The Egyptian Rheumatologist xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

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

Original Article

Association of neutrophil to lymphocyte ratio with disease activity indices and musculoskeletal ultrasound findings in recent onset rheumatoid arthritis patients

Rasha M. Fawzy [a,*], Emtethal A. Said [a], Amira I. Mansour [b]

[a] Rheumatology, Rehabilitation and Physical Medicine Department, Faculty of Medicine, Benha University, Egypt
[b] Clinical and Chemical Pathology Department, Faculty of Medicine, Benha University, Egypt

ARTICLE INFO

Article history:
Received 30 April 2017
Accepted 1 May 2017
Available online xxxx

Keywords:
Neutrophil lymphocyte ratio
Rheumatoid arthritis
Disease activity
Inflammation
Power-Doppler ultrasound

ABSTRACT

Aim of the work: To study the relation between neutrophil-lymphocyte ratio (NLR) with disease activity indices and with musculoskeletal ultrasonographic findings in recent onset rheumatoid arthritis (RA) patients.

Patients and methods: The study consisted of 40 recently diagnosed RA patients and 40 matched control. Patients' disease activity was assessed clinically by the disease activity score (DAS-28). Musculoskeletal ultrasound was performed to detect synovitis by Power-Doppler ultrasound (PDUS). The association of NLR with the disease activity indices and the PDUS score were analyzed.

Results: The mean age of the patients was 44.5 ± 2.7 years, disease duration 9.4 ± 4.5 months and the female:male ratio was 2.3:1. Their disease activity was 4.7 ± 1.33 and the PDUS score was 10.24 ± 4.56. The NLR was significantly increased in the RA patients (3.28 ± 0.59) compared to the control (1.7 ± 0.23) ($p < \mathbf{0.0002}$). There was a significant correlation between NLR with the disease duration ($p < \mathbf{0.015}$), tender joint count ($p < \mathbf{0.022}$), swollen joint count ($p < \mathbf{0.018}$), morning stiffness ($p < \mathbf{0.045}$), visual analogue scale ($p < \mathbf{0.026}$), DAS-28 ($p < \mathbf{0.049}$), erythrocyte sedimentation rate ($p < \mathbf{0.032}$), C-reactive protein ($p < \mathbf{0.017}$) and PDUS score ($p < \mathbf{0.037}$). NLR was significantly elevated in highly active RA patients compared to patients with moderate and low disease activity ($p < \mathbf{0.014}$).

Conclusion: NLR significantly correlated with disease activity indices in recent onset RA patients thus reflecting systemic inflammation with its advantages of being available, easy and cost accessible being as reliable as the DAS-28 hence it could be used as a marker of disease activity.

1. Introduction

Rheumatoid arthritis (RA) is perhaps the most common inflammatory arthritis, affecting 0.5–1% of the general population worldwide. RA is primarily a disease of the joints, but abnormal systemic immune responses are evident and cause a variety of extra-articular manifestations [1]. Alterations in circulating blood cells quantity and composition, usually accompany systemic inflammation as normochromic anemia, thrombocytosis, lymhopenia [2] with elevated neutrophil count. Hence, components of circulating blood cells could be used for the evaluation of inflammatory activity [3].

Neutrophil to lymphocyte ratio (NLR) is the proportion of absolute neutrophil count to lymphocyte count, that is derived from routine complete blood count (CBC) test [4] which has emerged as a marker of inflammation in neoplastic, cardiovascular disorders, ulcerative colitis and familial mediterranean fever [5,6]. Due to their reliability, reproducibility, and cost effectiveness, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are markers that are most extensively used for measuring acute phase response. Although they are affected by age, gender, and hemoglobin level; factors which are not related to inflammation, while NLR is not affected [4].

Rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) antibodies positive patients are more prone to develop joint erosions, though their levels do not dependably vary with disease activity [7]. Despite The DAS-28 is valid and widely used as a standard measure to assess RA disease activity, the visual analogue scale (VAS) for general health or a VAS for pain evaluated by

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
* Corresponding author at: Faculty of Medicine, Benha University, Benha, Egypt.
E-mail address: dr.rasha.fawzy@hotmail.com (R.M. Fawzy).

http://dx.doi.org/10.1016/j.ejr.2017.05.001
1110-1164/

Please cite this article in press as: Fawzy RM et al. Association of neutrophil to lymphocyte ratio with disease activity indices and musculoskeletal ultrasound findings in recent onset rheumatoid arthritis patients. The Egyptian Rheumatologist (2017), http://dx.doi.org/10.1016/j.ejr.2017.05.001

patients are subjective indices, thus an objective measure would be more valuable [8].

Power Doppler ultrasound (PDUS)-based RA disease activity depends on detecting and grading of synovitis with synovial proliferation, effusion and neoangiogenesis considered as the most common abnormalities remarking local inflammation [9,10], and thus could detect subclinical synovitis which may lead to the reclassification of oligo to polyarthritis [11]. In Egyptian RA patients, US provided valuable disease activity information [12], detected synovial thickness and increased signaling [13] with synovitis significantly evidenced in recent-onset cases [14]. Moreover, PDUS was useful in detecting subclinical synovitis in juvenile idiopathic [15] and gouty arthritis [16] patients. The aim of this work was to study the relation between NLR with disease activity and with musculoskeletal ultrasonographic findings in recent-onset RA patients.

2. Patients and methods

Forty recently diagnosed RA patients (disease duration ranged from 1–20 months) with a mean of 9.4 ± 4.5 months who met the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria of RA [17] and didn't receive any medications, collected from the outpatient and inpatient clinics of the Rheumatology, Rehabilitation and Physical Medicine Department of Benha University Hospitals during the period from December 2015 to June 2016 were enrolled in this study. Together with 40 age and sex matched healthy control subjects. Patients were excluded from this study if they have any hematological abnormality, any acute or chronic infection, cancer, a granulomatous chronic disease, or a metabolic disease, those who were pregnant or in the recent post-partum period (6 months); those with chronic renal failure, end stage liver disease and those receiving drugs that can affect complete blood count (CBC) or activity scores. The study was approved by the Research Ethics Committee, Faculty of Medicine, Benha University, Egypt. The aim of the study was explained to all participants, and informed consent was provided.

All patients were subjected to full history taking, through clinical examination and laboratory investigations including CBC, ESR, CRP, serum RF and anti-CCP antibodies. Disease activity score (DAS-28) [18] and its components were assessed in all patients including tender joint count (TJC), swollen joint count (SJC) and visual analogue score (VAS). Blood samples were obtained using a vacutainer and collected in tubes containing standard EDTA. The neutrophilic and lymphocytic counts were determined using hematology auto analyzer (Ruby – CELL – DYN 08H56 – 02) from Abbott Company USA. The NLR in patients and control were explored.

2.1. Ultrasonography assessment

PDUS examination was performed by a rheumatologist who was blinded to all clinical and laboratory findings for detection of increased microvascular blood flow from small vessels seen in active synovitis. In each patient 22 joints: wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints were examined to assess inflammation. Transverse and longitudinal scanning of the dorsal aspect of the joints were performed with linear array transducers (12 MHz for fingers and hands). Additionally, MCP2 and MCP5 were assessed from the lateral aspect (Logiqe 9 scanner, General Electrics MedicaL Systems, Milwaukee, WI, USA) a multi-frequency linear array transducer (8–13 MHz) for all examined regions according to the EULAR guidelines [19]. For better scanning Doppler settings were optimized with a lower pulse repetition frequency (PRF) and greater color gain settings. The color gain setting was adjusted on a level to some extent greater than noise to avoid artifacts. Subclinical synovitis and the presence of blood flow in the synovial proliferation was measured and graded using a semi-quantitative PDUS score of four-step scale graded on a scale of 0–3 (0 = absence or minimal flow; 1 = mild: single vessel signal or isolated signals; 2 = moderate: confluent vessels signals in <50% of the joint area; 3 = marked: intense vessel signals in >50% of the joint area) in relation to the signal intensity of each joint, and the sum score was 0–66 corresponding to the maximum score obtained from the synovial sites evaluated in each joint [20,21]. PD total score was defined as the sum of PD scores for each joint at each examination.

2.2. Statistical analysis

The data were recorded, tabulated, coded, and then statistically analyzed using the computer program statistical package for the social science (SPSS, version 16, Inc., USA). Qualitative data were expressed in numbers and percents and quantitative data were expressed as means ± standard. Mann-Whitney test was used for analysis of two non parametric quantitative data and Kruskal Wallis test for more than 2. Spearman's test was used for correlation analyses. A linear multiple regression analysis of the variables was performed. P value was considered significant if <0.05.

3. Results

This study included 40 RA patients; 28 females and 12 males (2.3:1) with a mean age of 44.5 ± 2.7 years and disease duration of 9.4 ± 4.5 months. Table 1 shows the demographic data and laboratory characteristics of patients and control as well as the clinical features, DAS-28 and PDUS of the patients. The NLR was significantly higher in RA patients compared to the healthy controls (p **< 0.0002**). No significant difference (p = 0.34) was found between male and female RA patients as regard NLR. There was a

Table 1
Demographic data, clinical features, disease activity, laboratory characteristics and power Doppler ultrasound score of the rheumatoid arthritis patients and control.

Variable mean ± SD or n (%)	RA patients (n = 40)	Healthy controls (n = 40)	p
Age (year)	44.5 ± 2.7	42.8 ± 1.6	>0.53
Sex: F:M	28:12	25:15	>0.27
Disease duration (months)	9.4 ± 4.5	–	–
Clinical:			
Hand arthritis	40 (100)	–	–
VAS	7.2 ± 8	–	–
Activity (DAS-28)	4.7 ± 1.33	–	–
Laboratory:			
ESR (mm\h)	49.15 ± 21.7	23.7 ± 12.4	**<0.021**
CRP (mg\dl)	20.4 ± 9.3	6.3 ± 4.7	**<0.035**
Hb% (g/dl)	9.8 ± 1.4	12.5 ± 2.9	**<0.0007**
Platelet (mm^3/ml)	347.7 ± 49.56	273 ± 41.5	**<0.045**
WBCs (mm^3/ml)	8.2 ± 13.6	7.3 ± 11.4	>0.071
Neutrophil count (10^3/μl)	5.9 ± 1.3	3.9 ± 1.4	**<0.0001**
Lymphocyte count (10^3/μl)	1.8 ± 0.87	2.2 ± 0.73	>0.06
NLR	3.28 ± 0.59	1.7 ± 0.23	**<0.0002**
RF positivity	35 (87.5)	2 (5)	**<0.0001**
ACPA positivity	32 (80)	0 (0)	**<0.0003**
PDUS score	10.24 ± 4.56	–	–

RA: rheumatoid arthritis, VAS: visual analogue scale, DAS-28: Disease activity score-28 joints, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: Hemoglobin, WBC: white blood cell, ACPA: anti citrullinated peptide antibody, NLR: neutrophil lymphocyte ratio, RF: rheumatoid factor, PDUS: power Doppler ultrasonography. Bold values are significant at p < 0.05.

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Table 2
Correlation of neutrophil lymphocyte ratio with different disease parameters in rheumatoid arthritis patients.

Variable r (p)	NLR in RA (n = 40)	
Disease duration	0.28	(**<0.015**)
TJC	0.35	(**<0.022**)
SJC	0.39	(**<0.018**)
MS duration	0.13	(**<0.045**)
VAS	0.32	(**<0.026**)
DAS-28	0.59	(**<0.049**)
ESR	0.42	(**<0.032**)
CRP	0.35	(**<0.017**)
Hb (g\dl)	-0.46	(>0.12)
RF titer	0.04	(>0.23)
ACPA	0.07	(>0.16)
PDUS score	0.46	(**<0.037**)

TJC: tender joint count, SJC: swollen joint count, MS: Morning stiffness, VAS: visual analogue scale, DAS-28: disease activity score-28, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Hb: hemoglobin, RF: rheumatoid factor, ACPA: anti citrullinated peptide antibody, PDUS: power Doppler ultrasonography. Bold values are significant at p < 0.05.

Table 4
Linear multiple regression analysis for predictors of NLR in rheumatoid arthritis patients.

Parameter	NLR in RA patients (n = 40)		
	β	t	p
Dis. Dur.	0.006	0.06	0.95
MS	−0.1	−0.95	0.35
VAS	0.03	0.3	0.77
TJC	−0.09	−0.78	0.44
SJC	0.06	0.51	0.62
DAS-28	0.38	3.01	**0.005**
ESR	0.57	2.77	0.01
CRP	−0.12	−1.19	0.25
PDUS	0.24	2.43	**0.02**

NLR: neutrophil-lymphocyte ratio, RA: rheumatoid arthritis, Dis. Dur.: Disease duration, MS: morning stiffness, VAS; visual analogue scale, TJC: tender joint count, SJC: swollen joint count, DAS-28: disease activity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PDUS: power Doppler ultrasound. Bold values are significant at p < 0.05.

significant correlation (p < 0.05) between NLR and disease duration, TJC, SJC, VAS, DAS-28, ESR, CRP and PDUS and insignificant correlation with RF titer and ACPA (Table 2). There was a significant difference as regard ESR, NLR, DAS-28, CRP, VAS and PDUS and insignificant as regard RF titer among RA patients with different disease activity being higher in patients with high disease activity compared to moderate and low (Table 3). After application of linear regression; model parameters significantly correlated with NLR were ESR (p = 0.01), PDUS (p = 0.02) and DAS-28 (p = 0.005) (Table 4).

4. Discussion

Chronic inflammatory disorders are characterized by immune system dysregulation and persistent inflammation, which affects adversely on the hematopoietic system. Suspicion of rheumatoid arthritis (RA) [3,4], systemic lupus erythematosus (SLE) [22,23] and systemic sclerosis (SSc) [24] could be confirmed by changes in peripheral blood cell components which could reflect disease activity. One or more cellular components of blood cells such as anemia, neutropenia, thrombocytopenia could be detected.

There was a highly significant increase in the neutrophil count and NLR in RA patients compared to healthy controls. These results were in line with three recently published reports that showed increased NLR in RA patients [4,25,26]. Several immune- and nonimmune-mediated mechanisms could explain changes in blood cells components in chronic systemic inflammatory disorders, such as plethora of cytokines production, antibodies, immune complexes, growth factor deficiencies, a shortened life span, deficiency in neutrophil functions, gastrointestinal losses and toxicities related to medications [24,27].

In this study, no significant difference was found between NLR and the gender of RA patients, (p = 0.34). This was in agreement with the results of Kweon et al. [28] as no significant difference was found between NLR as regards gender (P > 0.05) in an asymptomatic Korean population.

This study showed insignificant correlation between NLR with the hemoglobin, RF titer and ACPA but was significant with disease duration, TJC, SJC, VAS, and also with disease activity indices like DAS-28, ESR, CRP, and PDUS. NLR was significantly higher in highly active patients than in those with moderate and low disease activity. These results were in accordance with those of Mercan et al. [4] and Uslu et al. [26] who reported a significantly elevated NLR in active RA patients compared to those in remission.

Granulocyte colony-stimulating factor (G-CSF) which is the chief cytokine in the regulation of granulopoiesis, correlated well with the disease activity of RA [29] thus elevated NLR is accepted in active RA patients. Neutrophil homeostasis is regulated by steadiness between granulopoiesis, retention, and release from bone marrow and clearance with apoptosis [30]. G-CSF stimulates myeloid proliferation, differentiation, and mobilizes neutrophils from the bone marrow [30]. Also IL-17 and IL-23 which are elevated in RA patients, play roles in neutrophil homeostasis regulation [31,32].

Mikhael and Ibrahim [33] reported that there was a significant correlation between NLR with ESR and negatively with the Hb and weakly with CRP. They also noted that NLR didn't differ significantly between highly and moderately active RA patients. Accordingly, NLR could not be used as a marker of disease activity but could be used as a marker of ongoing inflammation; however, their patients were receiving MTX that may causes neutropenia and thrombocytopenia [34]. Moreover, active RA patients are associated with anemia, leucocytosis and thrombocytosis [35,36].

Table 3
Comparison of some parameters in rheumatoid arthritis patients according to disease activity.

Variable mean ± SD	Disease activity in rheumatoid arthritis patients (n = 40)			
	Low (n = 9)	Moderate (n = 11)	High (n = 20)	p
NLR	2.5 ± 0.26	3.1 ± 0.15	3.7 ± 0.25	**<0.014**
CRP	15.7 ± 0.6	18.2 ± 4.3	23.5 ± 3.2	**<0.023**
ESR	29.3 ± 3.3	39.7 ± 6.9	62.6 ± 9.6	**<0.0001**
VAS	5.55 ± 0.7	6.1 ± 1.13	8.2 ± 1.15	**<0.043**
RF titer	98.9 ± 37.6	102.3 ± 54.5	108.4 ± 33.1	>0.13
DAS-28	2.8 ± 0.15	4.1 ± 2.18	5.87 ± 0.48	**<0.047**
PDUS	5.6 ± 2.1	7.76 ± 3.15	14.1 ± 3.26	**<0.016**

NLR: neutrophil lymphocyte ratio, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, VAS: Visual analogue scale, RF: rheumatoid factor, DAS-28: disease activity score-28, PDUS: power Doppler ultrasonography. Bold values are significant at p < 0.05.

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Neutrophils, accounts for more than 50% of the total leucocytic count, and participate in the production of many lytic enzymes, free oxygen radicals, and cytokines [37] which play a chief role in the pathogenesis of a large number of inflammatory diseases. Yolbas et al. reported that NLR was significantly higher in the RA, SLE and SSc patients than in the healthy control; also the ratio was higher in active than inactive Behçet's disease patients [38].

In this study, only the ESR, PDUS and DAS-28 were predictors of the NLR. Similarly, Mercan et al. [4] found that DAS-28-CRP is the only determinant of NLR in RA patients among other variables including age, sex, hemoglobin levels, and disease-modifying anti-rheumatic drugs.

In conclusion, this study demonstrated that NLR significantly correlated with disease activity indices in recent onset RA patients thus reflecting systemic inflammation with its advantages of being available, easy and cost accessible being as reliable as the DAS-28 hence it could be used as a marker of disease activity.

Conflict of interest

None.

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