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# Increased Neutrophil to Lymphocyte Ratio (NLR) is a Sign of Disease Activity in Systemic Lupus Erythematosus Patients with Renal Involvement

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## Abstract

Systemic lupus erythematosus (SLE) is an idiopathic multi-systemic autoimmune disease that covers a wide array of clinical and laboratory findings. Neutrophil to lymphocyte ratio (NLR) is a simple onsite available recently emerged inflammatory marker which is evaluated in different inflammatory conditions such as infection, athero-embolic disease, malignancies and autoimmune disease. In this study we aimed to investigate any relation between disease activity and NLR of the SLE patients with renal involvement.

In this study we retrospectively analyzed hematological and laboratory parameters of SLE patients with renal involvement during both in active disease and in remission period. We investigated 36 SLE patients with renal involvement in their active and remission period of the disease.

Mean proteinuria and serum albumin level of the patients at active disease period were 5.26 ± 2.92 gr/day, 2.58 ± 0.71 gr/dl in orderly. Mean proteinuria and serum albumin level of the patients at remission period after cessation of intensive immunosuppression were 0.77 ± 1.59 gr/day, 4.08 ± 0.58 gr/dl inorderly. Mean NLR at active disease period of the patients was statistically significantly detected higher than at remission period (6.11 ± 5.89, 2.65 ± 1.53, p=0.00).

We detected that SLE patients with renal involvement has a high NLR during disease activation and statistically significantly lower NLR at remission period. We offer to investigate NLR as a disease activity marker for SLE patients with renal involvement via prospective randomized large scaled studies.

**Keywords:** SLE • Renal involvement • Disease activity • NLR

## Introduction

SLE is an auto inflammatory disease that presented with activation and remission periods, multisystemic and the exact etiology is not known yet. As it is has a multisystemic clinical scenarios; renal involvement was determined by biochemical renal function tests, urinary examination, proteinuria level and not evenly produced histopathological examination of kidney biopsy. So many clinical and laboratory parameters has a value to demonstrate activity of the disease. Evaluation of daily urinary protein loss either 24-hour urine colletion or urinary protein to urinary creatinine ratio in spot urinary sample has unique value for determination of activity or remission of Lupus Nephritis (LN) [1]. Up to 50% of SLE patients have renal involvement during any time of the disease and nearly 20% of them progresses to chronic renal failure (CRF) which increases the morbidity and contribute to mortality of the disease [2].

Neutrophil and lymphocyte has a basic role in inflammatory processes. During the inflammatory processes there were many important alterations take occur. Neutrophil to Lymphocyte Ratio (NLR) is calculated via dividing absolute Neutrophil count to absolute lymphocyte. In previous studies it was demonstrated that NLR may be regarded and had a utilization power as an inflammatory marker in such diseases like; chronic renal failure, hypertension, obesity, autoimmune diseases, malignity, coronary artery disease and infectious diseases [3-7].

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In this study we aimed to evaluate NLR as an inflammatory marker in activation and remission periods of LN.

## Material and Methods

The study was performed retrospectively in Atatürk University Medical Faculty Nephrology Department. The patients who were diagnosed with Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN) between 2005 and 2013 retrospectively collected. All the 37 LN patients were fulfilled at least ≥4 criteria for SLE according to The Systemic Lupus International Collaborating Clinics (SLICC) the American College of Rheumatology (ACR) group classification [8]. Kidney biopsy was performed 31 patients remaining 5 patients did not gived the informed consent for kidney biopsy so it was not performed. Renal biopsies were assessed according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification. Lupus nephritis (LN) was staged as class I (minimal mesangial LN), class II (mesangial proliferative LN), class III (focal LN, involving 50% of glomeruli), class IV (diffuse segmental or global LN, involving >50% of glomeruli), class V (membranous LN), and class VI (advanced sclerotic LN, ≥ 90% glomeruli globally sclerosed without residual activity) [9]. LN için relaps ve remisyon kriterlerini Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis belirledik [1] (Table 1). We exclude the patients with hematological involvement, active infection, diabetes mellitus, uncontrolled hypertension, hematologic of oncologic malignancies, patients with body mass index over 30 were all excluded. We aslo excluded the patients had elevated C-reactive protein in order to exclude possible undetected infection or inflammation for remission period of the patients. We investigated 36 SLE patients with renal involvement in their active and remission period of the disease.

Whole blood cell count and and hematological indices like absolute neutrophil count, absolute Lymphocyte count, neutrophil/Lymphocyte ratio, Erythrocyte sedimentation ratio, serum albumin, C-reaktive protein, urine

**Table 1.** Definitions of response to therapy in LN1.

| |
|---|
| **Complete response**: Return of SCr to previous baseline, plus a decline in the uPCR to <500mg/g (<50mg/mmol). |
| **Partial response:** Stabilization (±25%), or improvement of SCr, but not to normal, plus a ≥50% decrease in uPCR |
| If there was nephrotic-range proteinuria (uPCR ≥3000mg/g [≥300mg/mmol]), improvement requires a ≥50% reduction in uPCR, and a uPCR <3000mg/g [<300mg/mmol]. |
| **Deterioration:** There is no definition of deterioration in LN to define treatment failure that has been tested prospectively as an indication to change in initial therapy. |
| A sustained 25% increase in SCr is widely used but has not been validated. |

examination results and 24-hour urinary protein excretion were all recorded. Also demographic properties like; age, sex, body weight and Body Mass Indexes (BMI) were recorded.

### Statistical analysis

The collected data were analyzed with the use of SPSS for Windows 20.0 (SPSS, Chicago, Illinois). Parametric tests were applied to data with normal distribution, whereas nonparametric tests were applied to data with non-normal distribution. Chi-square tests were applied to categorical variables. The relationships among the variables were evaluated with the use of Pearson and Spearman rho correlation analysis. Predictive power of the investigated inflammatory markers evaluated via ROC analysis. Results were expressed as mean ± SD and median (interquartile range), and a P value of <.05 was considered to be statistically significant.

## Results

Majority of LN patients were female. 33 of the patients were female and 3 were male. The age distribution of the patients were between 21 and 58. Demographic properties were summarized in Table 2. According to ISN/RPS classification 14 patients (45%) were class IV, 11(35%) were class III LN, 3 were (10%) class II LN, two (7%) were class V LN and one (%3) was class VI LN.

It was detected that calculated NLR at the activation period of LN patients was statistically significantly higher than NLR at the remission period of the disease (6.11 ± 5.89 and 2.65 ± 1.53 in orderly) (p=0.00). Also calculated mean ESR value of LN patients at activation period was detected statistically significantly higher than ESR value of remission period (48±31mm/h and 23.6±13 mm/h accordingly) (p=0.02). As expectedly 24 hour urinary protein loss of the patients statistically significantly higher at activation compare to remission period and serum albumin levels at activation period was statistically significantly lower than remission period of the LN patients ( p=0.00) (Table 3).

Values are given as mean ± SD; p<0.05 is significant. WBC white blood cell count, ANC: Absolute Neutrophil count, ALC: Absolute Lyphocyte count, NLR: neutrophil–lymphocyte ratio, ESR erythrocyte sedimentation rate, CRP C-reactive protein, ALB: serum albumin, PROT: 24h urine protein. A: Activation perid of LN, R: Remission period of LN.

We applied the ROC analysis in order to validate the power of increased NLR, ESR, CRP, Urinary protein to detect the activity period of LN (Figure 1). Also the power of decreased serum albumin level in order to detect the activity of LN was analyzed via ROC analysis (Figure 2). It was detected that if NLR upper limit was set to 3,84 in case of LN activity it has a% 73 sensitivity as an inflammatory marker and it has a more predictive power than ESR at this level.

**Table 2.** Summary of the demographic properties of the Lupus Nephritis patients.

| | Mean |
|---|---|
| Age (year) | 33,3 ± 9,5 |
| Body weight (Kg) | 62,9 ± 10 |
| Body Mass Index (kg/m$^2$) | 23,1 ± 2,8 |
| Sex Female/Male n(%) | 33(92)/3(8) |

**Table 3.** Laboratory results of SLE patients with renal involvement remssion and activation periods of the disease.

| Parameters | Minimum | Maximum | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|
| WBC-A | 3800 | 15700 | 7864,52 | 2744,273 | 0,021 |
| WBC-R | 3100 | 10700 | 6948,48 | 1891,778 | |
| ANC-A | 2400 | 13000 | 5774,19 | 2475,610 | 0,002 |
| ANC-R | 2000 | 8000 | 4351,52 | 1462,686 | |
| ALC-A | 200 | 3300 | 1448,39 | 775,831 | 0,107 |
| ALC-R | 600 | 4200 | 1915,15 | 790,617 | |
| NLR-A | 1,00 | 25,00 | 6,1143 | 5,89039 | 0,007 |
| NLR-R | ,81 | 8,17 | 2,6570 | 1,53055 | |
| PROT-A | 1,40 | 15,00 | 5,2613 | 2,92617 | 0,000 |
| PROT-R | ,07 | 8,30 | ,7721 | 1,59150 | |
| ALB-A | 1,40 | 4,00 | 2,5887 | ,71224 | 0,000 |
| ALB-R | 2,40 | 5,00 | 4,0879 | ,58404 | |
| ESR-A | 2 | 120 | 48,05 | 31,068 | 0,002 |
| ESR-R | 4 | 60 | 23,69 | 13,686 | |
| CRP-A | 2,50 | 4,50 | 3,1847 | ,36473 | 0,079 |
| CRP-R | 1,00 | 4,60 | 3,0976 | ,65073 | |
| HB-A | 5,50 | 16,00 | 10,8968 | 2,53673 | 0,208 |
| HB-R | 8,00 | 16,00 | 12,0545 | 2,19119 | |

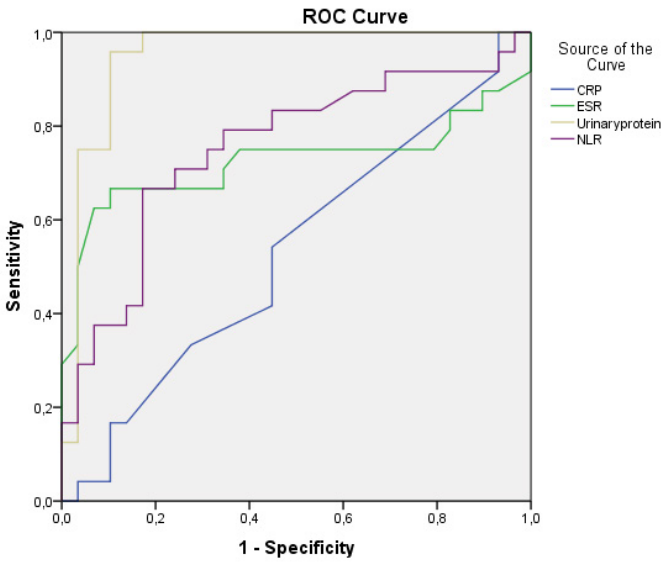


**Figure 1.** ROC curve analysis of SER, CRP, Urinary 24 Hour protein loss and NLR in state of activation and remission of LN. Elevated Urinary protein loss has the highest sensitivity followed by increased NLR. Elevation of ESR has a lower predictive value compare to NLR and 24-hour protein loss in case of LN. Elevation of CRP was the least potent predictive marker among the investigated ones. Area under the curve was % 95 for 24-hour urine output, %75,3 for NLR, %72,4 for ESR and % 52,9 for CRP.

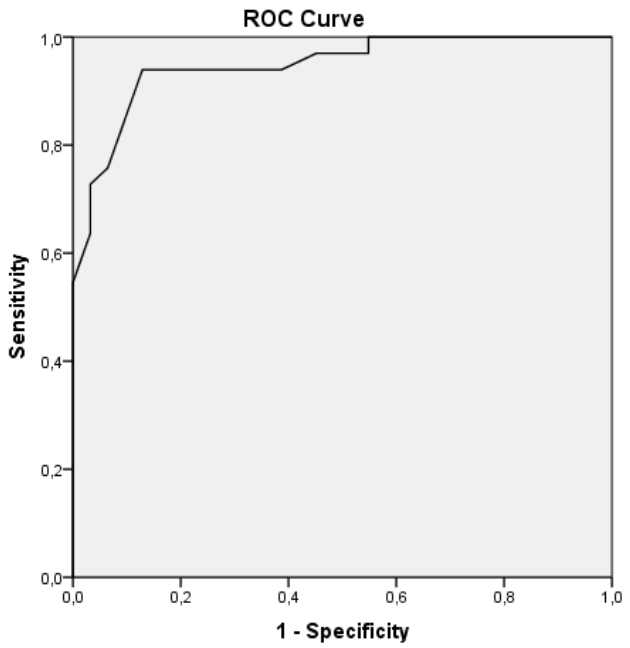


Figure 2. ROC analysis of decreased serum albumin level in case of LN activity. Decreased serum albumin has a %94,7 power to detect activity of the disease.

## Discussion

In the presented study; NLR was detected significantly higher in acitivation period of LN patients compare to remission period of the disease. In various of studies NLR was detected higher in inflammatory diseases like SLE [4,10-13].

Oehadian A and colloquia reported that they had detected the NLR of SLE patients were significantly higher compare to normal so it may have a potential as indicative inflammatory marker in SLE [13]. We had detected that NLR was increased during activation and replenished in remission period of the disease so it has potential both detection of inflammation and remission periods of SLE and LN.

In our study we excluded the LN patients who had comorbidities that potential affect to NLR beside that the patients with hematological involvement also excluded so the included patient number was decreased. But the power of NLR had presented obviously and without biases. Although lessen the number of included patients is a disadvantage of the disease LN is a rare disease and the number of included patients acceptable for such a study. We think that there is a need for studies in which patients with hemotological involvement will be evaluated separately.

The study of Baodong Qin and colleque has similarities with our study; they made compareme with the control group and detected the NLR has a power of inflammatory indicator and has positive correlation with the inflammation. Together with these results they stated and speculated that NLR has the power to detect the inflammation and state the activity of the disease in case of SLE patients. In our study we compared the NLR of LN patients during activation and remission periods of the same group of patients. As a result, the potential of NLR to detect activity of LN had more sophistically presented in the present study [12].

Ayna and colloque did compare the NLR of SLE patients with and without renal involvement and they had reported that LN patients had statistically higher NLR in case of renal involvement [14]. Accordingly in our study the NLR detected statistically high in LN patients. As a unique study design sole LN patient both in activation and remission period of the disease was compared in our study. This study design yields that NLR may be speculated as a factor both in detection of inflammation in LN and also it has a power in follow-up of state of remission. NLR may accompany other inflammatory markers during the judgment of activation and remission periods of the inflammatory diseases like SLE and LN.

Soliman WM and colloque had reported that NLR may have value in evaluation of disease activity of SLE patients and also NLR had a correlation with different histological stages of renal involvement and it has a power to reflect the renal involvement in SLE patients [15].

## Conclusion

As a result; in our study we detected that increased NLR had positive correlation with proteinuria, elevated ESR and activation period of LN, also had a negative correlation with serum albumin level. The increased NLR in state of activation period of LN decline significantly to lower levels if the patient get in remission period of the disease. We speculated that detection and follow-up of NLR in LN patients can be used as an inflammatory marker and detect the state of disease activity together with laboratory parameters like urinary protein loss, serum level of albumin. Further studies with crowded study population, healty control, various organ involvement of SLE required to poses ability of NLR in various situations.

## Conflict of Interest

All authors declare that they have no conflicts of interest.

## Contributions

All authors take full responsibility for the integrity of the manuscript. EÇ and YB conceived, designed and coordinated the search. EÇ, YB, NB and AU extract

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