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Original Article

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

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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

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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.