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ORIGINAL ARTICLE

A CLINICAL UTILITY OF NEUTROPHIL LYMPHOCYTE RATIO AS AN INDEPENDENT PREDICTOR OF SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY

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Abstract:

Background: *Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease and is associated with considerable morbidity. The neutrophil-to-lymphocyte ratio (NLR) has been chosen as a potential marker of inflammation in SLE. To evaluate the role of NLR as an independent predictor of SLE activity.* ***Methods:*** *This was a cross-sectional comparative study conducted in the Department of Physiology, Dhaka Medical College, Dhaka, Bangladesh from July 2016 to June 2017. In this study, 30 SLE patients, aged 18 to 55 years, were considered as the study group and 30 aged matched healthy subjects were considered as control group. SLE Disease Activity Index (SLEDAI) score was used to assess disease activity.NLR and ESR was estimated. Independent samples* t*-test, Chi Square test, Pearson's correlation co-efficient (r) test, Regression analysis and ROC curve analysis were performed as applicable. 95% confident interval was calculated and* p *value <0.05 was accepted as level of significance.* ***Results:*** *In this study, NLR was significantly (*p*=0.003) higher in SLE patients than control. SLEDAI score was 10 (1-18) and majority (19; 63.33%) of the SLE patients had SLEDAI score >9 (active disease). NLR was significantly (*p*=0.001) increased more in active SLE than inactive SLE and showed a significant association among NLR and active disease (OR; 6.56, 95% CI; 1.26 to 34.20, p=0.001). NLR was positively correlated with SLEDAI score and ESR in patients with SLE. The optimal NLR cutoff value of 2.2 had 95% sensitivity and73% specificity {AUC = 0.957, 95% CI, 0.892–1.000, p = <0.001}.* ***Conclusion:*** *This study concludes that NLR is significantly increased in SLE patients and can be served as an independent predictor of SLE activity.*

Key words: *Neutrophil-lymphocyte ratio (NLR), Systemic lupus erythematosus (SLE), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)*

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Introduction:

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune inflammatory disease with a variable severity and duration of flares[1]. Abnormal immune regulation, activation of T cells and B cells, excessive production of autoantibodies and cytokines leads to intense inflammation and multiple organ damage in SLE[2].

Inflammation and immunity play a critical role in many chronic diseases. Neutrophils and lymphocytes reflect the balance between these two aspects of the immune system. Acute and chronic inflammations are indicated by the circulating neutrophils and adaptive immunity is indicated by lymphocytes. The neutrophil-to-lymphocyte ratio (NLR)is the proportionof absolute neutrophil count to lymphocyte count[3]. NLR has been extensively evaluated and shown to be associated with outcome and predict disease course among patients with a variety of medical conditions including ischemic stroke, cerebral hemorrhage, major cardiac events, sepsis and infectious diseases[4]. Numerous inflammatory indicators such as interleukin 1 (IL1), IL6, IL8, tumor necrosis factor alpha (TNF á) and cytokines (interferon) are used as biomarkers for inflammatoryresponse or disease activity in SLE patient[5]. Lack of availability, expensive and difficult to assay limit their use in routine clinical practice[5].NLR is a readilyavailable, inexpensive classical inflammatory marker that can be calculated easily and convey reliable information about thepatient inflammatory activity[5,6].Very few studies[7,8] have been found to assess the association of NLR with disease activity of SLE previously,but less published data are available in our country. Therefore, present study has been designed to evaluate the role of NLR as an independent predictor of SLE activity.

Methods:

Setting & study participants

This was a cross-sectional study conducted in the Department of Physiology, Dhaka Medical College, Dhaka from July 2016 to June 2017. In this study, 30 diagnosed SLE patients aged 18 to 55 years with duration of diseased"5 years were enrolled from SLE clinic of DMCH by purposive sampling. They were diagnosed on the basis of American College of Rheumatology (ACR) Criteria.[9]Similar ageand BMI matched healthy subjects were taken as controls. ACR criteria was consist of 16 points based on clinical and laboratory judgment. The patients with 4 points out of 16 have definite diagnosis of SLE. With 3 points highly suggestive SLE and with 2 points probable SLE[9]. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score[10] was used to assess disease activity. According to the SLEDAI score, we categorized the SLE patients into 2 groups such as patients with mild/inactive disease if score was d"9 and severe/ active disease if score was >9. Sample size was calculated by a statistical formula based on effect size in published results by similar article.The patients having history of liver disease, renal disease (other than SLE), rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriasis and malignant disease, history of taking anticoagulant, chemotherapy and recent history of blood transfusion were excluded from the study.

Procedure

After selection of the subjects, the nature, purpose and benefit of the study were explained to the subject. Informed written consent was taken from the participants. The research work was carried out after obtaining ethical clearance from Ethical Review Committee of Dhaka Medical College Dhaka. All the information was recorded in a prefixed data schedule. With all aseptic precautions, 3.6 ml blood was collected from all subjects. NLR was estimated by Automated Hematology Analyzer (Sysmex XT-2000) and ESR was estimated by Westergren's method.

Statistical analysis

Data were expressed as frequency, percentage, mean ± SE, median and presented in appropriate tables and figures. Independent samples *t*-test, Chi Square test and Pearson's correlation co-efficient (r) test were performed as applicable. Binarylogistic regression analysis was performed to observe OR and the association of NLR and ESR with SLEDAI score in SLE patients. The area under the ROC curve (receiver operating characteristic curve) also accessed. Sensitivity and specificity of NLR was calculated from ROC curve. 95% confident interval (CI) was calculated and *p* value <0.05 was accepted as level of significance. Statistical analyses were performed by using IBM SPSS (statistical package for social sciences) Statistics for Windows version 26.0.

Results:

In this study, the control and the study groups were age, gender and BMI matched and no significant (p>0.05) differences were observed between the groups (Table- I). The mean±SE of NLR and ESR was significantly (*p*=<0.05) higher in SLE patients than control (Table-II). SLEDAI score was 10 (1-18) and majority (19; 63.33%) of the SLE patients had SLEDAI score >9 (active disease) (Table III). NLR and ESR was significantly (*p*<0.05) increased more in active SLE than inactive SLE and showed a significant association among NLR, ESR and active disease (OR; 6.56, 95% CI; 1.26 to 34.20, p=0.001 and OR; 5.66, 95% CI; 0.75 to 42.36, *p*=<0.001) (Table-IV).Correlation analysis showed, significant (*p*<0.05) positive correlation among NLR, ESR and SLEDAI score (Figure 1 & 2). Receiver Operating Characteristic curve (ROC) analysis of NLR to predict SLE activity (Figure 3). The optimal NLR cutoff value of 2.2 had 95% sensitivity and73% specificity {AUC = 0.957, 95% confidence interval (CI), 0.892–1.000, p = <0.001}.

Table-I : *General characteristics of the subjects in both groups (N=60)*

Parameters	SLE patients (n=30)	Control (n=30)	*p* value
Age (years) Median (range)	35.10 ± 1.93	34.89 ± 2.51	0.929 ns
Gender (%)			
Male	2 (6.7%)	4(13.3 %)	0.389 ns
Female	28(93.3%)	26(86.7%)	
BMI (kg/m^2)	20.34 ± 1.08	21.91 ± 1.18	0.387 ns

Data were shown as mean±SE. Statistical analysis was done by Independent samples *t*-test and Chi Square test (frequency, %). SLE= Systemic lupus erythematosus, Control= Healthy subjects,
BMI= Body mass index, ns= not significant, N= total number of subjects, n = number of subjects in each group

Table II: *NLR and ESR of the subjects in both groups (N=60)*

Parameters	SLE patients(n=30)	Control(n=30)	Mean difference (95% CI)	*p* value
NLR	4.74±0.77	2.28±0.14	2.45(0.902 to 4.003)	0.003***
ESR (mm in 1st hour)	47.60±2.91	9.47±0.73	38.13(32.13 to44.14)	<0.001***

Data were shown as mean±SE. Statistical analysis was done by Independent samples *t*-test. NLR= Neutrophil-lymphocyte ratio, ESR= Erythrocyte sedimentation rate, SLEDAI= Systemic lupus erythematosus disease activity index, CI= confident interval***= significant at p<0.001, N= total number of subjects, n = number of subjects in each group

Table III: *Distribution of the study subjects according to SLEDAI (N=30)*

SLEDAI	Frequency	%
d”9(Inactive SLE)	11	26.70%
>9 (Active SLE)	19	63.30%
Median (Range)	10 (1-18)	

Data were shown as frequency, percentage andmedian. SLEDAI= Systemic lupus erythematosus disease activity index, n = total number of SLE patients

Table IV : *Association of NLR and ESR with SLE activity (n=30)*

Parameters	Inactive SLE (n_1=11)	Active SLE (n_2=19)	Mean difference (95% CI)	OR (95% CI)	*p* value
NLR	1.58±0.30	6.56±0.99	-4.98 (-7.71 to 2.26)	6.563 (1.26 to 34.20)	0.001***
ESR (mm in 1st hour)	39.82±2.93	52.11±3.96	-12.29 (-0.63 to -23.94)	5.66 (0.75 to 42.36)	<0.001***

Data were shown as mean±SE. Statistical analysis was done by Independent samples *t*-test and Binarylogistic regression analysis. NLR= Neutrophil-lymphocyte ratio, ESR= Erythrocyte sedimentation rate, OR=Odd ratio,***= significant at p<0.001, n = number of SLE patients

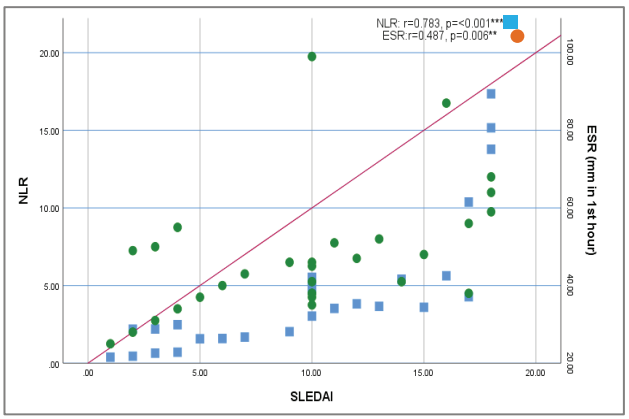

Figure 1: *Correlation of NLR and ESR with SLEDAI score in SLE patients presenting that there is positive correlation among NLR, ESR and SLEDAI score. *=significant*

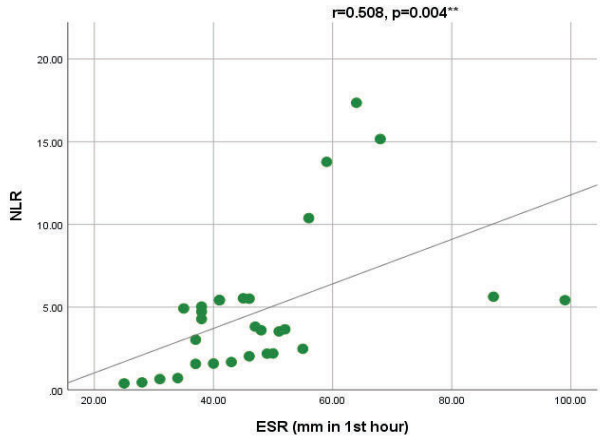

Figure 2: *Correlation of NLR with ESR in SLE patients presenting that there is positive correlation between NLR and ESR, ***=significant*

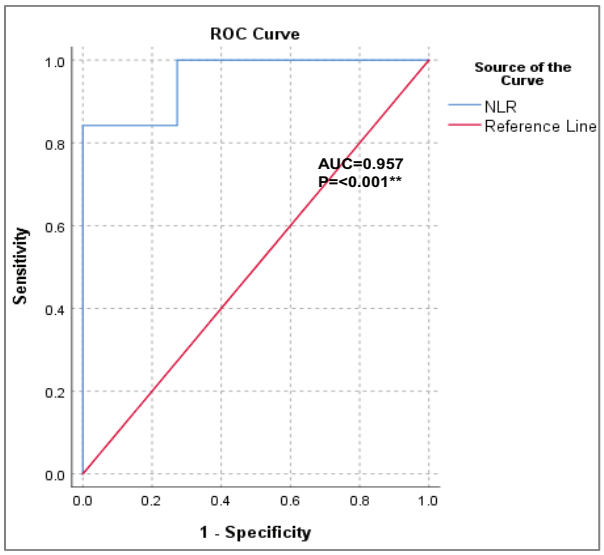

Figure-3: *Receiver Operating Characteristic curve (ROC) analysis of NLR to predict SLE activity(n=30)*

Discussion:

Now a day, there has been a growing emphasis on early diagnosis of SLE exacerbation and monitoring of disease activity. Concurrently, concentrated efforts have been made to assess hematological indicators that are capable for prognosing SLE exacerbation in the preclinical period, furthermore, indicates signs of exacerbation in a given organ[11]. The neutrophil-to-lymphocyte ratio (NLR) has been chosen as a potential marker of inflammation in SLE[12]. Neutrophils are the first inflammatory cells that are present at the site of inflammation and second, the pathway that is related to lymphocytes, which have a regulatory function[12]. The present study was undertaken to evaluate the role of NLR as an independent predictor of SLE activity.

In current study, NLR and ESR were significantly higher in SLE patients than healthy control. These findings are parallel to the observation of some groups of authors.[13-15]

Binary logistic regression analysis showed a significant association among NLR, ESR and active disease (SLEDAI score >9). Like other inflammatory marker (i.e., ESR) increased NLR was 6.6 times more risk of developing active disease in SLE patients. Some researchers of different countries found similar association but different methodology was used in those studies.[15,16]

In Pearson's correlation coefficient analysis, NLR and ESR showed positive correlation with active disease and NLR also showed positive correlation with inflammatory marker like ESR in patients with SLE. These findings are consistent to the observation of some other researchers.[13,14] It has been demonstrated that NLR is an index of systemic inflammation[13]. NLR is an easy, cheap and readily available marker that can convey important information about the patient inflammatory activity and prognostic prediction of diseases[13].

An interesting notice in present study was that NLR could predict SLE activity. The area of NLR under the ROC curve also considered as excellent for separating active from inactive SLE patients. These findings are parallel with other studies[12,13-15].

Though the explanation of these changes in NLR and ESR of SLE patients is not known but literature review suggests that increased ESR may be due to chronic inflammatory response with polyclonal increase in immunoglobulins[15,16].

An increase in NLR is determined by an increase of neutrophils and/or reduction in lymphocytes. An increase in circulating neutrophils is suggestive of

an acute or chronic inflammatory response. Lymphocytes generate adaptive immune responses to eliminate specific pathogens, infected cells etc[3]. Both innate and adaptive immune pathways become activated in SLE. So, immunosuppressive drugs (steroid, cyclophosphamide etc.) are used to suppress antibody production. They are bio-transformed in the liver. Their active metabolites inhibit purine synthesis and block the proliferation of activated T and B lymphocytes[17].

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology virtually affecting all organs of the body[18]. Beyond genetic and environmental factors, cytokine imbalances contribute to immune dysfunction, trigger inflammation and induce organ damage in SLE[9]. The key cytokine that is involved in SLE pathogenesis is interferon alpha. Neutrophils are important producers of type I interferon (IFN) via stimulation of plasmatic dendritic cells (pDC) by chromatin[19].Type I IFNs have potent ability to enhance lymphocyte recruitment to tissues, causing lymphopaenia[19]. Therefore, the increased neutrophil count was associated with the presence of markers of their activity and a decrease in the number of lymphocytes with activity and a high number of NLR in SLE. Han et al.[19] reported that Neutrophil-lymphocyte ratio (NLR) was more predictive than neutrophil and lymphocyte counts alone.

This increased NLR might be consequence of increased inflammation process in SLE patients which is evident from its relation to disease activity.

Conclusion:

Existing study revealed NLR is increased in systemic lupus erythematosus (SLE) patients and can be served as an independent predictor of SLE activity. NLR is inexpensive, widely available and easily measurable even in the simplest health care units. Therefore, NLR can be recommended to perceive disease activity in SLE. However, further prospective and multicenter studies with larger sample size are needed to corroborate the clinical value of NLR in patients with SLE and to determine a cut-off level for assessing disease activity with a high sensitivity and specificity.

Limitations:

Small sample size and this single hospital based study did not reflect exact scenario of the whole community.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

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Ethical consideration:

The study was conducted after approval from the ethical review committee of Dhaka Medical College. The confidentiality and anonymity of the study participants were maintained.

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