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ORIGINAL ARTICLE

Correlation between neutrophil to lymphocyte ratio and disease activity in patients with rheumatoid arthritis.

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ABSTRACT… Objective: To figure out correlation between neutrophils to lymphocyte ratio in rheumatoid arthritis and its relationship with the disease severity. **Study Design:** Prospective study. **Setting:** Department of Rheumatology Fauji Foundation Hospital, Rawalpindi, Pakistan. **Period:** July 1st to December 31st, 2021. **Methods:** Study population included rheumatoid arthritis patients fulfilling American college for rheumatology criteria. On the basis of disease activity score-28 (DAS-28), the subjects were categorised into active and remission groups. The control group consisted of healthy age and gender matched subjects. Relationship between neutrophils to lymphocytes ratio with disease activity was analyzed. Data was analysed using SPSS 21. **Results:** 140 patients with RA were evaluated along with 70 healthy control subjects. NLR was higher in active RA (1.99±0.84) as compared to RA with remission (1.76±0.41) and controls (1.77±0.79). p value<0.05 was obtained which was statistically significant. NLR is significantly correlated with CDAI and SDAI (r=0.24, p=0.04 each). CRP and ESR were also significantly higher in active RA patients compared to those in remission (p<0.005 and p<0.00 respectively) and control group. **Conclusion:** The neutrophil to lymphocyte ratio is a measure derived from a simple blood test. An elevated NLR is often considered an indicator of systemic inflammation. High NLR values may suggest increased inflammation and immune system activation, which are key features of RA. NLR may serve as a less expensive and easily accessible marker to detect inflammation in RA. It can be utilized in future as disease assessment tool.

Key words: Clinical Disease Activity Index CDAI, Disease Activity Score-28 DAS-28, Neutrophils to Lymphocytes Ratio NLR, Rheumatoid Arthritis RA, Simplified Disease Activity Index SDAI.

INTRODUCTION

Rheumatoid arthritis (RA) is an auto inflammatory disease. Its suffused as symmetrical polyarthritis of small joints leading to destruction and deformities which are irreversible in nature.[1] Global prevalence of RA is 0.5% - 1%.[2] In Pakistan, it is estimated upto 0.5%.[3]

In patients with RA, joint damage is mediated by antibodies, immune cells and pro inflammatory cytokines. In addition to joint involvement this inflammation leads to significant extra articular morbidities. Achieving minimal disease activity or remission is the goal of treatment for rheumatoid arthritis and ultimately to halt destruction to joints and comorbidities associated with it.[4] Disease activity is accessed by a number of tools such as clinical disease activity index(CDAI), simplified disease activity index(SDAI) and disease activity score-28(DAS-28).[5] CDAI incorporates clinical parameters alone whereas DAS-28 is a hybrid of swollen and tender joints counts, patient global assessment(visual analogue scale) and ESR laboratory parameters[6] (sensitivity 95% and specificity 84%).

Immune system dysregulation occurs in inflammatory diseases like RA and also attacks on blood cells and results in cascade of events with release of mediators of inflammation like cytokines, antibodies, complement complexes, growth factors, and toxicities related to medications.[7] Neutrophils, lymphocytes, monocytes, and platelets are immune system

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components that change as a result of inflammation. Inflammatory markers like ESR and CRP are generally high in acute phase of RA and correlate with disease activity.[8,9] In addition to these routine parameters research is going on to identify wide variety of easy available and accessible markers of inflammation to monitor disease activity. Hematological characteristics (Neutrophil-to-Lymphocyte ratio (NLR), Platelet-to-Lymphocyte ratio (PLR) and Lymphocyte-to-Monocyte ratio (LMR)) are investigated as indicators of systemic inflammation in various autoimmune disorders. These lab parameters are easy to attain with simpler lab facilities and are proving cost effective tool as well. Increased NLR and PLR have been linked to conditions such as cancer[10], diabetes[11], psoriasis[12], autoimmune rheumatic diseases[13] and heart failure.[14]

NLR and PLR studied in rheumatoid arthritis patients were substantially greater than those in the healthy control group.[15] These variables were found to have a favourable relationship with disease activity.[8] NLR and PLR also predicted rheumatoid arthritis treatment responses in patients who have had tumour necrosis factor alpha inhibitors treatment.[16] Though these parameters are not yet part of any validated tool for disease activity assessment and are not in routine use. These can prove to be cost effective tool in developing and resource poor countries. Scarce local data exists that have assessed the role of these laboratory parameters in our local population. The goal of this research is to establish correlation of NLR and PLR among individuals who have RA and its illness severity in our setup and as clinical tool for disease activity assessment.

METHODS

This cross-sectional investigation was conducted in the Fauji Foundation Hospital's Rawalpindi outpatient rheumatology clinic, from 1st July 2021 to 31st December 2021. As per hospital policy, approval was taken from the institutional ethical committee. Study reference number 616/RC/FFH/RWP/06-21. Sample size was calculated by WHO sample size calculator, following are the calculations, confidence level= 95%, population mean= 2.7, absolute precision required= 10%, population standard deviation =0.07, sample size(n) approximately =210, 70 in each three group(A,B & C).[17] 210 people with RA, as described by the 2010 classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)[18] were enrolled in study. Informed verbal consent was taken from patients before collecting their data. Patient's demographic information was entered in proforma and detailed interview of the patient was taken. The severity of the disease was determined by CDAI, SDAI & DAS-28.

Three groups of patients were made i.e.
Group A included 70 RA patients with active disease (DAS-28 score >2.6),

Group B patients included 70 RA people who are in remission from their illness (DAS-28 score <2.6)
Group C comprised of 70 age and gender-matched healthy volunteers served as a control group.

Patients with chronic ailments like diabetes mellitus, hypertension, chronic pulmonary diseases, end-stage renal illness, and ischemic heart disease, malignancies, hematological abnormalities, infections like tuberculosis and pregnant ladies were excluded. Patients with active acute infection were also excluded.

Patients were sent to the laboratory and 05 ml blood, 2 ml for the complete blood count (CBC) and 3 ml for chemical assays were taken from each patient and control. CBC included white blood cells (WBC) count (10^9\L), neutrophils (N) (10^9\L) and lymphocytes (L) counts(10^9\L), hemoglobin (Hb) concentration (gm/dl), platelets count(10^9\L).

The Neutrophil-Lymphocyte Ratio (NLR) was estimated as (neutrophil count/ lymphocyte count). The ESR mm/hour (Westergren method), CRP (latex slide test), rheumatoid factor (RF) (Latex agglutination slide test), and anti-cyclic citrullinated peptide antibodies (anti-CCP) were all tested in the lab. The primary result was a

comparison of NLR levels between these three groups, as well as their association to disease activity scores. Secondary outcomes included relationship of NLR with other parameters of CBC and relation of PLR with disease activity and other hematological parameters.

Analysis was done using SPSS v 21.0. The data was presented in the form of a mean, standard deviation, and percentages. Variables that are categorical were analyzed in univariate analysis using chi square test. Continuous variables were analysed using one-way ANOVA. Pearson's correlation was used to calculate the correlation between the variables. It was determined that $P<0.05$ was statistically significant.

RESULTS

140 patients altogether with RA who met ACR/EULAR criteria were studied. Group A included 70 Active RA patients, on average, had DAS-28 score of 4.39±0.95. Group B 70 patients in remission from RA were considered for the study and had a mean DAS-28 score of2.40±0.12. Group C comprised of 70 age matched controls. Mean age of our study population was 51.99±11.44 years. 201(95.7%) of the study patients were females. Age and gender composition of patients and controls was similar. Both RA groups had a similar proportion of seropositive patients (70%). Mean duration of RA was 120.54±86.91 months. Disease duration was less in active RA patients, compared to those in remission (115±83.2months vs 126±90.6 months). Table-I shows the demographic characteristics and medication of the study population.

NLR was higher in active RA (1.99±0.84) as compared to RA with remission (1.76±0.41) and controls (1.77±0.79). With a p value of <0.05., the difference was statistically significant. ESR and CRP were significantly more higher among RA patients who are active than in those who are in remission ($p<0.005$ and $p<0.00$ respectively) and the control group in lab parameters. Results are shown in Table-II.

NRL strongly correlated with SDAI and CDAI only in active RA patients. It was also associated with anemia in this group (Table-III).

	Active	Remission	Control
Age	51.9±10.4	52.4±12.06	51.43±11.87
Mean duration of disease(months)	114.9±83.2	126.1±90.6	
Gender Female Male	 63(90%) 7(10%)	 69(98.6%) 1(1.4%)	 69(98.6%) 1(1.4%)
Smoker	7(10%)	4(5.7%)	0(0%)
Seropositive RA	49(70%)	49(70%)	
Methotrexate Use	54(77.1%)	46(65.7%)	
Leflunomide Use	25(35.7%)	27(38.6%)	
HCQ Use	29(41.4%)	20(28.6%)	
SSZ Use	4(5.7%)	1(1.4%)	
Prednisolone Use	57(81.4%)	39(55.7%)	

Table-I. Baseline characteristics of the study population.

Parameters	Active	Remission	Control	P-Values
Hb (g/dl)	11.79±1.52	11.9±1.59	12.6±1.45	0.28
WBC(10^9\L)	8.7±2.4	8.2±2.11	8.68±1.75	0.86
Neutrophils(10^9\L)	5.02±1.91	4.77±1.38	4.77±1.38	0.51
Lymphocytes(10^9\L)	2.67±0.79	2.90±0.80	2.90±0.809	0.73
Platelets(10^9\L)	327.4±93.2	340.7±122.7	331.1±72.1	0.91
NLR ratio	1.99±0.84	1.76±0.41	1.77±0.79	0.019
PLR ratio	131.4±47.9	129.5±49.5	122.1±39.8	0.52
ESR(mm\1sthr)	27.8±4.4	24.2±3.36	20.9±5.1	0.00
CRP(ng\ml)	8290.1±3238.8	5799.1±2506.0	6123.5±3191	0.005

Table-II. Comparison of lab parameters between the three study groups.

Neutrophil-Lymphocyte Ratio (NLR)		
Parameters	**Active**	**Remission**
Hb(g\dl)	-0.30(0.01)	0.028(0.82)
WBC(10^9\L)	0.35(0.002)	0.310(0.009)
Neutrophils(10^9\L)	0.67(0.00)	0.56(0.00)
Lymphocytes(10^9\L)	-0.539(0.00)	-0.104(0.389)
Platelets(10^9\L)	.027(.82)	.216(0.07)
ESR (mm\$1^{st}$hr)	0.1(0.4)	-0.05(0.6)
CRP (ng\ml)	0.025(0.8)	0.106(0.38)
DAS-28	0.2(0.06)	-0.06(0.5)
CDAI	0.24(0.04)	0.01(0.9)
SDAI	0.24(0.04)	0.03(0.7)

Table-III. Correlation of neutrophil-lymphocyte ratio with disease parameters in rheumatoid arthritis in active disease versus remission.

DISCUSSION

Neutrophil lymphocyte ratio is a useful and easily accessible marker to detect inflammation. Its role is being investigated in various disorders including infections, malignancies and inflammatory or autoimmune disorders. Rheumatoid arthritis is an auto inflammatory state marked by aberrancies in innate and adaptive immune pathways. While, the activity RA is assessed by various scoring systems incorporating different aspects of the disorder, NLR may act as a specific indicator of inflammation in RA as it incorporates important effector cells from both of these pathways. This study assessed how rheumatoid arthritis disease activity is related to NLR.

Majority, both the sick and control groups of the study's population, were made up of women. Our hospital caters the families of ex-army servicemen, which explains the overall female predominance, in addition to the female predilection of RA.

In comparison to controls, NLR was considerably greater in active RA. Similar findings were reported in previous studies.[19] When comparing active RA patients to RA patients in remission, NLR was similarly considerably greater in active RA patients. These are corroborated by the previous findings.[20] This increase in NLR is thought to be due to lymphocyte sequestration to the synovium, causing relative lymphopenia in the blood. Degree of lymphocytopenia is a pointer of advancing inflammation and damage in RA. IL-6 involved in pathogenesis of RA is responsible for neutrophilia.[21]

NLR was discovered to be substantially linked with CDAI and SDAI in active RA patients in our research. Surprisingly though, we didn't come across anything significant relation of NLR with DAS 28 in any patient group. Mikhaeletal. also failed to find any significant relation between the two, but contrasting to our results they found no association of NLR with SDAI as well.[22] Elazeem et al.[20] and others[16] noted a significant positive relation between DAS 28 and NLR in active RA (r= 0.6, p value 0.001).[20] RA patients who have the illness in remission we didn't note any relation of NLR with disease activity scores. Other studies further reported that NLR levels are related to the worsening of DAS 28 score, progressively higher NLR with increasing severity of RA.[9,21]

In active RA, ESR and CRP were considerably greater than in the other two groups. These parameters showed no significant association with NLR. Previous work reported similar result for CRP, however, there was a strong connection between ESR (r 0.37, p .014).[22] Their results corroborate our finding of a significant negative relation of anemia with NLR in RA patients. Another study found significant positive correlation of both ESR and CRP with NLR[23], although their results conflicted our findings with regard to relation of anemia and NLR, as they found no relation between these. Several factors may play be responsible for such drastically different results for relation of these inflammatory parameters. Genetic polymorphism leading to predominance of different isoforms of CRP; body habitus; differential effect of individual disease modifying drugs on a particular pathway of inflammation and different methods of measurement may affect the levels of inflammatory cells and acute phase reactants.[24] Secondly, CRP and ESR can be normal in a significant portion of RA patients despite active disease, as pro inflammatory type of CRP is mainly concentrated at the sites of inflammation rather than serum due to its low solubility.

Patients in remission were slightly younger and had

longer duration than active RA patients, though the difference was not significant statistically. A previous study showed that active RA patient had shorter duration than remission group.[21] Our study did not show any significant difference of other hematological parameters between the study groups whereas Dechanuwong et al. noted significantly higher platelets, neutrophils; lower hemoglobin and lymphocytes in RA patients with higher disease activity.[21]

The platelet lymphocyte ratio did not differ substantially between the study groups and was not linked to RA disease activity. Lee et al. found a significant relation between disease severity and PLR.[16] Whereas a result of another study matched ours, stating that no such association was found.

CONCLUSION

NLR correlates with disease severity measures; CDAI and SDAI in patients with active RA. It may serve as cost effective and easily available tool for assessing disease activity in these patients. It is also correlated with degree of anemia in active RA.

LIMITATIONS

This study is limited by its smaller sample size. Effect of drugs and other patient factors on study parameters was not assessed. These factors may have impact on the study parameters. Further controlled studies with larger sample size are needed to explore these aspects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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