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Evaluation of the neutrophil to lymphocyte ratio in lupus patients with and without nephritis

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ABSTRACT

Introduction: Lupus nephritis (LN) is a significant source of morbidity in cases with systemic lupus erythematosus (SLE). The efficiency of neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker has been investigated in many diseases.

Objectives: In the present study, the clinical significance of NLR in SLE patients with nephritis was investigated.

Patients and Methods: A total of 100 SLE patients including 20 and 80 patients with and without nephritis, respectively, and 140 controls were included in this investigation. Clinical findings and laboratory data of whole participants were reported. Inflammatory indices [e.g., erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and NLR] were compared between patients and healthy controls and also between SLE patients with and without nephritis.

Results: NLR value was significantly higher in SLE patients [2.81 (1.57-16.07)] compared to controls [1.45 (1.01-4.43)] and in SLE without nephritis [2.60 (1.50-13)] compared to SLE with nephritis [5.82 (3.75-16.07)] ($P<0.001$). Based on the ROC/area under curve (AUC) analysis, NLR reflected SLE disease with AUC of 0.904, cut off value of 1.98, 86.2% sensitivity, and 82% specificity. Additionally, NLR with a cut-off value of 3.64 and AUC of 0.935 indicated good sensitivity of 100% and specificity of 81.25% for discriminating SLE patients with and without nephritis.

Conclusion: NLR could be considered as a discriminative parameter for SLE patients and for LN. Further investigations are required to consider NLR as an inflammatory parameter.

Implication for health policy/practice/research/medical education:
The efficiency of neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker has been investigated in many diseases. Our results indicated that NLR could be considered as a discriminative parameter for systemic lupus erythematosus (SLE) patients and for lupus nephritis.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease and is characterized by dysregulation of immune systems. SLE is initiated by auto-antigens and various environmental, genetic, and hormonal factors are involved in its development (1). Lack of tolerance against nuclear self-antigens induces self-reactive B and T cells and causes excessive cytokine release, production of anti-DNA autoantibodies, and immune complex deposition. Moreover, dendritic cells and macrophages and neutrophils as innate immune cells participate in the onset and progression of the disease (1). Infiltration of the leukocytes and inflammatory cells to different tissues leads to the onset of clinical manifestations of SLE (2). Lupus nephritis (LN) is an immune glomerulonephritis that occurs in about 50% of SLE patients due to deposition of anti-DNA antibody complexes in the kidney (3). In LN, after recruitment of immune cells to the kidney and induction of inflammatory responses, the manifestations of SLE are worsened and the occurrence of chronic kidney

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disease and end-stage renal disease is expected (2). Kidney involvement makes LN the major cause of morbidity and mortality in SLE patients (4). Hence, early diagnosis and following-up the progression of SLE is vital to limit its deleterious consequences. This necessitates investigations to define practical biomarkers to discriminate SLE patients with and without nephritis. Various biomarkers including C-reactive protein (CRP), procalcitonin, calcium-binding proteins (S100A8/A9), interferon, interleukin-6, and delta neutrophil index have been identified (5-7). Gelatinase-B-associated lipocalin produced by neutrophils and interleukin 18 has been suggested as a useful marker to assess renal disease activity (8, 9). Association of circulating blood cells count with inflammation has been indicated in inflammatory diseases such as psoriasis, familial Mediterranean fever, and active ulcerative colitis (10-12). Neutrophil to lymphocyte ratio (NLR) is a simple and nonaggressive method determined by dividing the neutrophil count by the lymphocyte count in a complete blood count. Usefulness of NLR as an inflammation prognosis has been demonstrated in cancer (13), predictor of mortality in cardiovascular disease (14), and predictive marker for diabetic nephropathy (15). Furthermore, the association of NLR with SLE systemic inflammation and disease activity has also been indicated (16, 17).

Objectives

In this study, we investigated the efficiency of NLR as an inflammatory marker in SLE patients with and without nephritis.

Patients and Methods

Study population

SLE patients included in this study were admitted to Imam Reza hospital, Tabriz, Iran, between September 2015 and October 2016. A total of 100 patients with SLE, 20 of whom had renal involvement diagnosed based on American College of Rheumatology classification criteria for SLE (18). Any of them received any treatment. Patients with other conditions including autoimmune diseases, such as rheumatoid arthritis, active infection, malignancies, acute poisoning, ischemic injury, heart failure, myocardial infarction, coronary artery disease, diabetic nephropathy, chronic renal disorders, and any hematological condition which affects white blood cell (WBC) counts were excluded from the study. The age- and gender-matched control group consisted of 140 healthy individuals who admitted to the hospital for a routine checkup.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study is certified by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.REC.1396.598). A written informed consent was obtained from all patients and healthy individuals. This article was extracted from the M.D, theses of Leila Emami (Thesis# 95/1-1/4).

Data collection

Information including age, gender, creatinine (Cr), WBC counts, neutrophil and lymphocyte count, NLR, erythrocyte sedimentation rate (ESR), CRP, 24 h proteinuria were obtained from all participants. NLR was calculated by dividing the neutrophil count by the lymphocyte count in the blood.

Statistical analysis

Data analysis was conducted using SPSS software (version 23). Distribution normality of data was determined by Kolmogorov–Smirnov test and according to normal or non-normal distribution parametric or non-parametric tests were used. Data were presented as mean ± standard deviation or median. An unpaired Student's *t* test or Mann–Whitney U test was used to compare the differences for parametric or non-parametric data between the groups, respectively. To determine the association between variables, the Spearman's correlation coefficient was calculated. Sensitivity and specificity of NLR in diagnosis of SLE was analyzed using ROC (receiver operating characteristic) curve. Statistical significance was defined as P value of < 0.05.

Results

Characteristics of subjects

A total of 100 SLE cases with and without nephritis participated in the present study. SLE patients (14 male, 86 female) had a mean age of 36.02 ± 11.32 years. Healthy people (n = 140) with gender distribution of 24 males and 116 females participated in the study as control group. Mean age of the healthy control group was 37.9 ± 11.31 years. For further investigation, SLE patient group was divided into SLE patients without nephritis (SLEn-) and SLE patients with nephritis (SLEn+). Eighty SLEn- patients (10 male, 70 female) had a mean age of 37.42 ± 11.06 years, and 20 SLEn+ patients (4 male, 16 female) had a mean age of 30.40 ± 10.84 years. LN was confirmed based on the pathological staining of renal biopsies from patients, among 20 SLE patients with nephritis, 7 (35%) and 13 (65%) were suffering from stage III and stage IV, respectively.

NLR increase in SLE and LN patients

Clinical features and laboratory findings of all participants are provided in Tables 1 and 2. There was a remarkable difference in absolute neutrophil and lymphocyte count, and NLR between SLE patients and controls and also between SLEn- and SLEn+ patients ($P < 0.001$). NLR was increased in SLE patients compared to the healthy control group and in the SLEn+ patients in comparison to SLEn- (Figure 1). In 6 of 80 SLEn+ patients and in 3 of the 20

Table 1. Laboratory and clinical findings of healthy control groups and patients with SLE

Parameter	Healthy control	SLE patients	*P* value
Cr (mg/dL)	0.94 (0.54, 1.25)	0.9 (0.6, 2.9)	0.385
WBC (10^3/mm^3)	6.4 (3.70, 11)	7.46 (2.2, 19.65)	0.012
RBC (10^3/mm^3)	4.98 (3.24, 6.50)	4.5 (3, 10.50)	<0.001
NC (10^3/mm^3)	3.50 (1.74, 7.19)	4.98 (1.32, 15.7)	<0.001
LC (10^3/mm^3)	2.27 (0.88, 4.63)	1.56 (0.57, 6)	<0.001
ESR (mm/h)	12 (2-23)	30.00 (3-110)	<0.001
NLR	1.45 (1.01, 4.43)	2.81 (1.57, 16.07)	<0.001
CRP (g/L)	-	8 (2, 28)	-

Data are presented as median (min, max). Cr: creatinine; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LC: lymphocyte count; NC: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; RBC: red blood cell; WBC: white blood cell.

Table 2. Clinical and laboratory findings of SLE patients with and without nephritis

Parameter	SLE without nephritis	SLE with nephritis	*P* value
Cr (mg/dL)	0.9 (0.6-1.7)	0.91 (0.6-2.9)	0.50
WBC (10^3/mm^3)	6.36 (2.2-18)	9.75 (5.40-19.65)	<0.001
RBC (10^3/mm^3)	4.71 (3-6.5)	3.99 (3.19-6.5)	0.014
NC (10^3/mm^3)	4.36 (1.32-12.6)	8.07 (4.55-15.70)	<0.001
LC (10^3/mm^3)	1.66 (0.57-6)	1.33 (0.59-2.92)	0.06
ESR (mm/h)	27 (3-89)	57.5 (12-110)	<0.001
NLR	2.60 (1.50-13)	5.82 (3.75-16.07)	<0.001
Proteinuria (mg/d)	-	393 (16.85-1455)	-
CRP (g/L)	-	53.65 (5-94.30)	-

Data are presented as median (min, max). Cr: creatinine; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LC: lymphocyte count; NC: neutrophil count; NLR: neutrophil-to-lymphocyte ratio; RBC: Red blood cell; WBC: white blood cell.

SLEn- patients NLR was higher than the upper limit of reference range (4.7) and (10.8), respectively. In SLE cases with and without nephritis, no significant correlation was detected between NLR and CRP or ESR. The study showed serum creatinine levels of patients and controls was normal.

Prediction of SLEn- and SLEn+ development by NLR

To calculate the predictive value of NLR as an inflammatory marker in diagnosing SLE and LN, ROC analysis was performed. For predicting SLE, the optimal cutoff value for 1.98 had a specificity of 82% and a sensitivity of 86.2% [AUC = 0.904, 95%CI 0.857-0.940] (Figure 2a). Furthermore, the ROC analysis showed a sensitivity of 100%, and a specificity of 81.25% for NLR to discriminate the LN when the optimal cutoff value of 3.64 was used [AUC = 0.935, 95% CI 0.867-0.974] (Figure 2b).

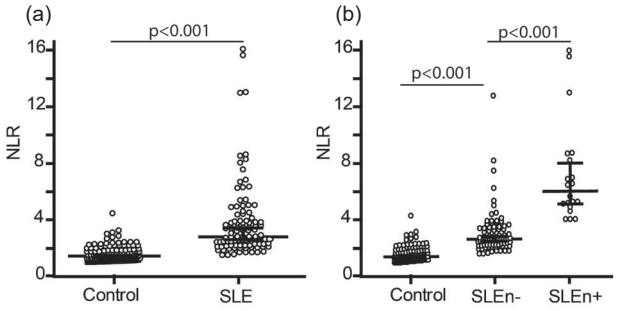

Figure 1. Comparison of NLR between the studied groups. Comparison of NLR between a) SLE patients and control group, and b) SLE patients with and without nephritis and control group.

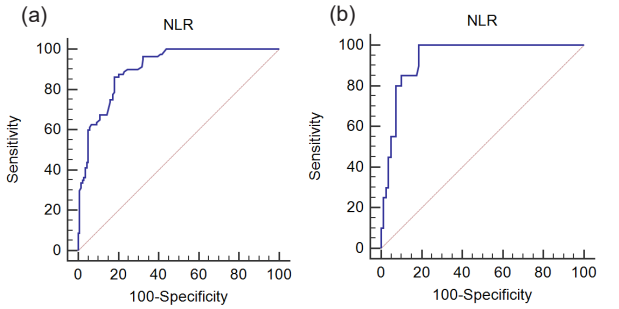

Figure 2. ROC curve analysis. ROC curve analysis of NLR for (a) SLE and (b) LN patients.

Discussion

In the present study, the efficiency of NLR was evaluated in differentiating 100 SLE patients from 140 healthy people and also in discriminating 80 SLE patients without nephritis from 20 SLE patients with nephritis. Here, we demonstrated that NLR is significantly increased remarkably in SLE patients compared to controls. Additionally, the increase was more noticeable in SLE patients when the kidney is involved. Based on our findings, NLR has the potential to be considered as a useful biomarker in diagnosing SLE patients from healthy people and also LN cases from SLE patients without nephritis.

In SLE, auto-reactive B and T cells produce a wide group of auto-antibodies and different cytokines that are involved in the pathogenesis of the disease. Different clinical abnormalities are associated with main immune subsets of inflammatory cells; leukocytes and neutrophils. Hematological manifestations including leucopenia, due to neutropenia and/or lymphopenia are common features of SLE and are associated with disease activity (19). Neutropenia and lymphopenia occur in 50%–60% and 20%-93% of SLE patients, respectively (20). In several other conditions such as stress, cancer, and systemic inflammatory diseases alterations in host's circulating WBC count, neutropenia, and lymphopenia are also indicated (21,22). Despite advances in revealing the

pathogenesis of SLE, there is no defined gold standard to diagnose SLE yet. Calculation of NLR is fast and affordable and its potential role in discriminating SLE patients from healthy people has been indicated (23). Wu et al evaluated the association of NLR, platelet-to-lymphocyte ratio (PLR) with SLE disease activity and indicated a noticeable difference in NLR between 116 SLE patients and 136 healthy controls. The calculated cut off value for SLE prediction in their study was 2.26, with 75% sensitivity and 50% specificity. Their findings suggest the potential value of NLR to monitor disease activity (17). In another study, the efficiency of NLR, monocyte to-lymphocyte ratio, and PLR was evaluated to detect infection in SLE patients. They indicated higher NLR with a cut-off value of 5.70 and PLR in SLE patients with infection compared to SLE patients with flare. The sensitivity and specificity of NLR in this study determined to be 75% and 90%, respectively (24). Moreover, NLR was significantly higher in SLE patients with LN compared to patients without LN (21, 25). Li et al indicated that NLR can reflect LN with cut off value of 4.40 (sensitivity 0.64, specificity 0.91(21). Based on Ayna et al NLR cut off value of 1.93 (sensitivity 83%, specifcity 54%) differentiates SLE patients with or without nephritis (25). Beside NLR, the correlation of other inflammatory factors such as CRP, ESR has been investigated to discriminate SLE (26). Sensitivity of NLR as an inflammatory marker is higher than overall measured sensitivity of SLE-associated antibodies (below 45%) (27). ESR is age-related and nonspecific parameter and should not be considered as a potential clinical test (28). Furthermore, in predicting bacterial infection, NLR is equal or more informative than measured CRP levels (29,30).

In our study, similar to other investigations on SLE, incidence of the disease was remarkably higher in females (86%) compared to males (14%) (17,21). Our findings indicate a significant increase in measured NLR between the SLE patients and control group that is in accordance with previously reported studies (16,17). Based on the ROC curve, NLR cut-off value of 1.98 (sensitivity 86.2%, specificity 82%) differentiated SLE patients from control group. Further investigations indicated that renal involvement caused a higher level of NLR compared to SLE patients without nephritis. The determined NLR test to diagnose SLE with and without nephritis had 100% sensitivity, 81% specificity and cut off value of 3.64.

ESR was significantly elevated in SLE patients compared to controls and also in SLEn+ compared to SLEn-. However, NLR was not correlated with ESR and CRP indices.

NLR is affected by different parameters and its usage as a clinical biomarker in SLE diagnosis is not verified yet. It should be noticed that high NLR is associated with systemic inflammation in a variety of diseases. However, WBC changes identified as lymphopenia is found in 93% of SLE patients (19). Combination of NLR and other inflammatory parameters such as ESR and CRP in reflecting systemic inflammatory responses in SLE patients is more informative (24).

Conclusion

As a conclusion, our data demonstrated a significant increase of NLR in SLE patients compared to healthy people and suggest the potential role of NLR in diagnosis of systemic inflammatory responses in SLE patients. Assessment of NLR can be also considered when SLE is associated with kidney function failure and nephritis.

Study limitations

The small sample size in LN group was the limitation of our study. To confirm the diagnostic value of NLR in SLE and LN further longitudinal larger scale studies are recommended.

Authors' contributios

TP and SA designed the study and selected the cases. LE did sampling. TP and MJN performed experimental analysis and interpretation of the data. SZV revised the draft. All authors read and signed the final paper.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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