International Immunopharmacology 36 (2016) 94–99

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with disease activity in patients with systemic lupus erythematosus

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ARTICLE INFO

Article history:
Received 26 December 2015
Received in revised form 2 April 2016
Accepted 5 April 2016
Available online 22 April 2016

Keywords:
Neutrophil-to-lymphocyte ratio
Platelet-to-lymphocyte ratio
Systemic lupus erythematosus
Disease activity

ABSTRACT

Objective: Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been investigated as two new inflammatory markers used in the assessment of systemic inflammation in many diseases. The purpose of the study was to investigate their relation with disease activity in newly diagnosed SLE patients.
Methods: The study population consisted of 116 SLE patients who did not receive any treatment and 136 healthy controls. We divided the patients into two groups according to the SLE Disease Activity Index 2000 (SLEDAI-2K) system. Group 1 included patients with a score of 9 and lower (patients with mild disease activity), and Group 2 included patients with a score of >9 (patients with severe disease activity). Correlations between NLR, PLR and disease activity were analyzed.
Results: The NLR and PLR of SLE patients were significantly higher compared to those of the controls (both $P < 0.001$). There was a statistically significant difference in NLR and PLR between Group 1 and Group 2 (both $P < 0.05$). SLEDAI scores positively correlated with NLR ($r = 0.312$, $P < 0.001$) and PLR ($r = 0.298$, $P < 0.001$). Furthermore, SLE patients with nephritis had higher NLR levels than those without nephritis ($P = 0.027$). Based on the ROC curve, the best NLR cut-off value to predict SLE patients with severe disease activity was 2.26, with 75% sensitivity and 50% specificity, whereas the best PLR cut-off value was 203.85, with 42.3% sensitivity and 83.9% specificity.
Conclusion: NLR and PLR were two useful inflammatory markers for assessment of disease activity in patients with SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease with unknown etiology, and has various clinical manifestations affecting different tissues. It is characterized by the deposition of immune complexes due to widespread loss of immune tolerance to nuclear self-antigens, as well as by excessive proinflammatory cytokine production, leading to damage of multiple organ systems [1]. Although the pathogenesis of SLE is not completely clear, genetic, environmental and hormonal factors have been found to play key roles in susceptibility and heterogeneous clinical manifestations [2,3]. Unrestricted hyperactivation of the immune system may lead to the overproduction of autoantibodies, immune complex deposition, inflammatory cytokine release, and eventually disease onset. Chronic inflammation is an important pathological development in the disease process for autoimmune diseases. The chronic inflammatory process, which is triggered by auto-antigens and maintained by both environmental and genetic factors, is a common characteristic for all autoimmune diseases [4]. Thus, inflammation plays an important role in SLE, although the pathophysiological process of SLE is complex.

Many different markers of inflammation, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interferon (IFN) and interleukin-6 (IL-6), have been used to assess inflammatory status in SLE. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been investigated as new prognostic indicators for a large number of malignancy studies [5,6]. Many cancer survival studies have suggested that the NLR is significant predictors of overall and disease-specific survival of patients [7–10]. Moreover, previous studies have shown that NLR and PLR are associated with morbidity and mortality in many chronic diseases, such as hypertension, heart failure, infective endocarditis, acute coronary syndromes and type 2 diabetes [11–15]. In recent years, NLR has been a marker of subclinical inflammation, and has been used in combination with other inflammatory markers to determine inflammation in many

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http://dx.doi.org/10.1016/j.intimp.2016.04.006
1567-5769/

diseases. As a novel marker for inflammation, NLR may be also useful to estimate the activity of autoimmune diseases. Previous studies have shown that NLR is associated with psoriasis [16] and rheumatoid arthritis (RA) [17]. A recent study has also shown that NLR is increased in patients with systemic lupus erythematosus (SLE) [18]. However, platelets also play an active role in inflammation, while having regulatory effects on the immune system as well [19,20].

Our study is actually very rare that assesses NLR and PLR in patients with SLE, and to investigate their relationship with inflammatory response and disease activity in SLE.

2. Materials and methods

2.1. Participants

The patients enrolled in this study were identified from the electronic database of the Second Affiliated Hospital of Shantou University Medical College. SLE patients who were admitted to the hospital between January 2012 and May 2015, were included in this study. The study included 116 patients with SLE, as assessed by the diagnosis was based on the criteria established by the American College of Rheumatology (ACR) [21]. None of the patients received any treatment. Patients were excluded if they had one of the following combined diseases/situations: 1) other autoimmune disease, such as Sjogren's syndrome (SS), Rheumatoid arthritis (RA) or Hashimoto's thyroiditis (HT); 2) malignant diseases; 3) using of medical treatment affecting the WBC counts, such as hematopoietic system disorders; 4) evidence of any concomitant inflammatory disease, acute infection, or chronic inflammation status; 5) coronary artery disease, heart failure, acute coronary syndrome (ACS), hypertension, history of chronic renal or hepatic disease and cerebrovascular disease; 6) hematological disease or had received blood transfusion during the past 4 months. The control group included 136 healthy individuals that visited the hospital for a routine checkup.

2.2. Data extraction

Disease activity was assessed by the SLE Disease Activity Index 2000 (SLEDAI-2K) system [22]. We divided the patients into two groups according to the SLEDAI-2K system. Group 1 included patients with a score of 9 and lower by the SLEDAI-2K system (patients with mild disease activity), and Group 2 included patients with a score >9 (patients with severe disease activity). The study protocol was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

2.3. Statistical analysis

Analyses were performed using SPSS software (version 20.0, SPSS, Chicago, IL, USA). The normality of distribution was checked by Kolmogorov–Smirnov test, and parametric or non-parametric tests were used on data according to normal or non-normal distributions. Continuous data were expressed as mean ± standard deviation while categorical data were presented as percentage. An unpaired Student's *t*-test was used for comparing the difference between two groups when the continuous data fitted a normal distribution. Mann–Whitney *U* test was used to compare the differences for non-parametric data between the groups. The Spearman correlation coefficient was computed to examine the association between two continuous variables. Furthermore, ROC curve analysis was performed to determine the sensitivity and specificity of NLR and PLR in predicting the high SLEDAI-2K scores. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. Basic characteristics of the study sample

Patients had a median age of 27 years (range: 5–73), with a gender distribution of 97 women (83.6%) and 19 men (16.4%). The median age was 27 years in the control group (range: 10–68) with a gender distribution of 111 women (81.6%) and 25 men (18.4%). No statistically significant differences were observed in age and gender between the patient and control groups ($P = 0.111$ and $P = 0.466$, respectively) (Table 1).

3.2. NLR and PLR levels were increased in SLE patients

NLR was 2.77 (1.81, 4.11) in the patient group and 1.64 (1.32, 2.09) in the control group. PLR was 138.52 (94.29, 222.65) in the patient group and 98.95 (84.84, 118.93) in the control group. There was a statistically significant difference in NLR and PLR between the patient and control groups (both $P < 0.001$). We found that the patients with SLE had lower lymphocyte counts than the healthy controls ($P < 0.001$) (Table 1, Fig. 1). The SLE patients also had significantly higher hs-CRP levels ($P < 0.01$) and ESR levels ($P < 0.001$) (Table 1). Furthermore, SLE patients with nephritis had higher NLR levels than those without nephritis ($P = 0.027$) (Fig. 1).

3.3. NLR and PLR were associated with clinical disease activity in patients with SLE

In our study, patients in Group 1 (SLEDAI-2K score ≤9) had an NLR of 2.34 (1.63, 3.28) and a PLR of 130.54 (110.79, 176.13). Patients in Group 2 (SLEDAI-2K score >9) had a higher NLR of 3.25 (2.27, 5.08) and a PLR of 171.79 (96.97, 296.23). The differences in NLR and PLR between the two groups were statistically significant (both $P < 0.05$). Total white blood counts, neutrophil and lymphocyte counts, NLR, PLR, ESR and hs-CRP levels according to SLEDAI-2K score subgroups were shown in Table 2. In patients with SLE, NLR and PLR increased with increasing SLEDAI-2K scores (both $P < 0.05$) (Table 2, Fig. 2). Similarly, the ESR

Table 1
Demographic, clinical characteristics and laboratory results of patients and control groups.

	SLE patients (n = 116)	Healthy controls (n = 136)	*P*-value
Age (years)	27 (18.75, 38.50)	27 (24.0, 36.0)	0.111
Gender (M/F)	19/97	25/111	0.466
Onset time (month)	2.0 (0.67, 8.0)		
SLEDAI-2K scores	11.39 ± 6.48		
Anti-dsDNA Antibody (%)	68.42		
ANA (%)	87.37		
ACA-IgM (%)	15.58		
ACA-IgG (%)	15.58		
ACA-IgA (%)	15.58		
C3 (g/L)	0.40 (0.26, 0.64)		
C4 (g/L)	0.07 (0.03, 0.13)		
Lupus nephritis (%)	64.66		
Lupus encephalopathy (%)	10.34		
Hs-CRP (mg/L)	2.73 (0.87, 14.21)	0.68 (0.38, 3.79)	0.006
ESR (mm/H)	60.0 (30.25, 97.0)	10.0 (7.25, 16.5)	<0.001
WBC ($\times 10^9$/L)	5.10 (3.50, 7.85)	6.65 (5.60, 7.70)	<0.001
Neutrophils ($\times 10^9$/L)	3.29 (1.95, 5.67)	3.76 (2.87, 4.61)	0.029
Lymphocytes ($\times 10^9$/L)	1.15 (0.74, 1.76)	2.30 (1.95, 2.63)	<0.001
Platelets ($\times 10^9$/L)	168.96 ± 89.72	233.46 ± 48.09	<0.001
NLR	2.77 (1.81, 4.11)	1.64 (1.32, 2.09)	<0.001
PLR	138.52 (94.29, 222.65)	98.95 (84.84, 118.93)	<0.001

F: female; M: male; dsDNA: anti-double stranded antibodies; ANA: anti-nuclear antibody; ACA: anticardiolipin antibody; Hs-CRP: high sensitive C reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; NLR: neutrophils-to-lymphocytes ratio; PLR: platelet-to-lymphocyte ratio.