ORIGINAL ARTICLE

PLATELET LYMPHOCYTE RATIO AS AN INFLAMMATORY MARKER IN RHEUMATOID ARTHRITIS

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Background: There is a marked difference in platelet lymphocyte ratio (PLR) between active patients of Rheumatoid Arthritis (RA) and controls. Our objective was to determine role of PLR as an inflammatory marker in RA. **Methods:** This study was conducted from Oct 2021 to Sep 2022. RA was defined according to the 2010 ACR Diagnostic Criteria for Rheumatoid Arthritis and disease severity was determined according to DAS-28 score. After approval from IRB 150 patients aged 21–80 years, diagnosed with RA were enrolled and divided into 2 groups as active disease (DAS-28 score ≥3.2) and Low Disease Activity/Remission (DAS-28 score <3.2). Demographics, medical history, and clinical parameters of DAS-28 score and CBC including PLR were recorded. **Results:** 124 (82.7%) were female and 26 (17.3%) were male having mean age 42.8±14.4 years. Mean duration of disease was 8.5±6.9 years and mean ESR was 31.9±23.3 mm/1st hr. Mean VAS score, tender and swollen joint count, and DAS-28 score were 3.8±2.8, 4.2±4.0, 2.3±2.6 and 4.0±1.6 respectively. RA Factor was positive in 112 (74.7%) and Anti-CCP antibody was seen in 94 (62.7%). Mean haemoglobin level was 12.2±1.6 g/dl and anaemia was found in 43 (28.7%) patients. Mean platelet count and TLC were 356,560±99,102/mm^3 and 8.9±2.7×10^9/L respectively. Mean PLR in LDA/remission group and active disease group were 149.5±82.6 and 202.8±92.8 respectively. High PLR was seen in 52 (69.3%) patients with active disease compared with 30 (40.0%) patients with LDA/remission (p<0.001). **Conclusion:** Raised Platelet Lymphocyte Ratio was more common in patients with active RA.

Keywords: DAS-28 score, Rheumatoid Arthritis (RA), Platelet Lymphocyte Ratio (PLR)

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INTRODUCTION

Rheumatoid arthritis (RA) is a commonly seen inflammatory arthritis, globally occurring in up to 1% of population.[1] Primarily a joint disease, RA can have extra-articular features and abnormal immune responses. Due to chronic inflammation, abnormalities in composition and quality of circulating blood cells can cause lymphopenia with raised neutrophils, thrombocytosis and normochromic anemia,[2] which are useful as markers of inflammation.[3] Platelet lymphocyte ratio (PLR) is the proportion of total platelet count to lymphocyte count in CBC,[4] and is often employed to see inflammation in ulcerative colitis, cardiovascular disorders, neoplasm and familial Mediterranean fever.[5,6] CRP and ESR, the commonly tested markers for determining acute phase response because of their cost effectiveness and reliability, can be affected by non-inflammatory factors such as sex, age, and haemoglobin level but these factors do not affect PLR.[4] A study by Uslu *et al*[7] showed a marked difference in PLR between active patients and controls (136.5±53.5 and 114.8±29.4 respectively, p=0.001). CBC is routinely done in RA patients to monitor adverse effects of medicines and other disease associated abnormalities. However, the link of PLR disease severity in chronic arthritis is not strongly established. The purpose of the present study was to document alterations in PLR with disease severity in RA and to determine role of PLR as a marker of inflammation in RA.

MATERIAL AND METHODS

This cross-sectional study was done at Department of Medicine and Allied, Azra Naheed Medical College, Superior University Lahore from October 2021 to September 2022. RA was defined according to the 2010 ACR Diagnostic Criteria for Rheumatoid Arthritis. Disease severity of RA was determined according to DAS-28 score (Table-1).

Platelet Lymphocyte Ratio was defined as absolute number of platelets divided by absolute number of lymphocytes. Normal range of PLR was considered up to 150. Keeping margin of error of 5% and confidence interval of 95% a sample size of 150 participants was required,[7] with 75 participants each in active disease group (DAS-28 score ≥3.2) and LDA/ remission group (DAS-28 score <3.2).

Patients currently on steroids and biologic DMARDS, patients with history of steroid or biologic DMARDs use in last 12 weeks, patients with chronic diseases including hypertension, diabetes mellitus, coronary artery disease, chronic renal failure, chronic obstructive pulmonary disease, hematologic diseases and malignancy, and patients with pregnancy or breast feeding as assessed by detailed history, clinical examination and previous medical records were excluded from the study.

Approval from Institutional Ethical Review Board was taken and 150 patients of both genders, aged 21–80 years, with Rheumatoid Arthritis were enrolled

using non-probability consecutive sampling technique. After informed consent, demographic information, e.g., age, sex, socioeconomic status, duration of disease, educational status, along with medical history was obtained from each participant. Patients were divided into 2 groups of 75 participants each. In active disease group, patients having DAS-28 score ≥3.2 were included who were either treatment naïve or had stopped taking conventional DMARDs for more than 12 weeks. In low disease activity/remission group, patients taking conventional DMARDs with DAS-28 score <3.2 were included. Three ml of blood was taken form each patient in CBC vial and sent to laboratory for CBC estimation including PLR. Clinical parameters of DAS-28 score and CBC report including PLR of each participant were recorded. Standard treatment as per hospital protocol was given to all patients.

Table-1: DAS-28 Score to assess disease severity in Rheumatoid Arthritis

Scoring items
Tender joint count: 0–28 joints
Swollen joint count: 0–28 joints
ESR: in mm/1st hour
Patient global assessment (VAS): 0–10
Interpretation
Remission: ≤2.6
Low Disease Activity: 2.7–3.2
Moderate Disease Activity: 3.3–5.1
High Disease Activity: >5.1

Data was entered in and analysed using SPSS-20. For numerical quantitative variables, mean and standard deviation were calculated. For qualitative variables, frequency and percentage were calculated. To reduce effect modifiers and confounders, data was stratified and post-stratification Chi-square test was applied taking $p \leq 0.05$ as significant.

RESULTS

Out of the 150 patients enrolled in our study, 124 (82.7%) were female and 26 (17.3%) were male having mean age 42.8±14.4 years. Sixty-nine (46.0%) patients were <40 years old, 61 (40.7%) were aged 41–60 years and 20 (13.3%) were older than 61 years. Mean duration of disease was 8.5±6.9 years with 110 (73.3%) having duration of disease >3 years. Mean ESR was 31.9±23.3 mm/1st hour. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 3.8±2.8, 4.2±4.0, 2.3±2.6 and 4.0±1.6 respectively. RA Factor was positive in 112 (74.7%) and Anti-CCP antibody was seen in 94 (62.7%) cases. Mean haemoglobin level was 12.2±1.6 g/dl. Anaemia was seen in 43 (28.7%) patients. Mean platelet count and TLC were 356,560±99,102/mm^3 and 8.9±2.7×10^9/L respectively. Mean PLR was 176.2±91.6%, and high PLR was seen in 82 (54.7%) patients.

On stratification, mean PLR in LDA/remission group and active disease group were 149.5±82.6 and 202.8±92.8 respectively. High PLR was seen in 52 (69.3%) patients with active disease compared with 30 (40.0%) patients with LDA/remission showing a statistical significant association (p<0.001). No statistically significant association of raised PLR was seen with age (p=0.806), gender (p=0.164), duration of disease (p=0.030), RA factor positivity (p=0.932), Anti-CCP antibody positivity (p=0.137) and anaemia (p=0.205).

Among the 75 patients with LDA/remission, 60 (80.0%) were females and 15 (20.0%) male having mean age 44.7±15.6 years. Thirty-one (41.3%) patients were <40 years old, 32 (42.7%) were aged 41–60 years, and 12 (16.0%) were >60 years old. Mean duration of disease in years was 8.6±7.5 with 50 (66.7%) patients having duration of disease >3 years. Mean ESR was 15.1±4.6 mm/1st hour. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 1.3±1.2, 1.2±1.0, 0.3±0.7 and 2.6±0.5 respectively. RA factor was positive in 60 (80.0%) and Anti-CCP antibody was seen in 53 (70.7%) cases. Mean haemoglobin level was 12.6±1.8 g/dl and anaemia was found in 17 (22.7%) patients. Mean TLC and platelet count were 8.9±3.1×10^9/L and 335,030±107,611/mm^3 respectively.

In the LDA/Remission group, 26 (34.7%) patients were being treated with methotrexate alone, 18 (24.0%) with leflunomide alone, 13 (17.3%) with methotrexate and hydroxychloroquine combination, 7 (9.3%) with methotrexate and leflunomide combination, 6 (8.0%) with sulfasalazine alone and 5 (6.7%) with methotrexate and sulfasalazine combination.

Among the 75 patients with active disease, 64 (85.3%) were female and 11 (14.7%) were male having mean age 40.9±13.0 years. Thirty-eight (50.7%) patients were <40 years old, 29 (38.7%) were aged 41–60 years, and 8 (10.7%) were older than 60 years. Mean duration of disease in years was 8.4±6.2 with 60 (80.0%) patients having duration of disease greater than 3 years. Mean ESR was 48.7±22.3 mm/1st hour. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 6.3±1.5, 7.1±3.7, 4.3±2.3 and 5.4±0.9 respectively.

RA Factor was positive in 52 (69.3%) and Anti-CCP antibody was seen in 41 (54.7%). Mean haemoglobin level was 11.7±1.1 g/dl, and anaemia was found in 26 (34.7%) patients. Mean TLC and platelet count were 8.8±2.3×10^9/L and 378,280±85,128/mm^3 respectively. Mean PLR was 202.8±92.8 and high PLR was seen in 52 (69.3%) patients.

Comparison of qualitative clinical parameters with regards to disease severity of Rheumatoid Arthritis is shown in Table-2 which demonstrates a statistically significant association of disease severity with Anti-CCP antibody positivity (p=0.040) but not with other variables.

Table-2: Comparison of qualitative clinical parameters according to disease activity [n (%)]

Clinical Parameters	Group according to disease activity		*p*
	LDA/Remission (n=75)	Active Disease (n=75)	
Gender			
Female	60 (48.4)	64 (51.6)	0.388
Male	15 (57.5)	11 (42.5)	
Age			
≤40 years	31 (44.9)	38 (55.1)	0.437
41–60 years	32 (52.5)	29 (47.5)	
≥61 years	12 (60.0)	8 (40.0)	
Duration of disease			
Less than 3 years	25 (62.5)	15 (37.5)	0.065
More than 3 years	50 (45.5)	60 (54.5)	
RA Factor status			
Positive	60 (53.6)	52 (46.4)	0.133
Negative	15 (39.5)	23 (60.5)	
Anti-CCP Antibody status			
Positive	53 (56.4)	41 (43.6)	0.043
Negative	22 (39.3)	34 (60.7)	
Anaemia			
Present	17 (39.5)	26 (60.5)	0.104
Absent	58 (54.2)	49 (45.8)	
Platelet Lymphocyte Ratio			
Normal	45 (66.2)	23 (33.8)	<0.001
High	30 (36.6)	52 (63.4)	

DISCUSSION

The current study comprising of 150 patients showed a significant association (p<0.001) of PLR with disease activity in patients with RA. Rheumatoid arthritis, a frequently seen inflammatory arthritis, is primarily a joint disease however abnormalities in systemic immune reactions lead to a variety of extra-articular features.[1] Being an autoimmune and chronic disease, RA is heralded by infiltration of inflammatory cells such as neutrophils, macrophages and dendritic cells in the synovium, leading to continuous destruction of joints, cartilage and bone and therefore significant disability, morbidity and reduced life expectancy.[8] Due to chronic inflammation, abnormalities in composition and quantity of circulating blood cells leads to lymphopenia with raised neutrophils, thrombocytosis and normochromic anemia.[2] The plethora of cytokines, auto-antibodies and immune complexes production, deficiencies growth factors, reduced life span and deficiency of platelet functions and medicine related toxicity can help to explain the changes in blood components in longstanding systemic inflammation.[3] Therefore components of circulating blood cells are often employed in evaluating severity of inflammation.

In clinical practice, to estimate presence and severity of inflammatory conditions ESR and CRP are usually used but their use is restricted due to limitations such as low specificity and only reflection of short-term inflammation.[9] Various non-inflammatory factors such as gender, anaemia, fibrinogen levels, plasma viscosity and hypergammaglobulinemia, confound the use of these markers.[4] PLR is relatively more stable and offers a cheap and easily available objective marker for assessing inflammation and disease activity in RA in routine clinical practice.[7]

Disease severity in RA is generally assessed by the DAS-28 score at baseline and follow up, which is calculated by the swollen joint count, tender joint count, patient global assessment on VAS and ESR.[10] The positive correlation of PLR with DAS-28 will aid in estimating disease severity in RA. Certain aspect of the study needs elaboration. The positive correlation of PLR with DAS-28 in our study is concordant to previous international studies. The study by Uslu *et al*[7] showed PLR as a marker of inflammation that helps in assessment of disease activity in RA. They included 50 RA patients with segregation into 2 groups: active disease (DAS-28 ≥2.6) versus remission (DAS-28 <2.6), showing significant difference of PLR between the 2 groups (136.5±53.5 and 114.8±29.4 respectively, p=0.001). A meta-analysis by Lee *et al*[11] showed PLR to be significantly raised in RA patients. Fu *et al*[12] reported PLR to be significantly raised in patients with RA. PLR was positively associated with CRP and disease severity by DAS-28 score, but had no association with ESR.[12] In the present study, high PLR was seen in 52 (69.3%) patients with active disease compared with 30 (40.0%) patients with LDA/remission showing a statistical significant association (p<0.001) showing that there was a highly significant increase in PLR in RA patients depending on disease activity. These results are in accordance with three recent studies[13–15] that demonstrated high NLR in RA.

In the present study, a rise in PLR was not associated with age, gender, duration of disease, RA factor positivity, Anti-CCP antibody positivity or anaemia. Various cytokines that affect granulopoiesis and neutrophil homeostasis including granulocyte colony-stimulating factor, IL-17 and IL-23 are raised in active RA and correlate with disease activity.[16] In addition, many active RA patients have anaemia, leucocytosis and thrombocytosis. Time-integrated CRP in RA is linked to pronounced radiologic progression[17] but data on relationship of PLR to radiologic progression is scarce; more studies are required to elaborate this.

The current study has some limitations as well which should be considered. Based in a single centre, the present study had a relatively small sample size and enrolled outpatients only. Case control or cohort studies are a better option but require more resources and time. Using the results of our study as baseline data, researchers could plan more studies and generate further evidence regarding association of PLR and RA.

CONCLUSION

Raised Platelet Lymphocyte Ratio was seen more commonly in patients with active rheumatoid arthritis as

opposed to patients with LDA/remission. PLR being an economical and easily available, objective, inexpensive and readily reproducible clinical inflammatory marker, may be used for indicating disease activity in RA, so that treatment may be modified accordingly to control and reduce disease morbidity and disability.

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