Neutrophil / Lymphocyte Ratio is not Correlated with Disease Activity in Rheumatoid Arthritis Patients

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Abstract

Rheumatoid arthritis is a chronic systemic inflammatory disease. Inflammation leads to joint damage and increases the risk of cardiovascular diseases. Neutrophil lymphocyte ratio (NLR) is a measure of inflammation in many diseases. Therefore, we aimed to evaluate the usefulness of NLR to detect inflammation in RA, and its correlation to RA disease activity indices and some hematological parameters. A cross-sectional study involving 24 patients with active rheumatoid arthritis (RA) who are using MTX participated in this study. All patients were clinically evaluated using disease activity score of 28 joints (DAS28) and simplified disease activity index (SDAI), whereas functional disability was assessed by health assessment questionnaire disability index (HAQDI); Moreover, blood specimen of each patient was used for measuring erythrocyte sedimentation rate (ESR), C – reactive protein (CRP), rheumatoid factor (RF), hemoglobin (Hb), white blood cells (WBC) count, platelets and red blood cells (RBCs) count, and NLR ratio.NLR was positively correlated with ESR and inversely correlated with Hb, but it didn't show any correlation with other clinical and laboratory parameters. In conclusion NLR is less correlated with inflammation and not suitable to monitor disease activity in RA patients using MTX.

Keywords: Rheumatoid arthritis, Inflammation, Neutrophil lymphocyte ratio.

نسبة كريات الدم البيض العدلة إلى كريات الدم البيض اللمفاوية لاترتبط مع فاعلية المرض عند المصابين بالتهاب المفاصل الروماتويدي

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الخلاصة

التهاب المفاصل الروماتويدي مرض التهابي مزمن وهذا الالتهاب يؤدي إلى تلف المفصل وكما يزيد من خطورة الأمراض القلبية الوعائية. إن نسبة كريات الدم البيض المعتدلة إلى كريات الدم البيض اللمفاوية يعتبر قياسا لنسبة الالتهاب في كثير من الأمراض. ولذلك كان هدفنا تقييم فائدة هذه النسبة لقياس مستوى الالتهاب عند مرضى التهاب المفاصل الروماتويدي وعلاقة هذه النسبة بفاعلية مرض التهاب المفاصل الروماتزمي وبعض المعايير الدموية. شملت الدراسة ٢٤ مصابا بالتهاب المفاصل الروماتويدي والذين يستعملون الميثوتركسيت. تم تقييم جميع المرضى سريريا بواسطة معيار فاعلية المرض ل ٢٨ مفصل (DAS28) وملحق فاعلية المرض المبسط (SDAI), أما مقدار الإعاقة فتم تقييمه بواسطة استبيان تقييم الصحة – ملحق العجز. إضافة لذلك عينات الدم سحبت لقياس نسبة ترسب كريات الدم الحمر, بروتين سي الفعال, مقياس الروماتويد, الهيموغلوبين, عدد كريات الدم الحمر والبيض والصفيحات الدموية و نسبة كريات الدم البيض العدلة إلى كريات الدم البيض اللمفاوية. إن نسبة كريات الدم البيض العدلة إلى كريات الدم البيض اللمفاوية كان لها علاقة ايجابية مع نسبة ترسيب كريات الدم الحمر وعلاقة عكسية مع الهيموغلوبين ولكنها لم تظهر أي علاقة مع باقي المعايير السريرية والمختبرية. يستنتج من ذلك إن نسبة كريات الدم البيض العدلة إلى كريات الدم البيض اللمفاوية ترتبط بعلاقة ضعيفة مع الالتهاب وغير ملائمة لمتابعة فاعلية التهاب المفاصل الروماتويدي للمرضى الذين يستعملون ميثوتركسيت.

الكلمات المفتاحية: التهاب المفاصل الروماتويدي, التهاب, نسبة كريات الدم البيض العدلة الى كريات الدم البيض اللمفاوية .

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology that characterized by both articular and extra articular features [(1)]. Local inflammation of the joints is correlated to joint damage [(2)] whereas systemic inflammation increases the risk of atherogenesis and coronary heart disease in RA patients [(3)]. Several studies have explored the relationship between systemic inflammation and cardiovascular mortality [(4, 5)].Systemic inflammation can be measured by using a variety of biochemical and hematological markers [(6)] CRP is a strong predictor of future

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cardiovascular events in individuals both with and without overt cardiovascular disease (CVD) [7]. Additionally, CRP correlates directly with the presence of atherosclerosis in patients with RA [8] whereas; ESR is significantly associated with the risk of CVD in RA [9].

Neutrophil lymphocyte ratio (NLR) is an important measure of systemic inflammation as it is readily available and could be calculated easily [10]. Many studies found that NLR is a useful measure to detect inflammation and predict long term outcomes in patients with renal failure, cancer and heart diseases [11 -13].

Aim of the Study

To evaluate the usefulness of NLR to detect inflammation in RA, and its correlation to various RA disease activity indices and some hematological parameters.

Patients and Methods

A cross-sectional study was conducted in Baghdad Teaching Hospital, Rheumatology Unit from December 2011 to May 2012. A total of 24 patients (7 males and 17 females) with active RA were involved in this study. Patients were diagnosed to have RA by the rheumatologist according to American College of Rheumatology (ACR) classification criteria for RA [14]. All patients included in the study signed an informed consent form according to the declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Baghdad University, College of Medicine, Department of Medicine. Patients with diseases other than rheumatoid arthritis were excluded from the study. Demographic data of patients were reported regarding their age, duration of the disease, and medication history (Table 1).

Laboratory Investigations

Blood specimens were taken from all patients. Hematological investigations that include complete blood count (WBC, RBC and Platelet), differential WBC count and Hb were measured using hematology auto analyzer (Ruby – CELL – DYN 08H56 – 02) from Abbott Company USA. ESR was measured by Westergren method [15]. CRP was measured semi quantitatively according to method of Singer *et al* using serial dilutions of serum; each dilution was mixed with a latex reagent and observed for the presence of Agglutination [16] using a ready made kit (Agapee, Switzerland) whereas RF was measured qualitatively [16] by a ready made kit (Spectrum, Egypt).

Clinical Evaluation

The 28 joints included bilateral knees, shoulders, elbows,wrists, metacarpophalangeal and proximal interphalangeal joints, were palpated to count the number of tender and swelling joints.

The patients were asked to mark on the VAS of 0 – 100mm according to their global assessment of their general health and pain. The physician marked on the VAS of 0-10 cm according to the physician global assessment of the disease activity. Disease activity was measured by both DAS28 and SDAI.

DAS28 was calculated from the TJC, SJC and ESR according to the following formula [17]:

DAS28 = $\{(0.56 \bullet \sqrt{[TJC28]}) + (0.28 \bullet \sqrt{[SJC28]}) + (0.70 \bullet \ln[ESR])\} \bullet 1.08$

Whereas SDAI was calculated by the following formula [18]:

SDAI = CRP + TJC + SJC + VAS (0-10) + EGA (0-10)Functional status of the patients was measured using Health assessment questionnaire disability index [19]. Additionally morning stiffness of each patient was calculated according to patient approximate.

Statistical Analysis

SPSS version 12 was used for data input and analysis. Shapiro wilk test (web version) used to check if data is normally or abnormally distributed. Spearman correlation coefficient was used to assess the correlation between abnormally distributed continuous variables. All p values used were asymptotic and two sided. Values with $p < 0.05$ were considered significant.

Results

Table (1) showed general demographic data for the patients that participated in this study. Table (2) showed the values (mean ± SD) for the different studied variables, When these valuescorrelated, with neutrophil/lymphocyte ratio there was a significant positive correlation with ESR ($r = 0.495$, $P = 0.014$) and a significant negative correlation with Hb ($r = -0.426$, $P = 0.034$), CRP has a weak positive correlation that didn't achieve statistical significance , whereas other parameters didn't show a significant correlation with NLR (Table 3).

Table (1): General demographic data of the patients

Parameter	Patients with Moderate Disease activity	Patients with High disease activity	All participated patients
Age, years Mean ± SD	51±12.11	45.24±11.08	46.92±11.44
Female percent	14.85	88.24	66.67%
Disease duration, years Mean ± SD	6.71±4.57	5.88±5.16	6.13±4.91
Drug used (MTX/HCQ)	(5/2)	17/0	(22/2)
RF positive n (%)	5 (71.4)	9 (52.94)	14 (58.33)
Smoking percent	42.86	0	12.5%

MTX = Methotrexate; HCQ = Hydroxychloroquine; SD = Standard deviation; RF = rheumatoid factor.

Table (2): Clinical and laboratory parameters in RA patients participated in the study

Parameter	Value (Mean ± SD)
TJC	10.54±4.53
SJC	5.13±3.03
VAS	54.17±25.70
EGA	5.13±2.35
Morning stiffness	26.2±38.1
DAS28	5.43±1.46
SDAI	27.92±13.62
CRP (mg/dl)	1.65±2.34
ESR (mm/hr)	38±22.14
RF	0.58±0.50
Hb (g/dl)	12.28±1.62
WBC (cell/ nano liter)	9.75±3.27
RBC (cell / nano liter)	4.67±0.76
Platelet (cell/ nano liter)	288±87.82
HAQDI	1.36±0.74

JC = Tender joint count; SJC = Swelling joint count; VAS = Visual analogue scale; EGA = Evaluator global assessment; DAS28 = Disease activity score 28 joints; SDAI = Simplified disease activity score; CRP = C – reactive protein; ESR = Erythrocyte sedimentation rate; RF = Rheumatoid factor; Hb = Hemoglobin; WBC =White blood cells; RBC = Red blood cell HAQDI = Health assessment questionnaire disability index.

Table (3): Correlation of different parameters with NLR

Parameter	Correlation Coefficient	P Value
TJC	-0.001	0.997
SJC	0.051	0.813
VAS	0.179	0.404
EGA	0.232	0.276
Morning stiffness	-0.139	0.516
DAS28	0.351	0.093
SDAI	0.150	0.484
CRP (mg/dl)	0.368	0.077
ESR (mm/hr)	0.495	0.014
Hb (gm/dl)	-0.435	0.034
WBC (cell/ nano liter)	0.306	0.146
RBC (cell/ nano liter)	-0.084	0.698
Platelet (cell/ nano liter)	0.339	0.105
HAQDI	0.146	0.496

JC = Tender joint count; SJC = Swelling joint count; VAS = Visual analogue scale; EGA = Evaluator global assessment; DAS28 = Disease activity score 28 joints; SDAI = Simplified disease activity score; CRP = C – reactive protein; ESR = Erythrocyte sedimentation rate; RF = Rheumatoid factor; Hb = Hemoglobin; WBC =White blood cells; RBC = Red blood cell HAQDI = Health assessment questionnaire disability index.

Additionally Table (4) showed that NLR not differ significantly between highly active and moderately active RA (P = 0.07), while ESR, CRP and DAS28 values varied significantly (P<0.05) between moderately and highly active RA patients. Table (5) showed a highly positive correlation between VAS and EGA.

Table (4): Comparison of some parameters between patients with highly active RA and those with moderately active RA

Parameter	Patients with moderate RA disease activity (7)	Patients with high RA activity (17)	P Value
NLR	2.11±0.46	3.17±1.68	0.070
DAS28	3.85±1.49	6.08±0.85	0.000
CRP	0.43±0.90	2.15±2.57	0.047
ESR	18.86±14.96	45.88±19.86	0.004

NLR= Neutrophil lymphocyte ratio; DAS28 = Disease activity score of 28 joints;
CRP = C – reactive protein; ESR = Erythrocyte sedimentation rate

Table (5): Correlation between Visual Analogue Sale (VAS) and Evaluator Global Assessment (EGA)

Disease activity	Number of cases	VAS	EGA	Spearman Correlation coefficient	P value
Moderate	7	31.43±20.35	27.14±18.90	**0.924**	**0.003**
High	17	63.89±21.18	60.56±16.97	**0.795**	**0.000**
Moderate and high	24	54.8±25.35	51.2±22.97	**0.867**	**0.000**

Discussion

This study showed that NLR as a measure of inflammation in RA patients was positively correlated with ESR, similar finding was observed when NLR was evaluated as a measure of inflammation in ulcerative colitis patients [(20)]. Moreover, NLR was inversely correlated with Hb, however, there is no any study in this respect and it is the 1st time to get such result. This finding is acceptable since Hb in RA patients is inversely correlated with inflammation and RA disease activity [(21)].

Regarding CRP, there is a modest but a non significant correlation with NLR, there is an agreement of this finding in a trial that followed up patients with cancer [(22)]. According to the above, and since NLR is well correlated with ESR and not well correlated with CRP, so NLR may be not sufficient laboratory test to predict CVD risk in RA patients and further studies areneeded to evaluate the association of NLR with the severity and extent ofcoronary atherosclerosis.

Results from the current study also showed that NLR didn't correlate with RA clinical parameters like tender joint count, swelling joint count and HAQDI, this result may be rationale since it has been found that many of clinical parameters that were used to diagnose RA like TJC, SJC, morning stiffness and HAQDI were less correlated with inflammation [(23-25).]

This study showed a direct positive correlation between VAS and EGA and also showed that there is no correlation between VAS and EGA with NLR. This finding can be explained according to the finding of Naredoetal[(24)] at which VAS was not correlated with inflammation (especially with ESR) and since this study showed that NLR was directly correlated with ESR, so it can be concluded that there is no correlation between VAS or EGA with NLR .

Additionally hematological parameters like WBC, RBC and platelets count were not correlated with NLR. There was very complex hematological parameters in active RA patients that use MTX who participated in this study, since active RA disease is associated with anemia, leucocytosis and thrombocytosis [(26,27)], whereas MTX may causes neutropenia and thrombocytopenia [(28)]. Consequently absence of correlation between NLR and hematological parameters may result from the unsuitable patient sample selection and further studies are needed to correlate between NLR and hematological parameters in RA patients using DMARDs other than MTX.

Finally, results from the current study showed that NLR is not correlated with RA disease activity as measured by either DAS28 or SDAI; similarly FauziaImtiaz*et al* also found that there was a non significant relationship between NLR and rheumatoid arthritis [29].

This finding was strengthened by absence of statistical difference in NLR between patients with moderately and those with highly active RA, and only CRP and ESR showed a significant difference between the 2 groups of patients similar to that of DAS28; Consequently ESR and CRP is better than NLR to detect RA disease activity.

Conclusion

NLR is less correlated with inflammation and not suitable to monitor disease activity in RA patients using MTX.

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