Metode.** Kliničko ispitivanje je

obuhvatilo grupu od 92 ispitanika: 67 bolesnika sa LN (34 bolesnika je bilo u fazi aktivne bolesti – grupa LNa, a 33 je bilo u fazi remisije – grupa LNr) i 25 zdravih ispitanika u kontrolnoj grupi. Uz standardne laboratorijske parametre i parametre aktivnosti LN, određivani su i izvedeni parametri:  $PNI = 10 \times \text{serumski albumin (g/dL)} + 0,005 \times \text{ukupni broj limfocita/mm}^3$ ;  $NRI = 1,519 \times \text{serumski albumin (g/dL)} + 41,7 \times \text{trenutna težina (kg)/uobičajena telesna težina (definisana kao stabilna telesna težina u poslednjih šest meseci) (kg)}$ ;  $CONUT \text{ skor} = \text{serumski albumin (g/dL)} + \text{ukupni broj limfocita/mm}^3 + \text{ukupan serumski holesterol (mmol/L)}$ . **Rezultati.** Statistički značajna razlika između sve

tri grupe zapažena je za PNI ( $p = 0,001$ ) i za CONUT skor ( $p = 0,000$ ), dok za NRI nije zabeležena statistički značajna razlika. U grupi LNa nađena je statistički značajna korelacija za PNI u odnosu na albumin, komplement C3 i C4, a statistički značajna negativna korelacija sa nivoom antitela (At) prema dvolančanoj DNK (*double stranded DNA* – dsDNA). Za NRI je nađena značajna korelacija samo sa proteinurijom, u grupi LNa. CONUT je pokazao značajnu korelaciju sa najvećim brojem parametara za aktivnost bolesti: negativnu korelaciju sa albuminom i komplementom C3 ( $p = 0,000$ ), a pozitivnu korelaciju sa anti-dsDNA At

( $p = 0,002$ ), sa indeksom *Systemic Lupus Erythematosus Disease Activity Index/renal* - SLEDAI/r i sa proteinurijom/24hrs ( $p = 0,000$ ). **Zaključak.** Nutritivni indeksi CONUT i PNI pokazali su statistički značajnu razliku između grupa LNa i LNr. Korelacija pomenutih indeksa sa standardnim parametrima aktivne bolesti bila je značajna za većinu parametara u grupi LNa bolesnika.

#### Ključne reči:

**autoimunske bolesti; lupus, eritematozni, sistemski; lupus nefritis; nutritivni status.**

## Introduction

Nutritional status disorder is a prognostic parameter of unfavorable outcomes in many diseases (infectious, malignant, cardiovascular, autoimmune, etc.)<sup>1-7</sup>. In patients with chronic kidney disease, especially when glomerular filtration parameters are reduced, there is an increased risk of nutritional status disorders, which is also an indicator of unfavorable prognosis<sup>8</sup>. Lupus nephritis (LN) is a kidney lesion in systemic lupus erythematosus (SLE), the severity of which is emphasized by the fact that 4.3–10.1% of these patients develop end-stage kidney failure<sup>9</sup>. LN, as an immune-inflammatory kidney manifestation of SLE, manifests many disorders, among which is a disorder of nutritional status<sup>10, 11</sup>. Many factors influence its development: physical inactivity, dietary restrictions, corticosteroid and other immunosuppressive therapy, infectious complications, and others<sup>12, 13</sup>. Some authors state that the nutritional status disorder in LN is related to the activity of the disease and has an impact on the course and the outcome of the disease<sup>10-13</sup>. Significant data on the immuno-nutritional status of patients are obtained using several different indices, which are mainly derived from parameters such as serum albumin level, number of lymphocytes in peripheral blood, total cholesterol, body mass index (BMI), and others. Hypoalbuminemia is a consequence of inadequate food intake, catabolism due to inflammation, nephrotic syndrome, and transfer outside blood vessels; it is an indicator of disease activity and leads to an increase in morbidity and mortality of patients with LN<sup>14, 15</sup>. Lymphopenia is common in LN and correlates with parameters of disease activity and inflammation, and is also an effect of corticosteroid and other immunosuppressive therapy<sup>16</sup>. Accelerated atherosclerosis and cardiovascular comorbidity in LN are associated with dyslipidemia, especially with a reduced concentration of high-density cholesterol, which is also dysfunctional, and reduced activity in these patients is often the cause of obesity<sup>17</sup>. Increased BMI, or obesity, is a traditional risk factor for cardiovascular events in patients in general, and in patients with lupus, it is also related to active disease<sup>17</sup>.

In recent years, several studies have been published in which the importance of determining certain nutritional indices such as prognostic nutritional index (PNI), nutritional risk index (NRI), and Controlling Nutritional Status

(CONUT) score has been highlighted in many diseases<sup>1-5</sup>. Although it is known that patients with SLE and LN have inadequate nutrition, there are not many studies in which the results related to the determination of the nutrition index, their importance in these patients, and the connection with the active disease are presented<sup>18, 19</sup>.

The aim of this study was to examine the importance of determining nutritional indices PNI, NRI, and CONUT score, and their association with other standard parameters of active LN disease.

## Methods

The clinical study included a group of 92 subjects: 67 patients with LN and 25 healthy controls of both sexes, older than 18 years, who were examined from 2012 to 2019. This study was conducted in accordance with the Declaration of Helsinki principles. This study was approved by the Ethics Committee of the Military Medical Academy, Belgrade, Serbia (from March 24, 2011).

The diagnosis of SLE in patients was confirmed by the criteria of the American College of Rheumatology and the European League Against Rheumatism<sup>20, 21</sup>. Renal disease activity is also classified according to the Systemic Lupus Erythematosus Disease Activity Index/renal (SLEDAI/r)<sup>20</sup>. The SLEDAI/r score consists of four criteria that assess kidney damage within the SLEDAI 2000 criteria of SLE activity<sup>22</sup>. The patients were divided into three groups: the first group consisted of patients who had active LN disease (LNa group,  $n = 34$ ), the second group consisted of patients with LN in remission (LNr group,  $n = 33$ ), and the third group consisted of healthy control subjects (control group,  $n = 25$ ).

Active LN is defined as proteinuria  $\geq 0.5$  g/24 hrs, SLEDAI/r score  $> 4$ , hypocomplementemia of C3, C4, positive anti-double stranded DNA antibodies (anti-dsDNA Ab), and pathohistological findings of kidney biopsy. All patients had a glomerular filtration rate (GFR)  $\geq 60$  mL/min/1.73m<sup>2</sup>, according to the Chronic Kidney Disease (CKD) Epidemiologic Collaboration (CKD-EPI) research group<sup>23</sup>. The second group consisted of patients with LN in complete remission (according to criteria: proteinuria  $\leq 0.5$  g/24 hrs; SLEDAI/r score  $< 4$ , negative anti-dsDNA Ab, complement C3 and C4 within the reference range and GFR  $\geq 60$  mL/min/1.73m<sup>2</sup>). The healthy control group

consisted of patients who did not have SLE or LN and did not have autoimmune diseases. They had preserved kidney function ( $GFR \geq 60 \text{ mL/min/1.73m}^2$ ).

Exclusion criteria for all groups were as follows: kidney failure ( $CKD \text{ GFR} < 60 \text{ mL/min/1.73m}^2$ ); infection; positive results of urine culture; other autoimmune diseases; other inflammatory diseases; malignant diseases; hematological diseases; with previously applied corticosteroid therapy for some other reasons; patients with repeated transfusions.

Among the other characteristics of the research, we underscore the following: in the LNa group, laboratory parameters were determined before the start of immunosuppressive treatment (there is no influence of immunosuppressive therapy on laboratory analyses). The second group consisted of patients in LNr who received maintenance therapy: 5–10 mg/day of corticosteroids and 50–75 mg/day of azathioprine. Subjects in the third group did not take any immunosuppressive therapy. The authors had access to information that identified study participants.

Standard laboratory and kidney function parameters were monitored: C-reactive protein (CRP), complete blood count, creatinine, albumin, cholesterol, triglycerides, and GFR. Among immunological parameters, complement C3 and C4, antinuclear antibodies (ANA), and anti-dsDNA Ab were monitored. From the urinary analyses, the following were monitored: urine sediment, SLEDAI/r, proteinuria g/24hrs, and urine culture. We also determined the following markers – PNI, NRI, and CONUT scores.

PNI was calculated as follows:  $10 \times \text{serum albumin value (g/dL)} + 0.005 \times \text{total lymphocyte count in the peripheral blood/mm}^3$  <sup>19</sup>.

NRI was calculated as follows:  $1.519 \times \text{serum albumin value (g/dL)} + 41.7 \times \text{present weight (kg)/usual weight}$  (defined as stable body weight for last six months) (kg).

The patients with an NRI score  $> 100$  were considered the no-risk group, those with a score of 97.5–100 were considered a mild risk group, those with a score of 83.5–97.5 were in the moderate risk group, and those with a score  $< 83.5$  were in the severe risk group <sup>19</sup>.

CONUT score was calculated as follows: serum albumin value (g/dL) + total lymphocyte count in the peripheral blood/mm<sup>3</sup> + total cholesterol level (mmol/L) <sup>24</sup>. The patients were categorized, depending on undernutrition severity points, into the following groups: normal (0), light (1), moderate (2), and severe (3) <sup>19, 24</sup>.

#### Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences IBM-SPSS, version 26.0. Categorical variables were presented as frequency and were analyzed using the Chi-square test. All continuous variables are presented as mean  $\pm$  standard deviation. The Kolmogorov-Smirnov test was used to test the normality of data distribution. For intergroup comparisons, ANOVA with Bonferroni correction and *post-hoc* Tukey test for parametric variables was used. Pearson's correlation test was applied for the relationship between variables. Optimal thresholds (cut-off) of index values (NRI, PNI, and CONUT) for assessment of LN activity were determined by receiver operating characteristic (ROC) curve analysis. Statistical significance was defined as  $p < 0.05$  for all comparisons.

#### Results

The basic clinical and laboratory data of our patients, which were divided into three groups, are shown in Table 1. A statistically significant difference between the groups was

**Table 1**

**Comparison of baseline clinical and laboratory data**

Parameters	RR	Groups			p-value
		LNa n = 34	LNr n = 33	Control n = 25	
Age (years)	/	40.76 $\pm$ 16.51	45.03 $\pm$ 11.86	53.28 $\pm$ 11.14	<b>0.003</b>
BMI (kg/m <sup>2</sup> )	/	24.84 $\pm$ 5.29	25.74 $\pm$ 4.37	25.35 $\pm$ 2.87	0.912
CRP (mg/L)	0.00–4.00	4.93 $\pm$ 5.44	3.37 $\pm$ 1.64	2.21 $\pm$ 1.40	<b>0.015</b>
WBC ( $\times 10^9/L$ )	4.00–11.00	6.30 $\pm$ 2.73	6.79 $\pm$ 2.68	6.20 $\pm$ 1.53	0.601
Hb (g/L)	115.0–165.0	108.13 $\pm$ 20.14	126.72 $\pm$ 14.47	140.04 $\pm$ 9.38	<b>0.000</b>
PLT ( $\times 10^9/L$ )	160.0–370.0	206.44 $\pm$ 56.05	232.94 $\pm$ 91.35	221.24 $\pm$ 53.16	0.306
Creatinine ( $\mu\text{mol/L}$ )	44–88	103.71 $\pm$ 64.61	83.55 $\pm$ 21.42	69.72 $\pm$ 9.24	<b>0.009</b>
GFR (mL/min/1.73m <sup>2</sup> )	$> 60$	79.42 $\pm$ 33.60	83.22 $\pm$ 26.36	96.97 $\pm$ 4.77	<b>0.035</b>
Albumin (g/L)	32–50	32.12 $\pm$ 7.25	40.30 $\pm$ 4.30	43.76 $\pm$ 3.07	<b>0.000</b>
Cholesterol (mmol/L)	$< 5.2$	6.15 $\pm$ 1.81	5.49 $\pm$ 1.11	5.46 $\pm$ 1.20	0.097
Triglyceride (mmol/L)	$< 1.7$	2.41 $\pm$ 2.08	1.67 $\pm$ 0.91	1.58 $\pm$ 0.56	<b>0.044</b>
C3 (g/L)	0.80–1.60	0.64 $\pm$ 0.20	0.90 $\pm$ 0.15	/	<b>0.000</b>
C4 (g/L)	0.1–0.4	0.10 $\pm$ 0.06	0.15 $\pm$ 0.04	/	<b>0.003</b>
Anti-dsDNA Ab (IgG) (IU/mL)	$< 100$	121.03 $\pm$ 123.36	26.34 $\pm$ 27.87	/	<b>0.000</b>
Proteinuria (g/24hrs)	0.000–0.150	4.74 $\pm$ 5.22	0.33 $\pm$ 0.29	0.30 $\pm$ 0.43	<b>0.000</b>
SLEDAI/r score	/	5.41 $\pm$ 2.38	0.27 $\pm$ 0.45	/	<b>0.000</b>

RR – reference range; LNa – lupus nephritis (LN) active; LNr – LN in remission; BMI – body mass index; CRP – C-reactive protein; WBC – white blood cells; PLT – platelets; C3 – complement C3; C4 – complement C4; GFR – glomerular filtration rate; SLEDAI/r – Systemic Lupus Erythematosus Disease Activity Index/renal; anti-dsDNA Ab – anti-double stranded DNA antibody; / – values not applicable.

Results are shown as mean  $\pm$  standard deviation.

Bolded values are statistically significant.

observed for CRP, creatinine, triglyceride, anti-dsDNA Ab, proteinuria, and the SLEDAI/r score, which was the highest in the group with active disease, as well as for hemoglobin, GFR, albumin, C3, C4, which were the lowest in the LNa group.

Table 2 shows the values of nutritional indices PNI, NRI, and CONUT score in relation to groups.

Observing the PNI, NRI, and CONUT between the groups, a statistically significant difference is found for PNI ( $p = 0.001$ ), whose value is the lowest in the LNa group, as well as for CONUT ( $p = 0.000$ ), whose value is the highest in the LNa group. For NRI, we did not record statistically significant differences between groups.

Multiple comparison tests (Tukey's test and Bonferroni test) did not show any statistical significance for NRI values compared between groups. For PNI, a statistically significant difference was found between the LNa and the LNr group ( $p = 0.002$ ) and between the LNa group and the control group ( $p = 0.003$ ). The difference between the LNr and the control

group had no statistical significance. Multiple comparisons for CONUT showed statistically significant differences between the LNa group and the LNr group and between the LNa group and the control group ( $p = 0.000$ ), while there was no significant difference between the LNr and control group.

PNI showed a statistically significant positive correlation in the LNa group in relation to albumin, C3, and C4 and a statistically significant negative correlation with anti-dsDNA Ab. NRI correlated statistically significantly only with proteinuria in the LNa group. For CONUT, statistical significance was recorded in correlations with the most parameters for disease activity: negative correlation with albumin and complement C3 ( $p = 0.000$ ), and positive correlation with anti-dsDNA Ab ( $p = 0.002$ ), SLEDAI/r score, and proteinuria ( $p = 0.000$ ) (Table 3).

In the LNr group, statistical significance was observed for PNI in relation to C4, SLEDAI/r score, and proteinuria, for NRI only for SLEDAI/r score, and for CONUT for C3 and proteinuria (Table 4).

**Table 2**

**Comparison of parameters between groups**

Parameter	RR	Groups			<i>p</i> -value
		LNa	LNr	Control	
Neutrophils ( $\times 10^9/L$ )	1.90–8.00	4.57 $\pm$ 1.89	4.29 $\pm$ 2.03	3.52 $\pm$ 1.25	0.086
Lymphocytes ( $\times 10^9/L$ )	0.900–5.200	1.39 $\pm$ 1.04	1.79 $\pm$ 0.73	1.75 $\pm$ 0.47	0.088
Monocytes ( $\times 10^9/L$ )	0.000–1.320	0.40 $\pm$ 0.24	0.52 $\pm$ 0.27	0.39 $\pm$ 0.12	<b>0.047</b>
PNI		63.65 $\pm$ 14.95	74.29 $\pm$ 12.55	74.80 $\pm$ 8.17	<b>0.001</b>
NRI		52.22 $\pm$ 12.46	52.98 $\pm$ 12.05	56.56 $\pm$ 5.81	0.293
CONUT		3.62 $\pm$ 2.67	1.00 $\pm$ 1.11	0.76 $\pm$ 1.05	<b>0.000</b>

PNI – prognostic nutritional index; NRI – nutritional risk index; CONUT – controlling nutritional status. For other abbreviations, see Table 1.

Results are shown as mean  $\pm$  standard deviation.

Bolded values are statistically significant.

**Table 3**

**Correlation of PNI, NRI, and CONUT with standard parameters of LN activity in the LNa group**

Parameters	Statistical analysis	CRP	Creatinine	GFR	Albumin	C3	C4	Anti-dsDNA Ab	SLEDAI/r	Proteinuria (g/24hrs)
PNI	<i>r</i>	-0.207	0.087	0.035	<b>0.411*</b>	<b>0.609**</b>	<b>0.397*</b>	<b>-0.523**</b>	-0.325	-0.154
	<i>p</i>	0.239	0.623	0.845	<b>0.016</b>	<b>0.000</b>	<b>0.020</b>	<b>0.002</b>	0.061	0.384
NRI	<i>r</i>	0.021	0.173	-0.191	0.190	0.247	0.182	-0.172	-0.158	<b>-0.497**</b>
	<i>p</i>	0.906	0.329	0.279	0.283	0.159	0.303	0.340	0.373	<b>0.003</b>
CONUT	<i>r</i>	0.301	-0.002	0.038	<b>-0.761**</b>	<b>-0.591**</b>	-0.149	<b>0.514**</b>	<b>0.566**</b>	<b>0.660*</b>
	<i>p</i>	0.084	0.991	0.833	<b>0.000</b>	<b>0.000</b>	0.402	<b>0.002</b>	<b>0.000</b>	<b>0.000</b>

*r* – correlation coefficient. For other abbreviations, see Tables 1 and 2. \* $p < 0.05$ ; \*\* $p < 0.005$ .

Bolded values are statistically significant. Pearson's correlation rank test was applied.

**Table 4**

**Correlation of PNI, NRI, and CONUT with standard parameters of LN activity in the LNr group**

Parameters	Statistical analysis	CRP	Creatinine	GFR	Albumin	C3	C4	Anti-dsDNA Ab	SLEDAI/r	Proteinuria (g/24hrs)
PNI	<i>r</i>	0.072	0.091	-0.174	-0.040	0.246	<b>0.390*</b>	0.030	<b>0.380*</b>	<b>-0.374*</b>
	<i>p</i>	0.690	0.615	0.331	0.824	0.168	<b>0.025</b>	0.868	<b>0.029</b>	<b>0.032</b>
NRI	<i>r</i>	-0.095	0.021	-0.043	0.128	0.114	0.258	0.171	<b>-0.413*</b>	-0.133
	<i>p</i>	0.598	0.908	0.814	0.478	0.526	0.147	0.351	<b>0.017</b>	0.461
CONUT	<i>r</i>	-0.265	-0.003	0.109	-0.273	<b>-0.349*</b>	-0.197	-0.312	0.309	<b>0.368*</b>
	<i>p</i>	0.136	0.615	0.546	0.125	<b>0.047</b>	0.271	0.082	0.080	<b>0.035</b>

*r* – correlation coefficient. For other abbreviations, see Tables 1 and 2.

Bolded values are statistically significant. \* $p < 0.05$ . Pearson's correlation rank test was applied.

Table 5

## Receiver operating characteristic (ROC) curve analysis for PNI, NRI, and CONUT

Variables	AUC	AS	Asymptotic 95% CI				
			lower bound	upper bound	sensitivity (%)	specificity (%)	cut-off value
PNI	0.231	<b>0.000</b>	0.125	0.338	61.8	12.1	60.32
NRI	0.420	0.201	0.291	0.549	29.4	70.7	59.31
CONUT	0.835	<b>0.000</b>	0.750	0.921	73.5	74.1	0.55

AUC – area under the ROC curve; AS – asymptotic significance; CI – confidence interval.

For other abbreviations, see Table 2.

Bolded values are statistically significant.

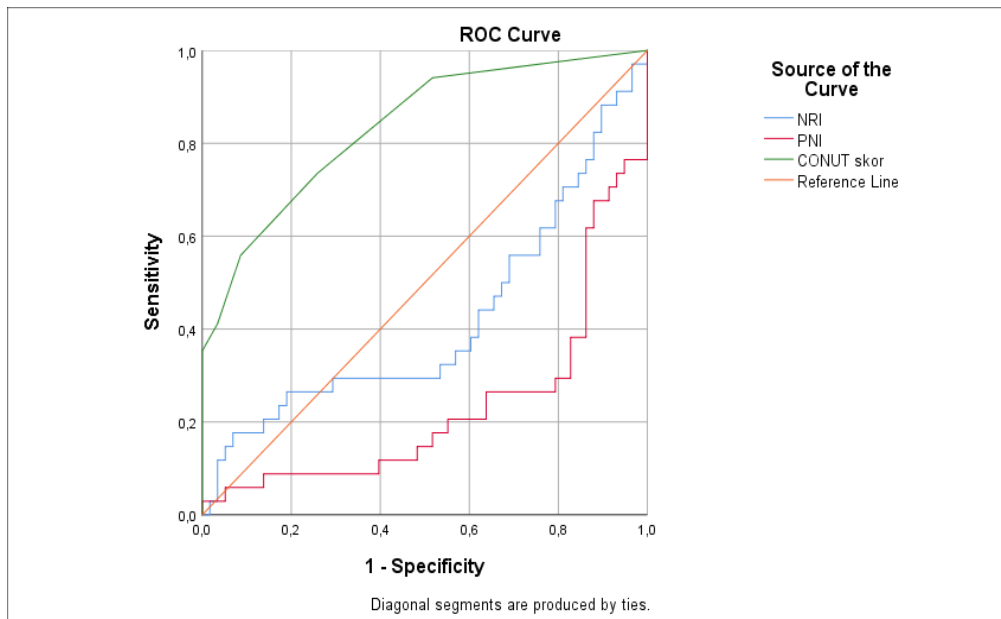


Fig. 1 – Receiver operating characteristic (ROC) curve for PNI, NRI, and CONUT for the LNa group.

For abbreviations, see Table 2.

Results for ROC curve analysis for PNI, NRI, and CONUT are shown in Table 5 and Figure 1. The area under the curve (AUC) value for PNI was 0.231 and the best threshold value was 60.32 ( $p = 0.000$ ); the sensitivity was 61.8%, and the specificity was only 12.1%. The AUC value of NRI was 0.420, and the best cut-off value was 59.31 ( $p = 0.201$ ). The AUC value for CONUT was 0.835, and the best cut-off value was 0.55 ( $p = 0.000$ ), with a sensitivity of 73.5% and a specificity of 74.1%.

## Discussion

LN activity is defined by standard parameters, also known as immuno-inflammatory parameters. By combining certain clinical and laboratory parameters, new indices known as nutrition indices were obtained, which provide us with data important for the course and prognosis of the disease. There are few studies investigating these markers and their association with active LN.

The connection between PNI and SLE was the subject of a study by Ahn et al.<sup>25</sup>, who examined a group of 217 patients with SLE, in whom, by determining the PNI index, they indicated a significant correlation ( $p < 0.001$ ) with active disease, and PNI had lower values in the group with

active SLE. By monitoring patients with active SLE who achieved remission, this group of authors noticed an increase in PNI values. Lymphopenia is statistically more significant in active SLE disease, and this was confirmed by other studies<sup>18, 25, 26</sup>.

In our group of patients with LN, there was also a lower value of the PNI in the LNa group compared to the LNR group and the control group, and this difference was statistically significant ( $p = 0.001$ ). Likewise, in our LNa group, the absolute number of lymphocytes was lower compared to the other two groups, but the comparison did not show statistical significance.

In a multiethnic cohort that included 591 patients with SLE, Vilá et al.<sup>27</sup> showed that lymphopenia positively correlates with renal lesions, elevated anti-dsDNA Ab, anti-Ro Ab, use of corticosteroids, azathioprine, methotrexate, and negatively with photosensitivity.

According to the Correa-Rodríguez et al.<sup>18</sup> study, PNI and NRI are very significant markers of nutritional status and SLE activity. In a group of 172 patients with SLE, of whom 41 had active disease, they determined that the value of NRI, as well as PNI, was lower in the group with active SLE, and that difference was statistically significant in the comparison of the group with active SLE and group with SLE in

remission. CONUT was higher in the group with active SLE but without a statistically significant difference.

Similar results were obtained in our study. In LNa patients, the PNI and NRI had lower values compared to the other groups, and the value of the CONUT index in the LNa group was higher compared to the other two groups. Statistical significance in the comparison of our groups was recorded for PNI and CONUT, while NRI did not show a significant difference.

In a group of 207 patients with biopsy-proven LN, Ahn et al.<sup>19</sup> described a statistically significant correlation of PNI and CONUT with active disease, while no significance was observed for NRI. In this study, patients with LN were divided into two groups according to renal failure, and in the group with end-stage renal disease, a statistically significant association with the PNI index was observed.

Atherosclerosis in LN is associated with many traditional risk factors (increased BMI, arterial hypertension, diabetes mellitus, dyslipidemia, smoking), as well as with non-traditional risk factors (disease activity, disease duration, renal dysfunction, etc.)<sup>28</sup>. According to many authors, the determination of nutritional indices is significant and is associated with risk factors for the development and progression of atherosclerosis in patients with LN, who otherwise have an increased risk of cardiovascular events<sup>17</sup>.

By monitoring the child population, Thomas et al.<sup>29</sup> indicated that obesity has a significant impact on the occurrence of SLE. In a large Danish study involving 346,627 school children (7–13 years), 473 of them developed SLE (of which 366 were female). They found that birth weight was not associated with the onset of SLE, but as early as seven years of age, BMI and height were positively linearly associated with the risk of developing SLE.

Our LNa patients also had a disorder of lipid status: higher cholesterol and triglyceride levels compared to the other groups, but this difference was statistically significant only for triglycerides. The correlation of disease activity and nutritional indices in our study showed that CONUT had statistically significant correlations with most of the standard parameters of active disease (albumin, C3, anti-dsDNA Ab, SLEDAI/r score, proteinuria), and with NRI the least (only for proteinuria). Similar results related to patients with LN were observed in the study by Ahn et al.<sup>19</sup>, who described

significant correlations of CONUT with CRP, albumin, complement C3 and C4, anti-dsDNA Ab, SLEDAI/r activity score, urinary protein/creatinine ratio. In their study, similar to our patients with LN, the marker NRI showed the lowest association with parameters of active disease (C3, albumin, SLEDAI/r score), and PNI significantly correlated with albumin, cholesterol, complement C3, C4, and SLEDAI/r score. In our LNa patients, PNI was significantly associated with albumin, complement C3, C4, anti-dsDNA Ab. In the study by Ahn et al.<sup>19</sup>, which represents the first study in which it was noted that although the NLR index is lower in class IV LN than in class II and III, this difference is not statistically significant. Statistical significance has been described for the platelet-to-lymphocyte ratio, which is lower in class IV compared to class II and III LN, as well as for CONUT, which is significantly higher in class IV LN.

The AUC value for CONUT in our study was 0.835, and the best cut-off value was 0.55 ( $p = 0.000$ ), while the sensitivity was 73.5% and the specificity 74.1%, and for PNI AUC was 0.231, and the best cut-off value was 60.32 ( $p = 0.000$ ). Bearing in mind that there are not many studies in which these indices were investigated in patients with LN, we can show the comparison only for the study by Ahn et al.<sup>19</sup>. In that study, it was found that only PNI was able to predict end-stage renal disease in the group with LN (AUC = 0.671, sensitivity 90.0%, specificity 46.0%, 95% confidence interval (CI): 0.602–0.734,  $p = 0.002$ ), and the optimal cut-off value of PNI in predicting end-stage renal disease was  $\leq 35.41$ . We are convinced that future studies that would include a larger number of patients could further confirm these results and that nutritional indices can be significant for the activity and follow-up of patients with LN.

## Conclusion

In patients with LN, the nutritional indices CONUT and PNI showed a statistically significant difference between the groups, and their correlation with standard parameters of active disease was significant for most parameters in the group of patients with active LN.

## Conflict of Interest

The authors declare no conflict of interest.

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