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Does Disease Severity affect Anemia in Rheumatoid Arthritis?

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Abstract

Objective: To determine prevalence of anemia in patients of Rheumatoid Arthritis depending on disease severity: LDA/Remission Versus Active Disease.

Methods: This cross-sectional study was conducted at Department of Medicine & 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 was determined according to DAS-28 score. Anemia was defined as hemoglobin level less than 12 g/dl in females and less than 13 g/dl in males. After IRB approval, 130 patients aged 21 to 80 years, of both genders, with Rheumatoid Arthritis were enrolled using non-probability consecutive sampling technique. Informed consent was taken and demographic information. In active disease group, 65 patients having DAS-28 score $\geq$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, 65 patients taking conventional DMARDs with DAS-28 score <3.2 were included. All clinical parameters of DAS-28 score and CBC report including hemoglobin level of each participant were assessed and recorded.

Results: Mean age was 42.8$\pm$14.4 years with 108 (83.1%) females. Mean duration of disease was 8.3$\pm$6.9 years with 92 (70.8%) having disease for >3 years. RA Factor was positive in 96 (73.8%) and Anti-CCP antibody was seen in 80 (61.5%). Mean ESR, VAS score, tender joint count, swollen joint count and DAS-28 score were 32.0$\pm$23.1 mm/hr, 3.8$\pm$2.9, 4.2$\pm$4.0, 2.2$\pm$2.6 and 4.0$\pm$1.6 respectively. Mean Hemoglobin level was 12.2$\pm$1.5 g/dl and anemia were found in 36 (27.7%) patients. Mean platelet count and TLC were 356.4$\pm$99.3 $\times 10^9$/L and 9.0$\pm$2.8 $\times 10^9$/L respectively. On stratification, mean Hemoglobin level in LDA/remission group and active disease group were 12.6$\pm$1.8 g/dl and 11.8$\pm$1.1 g/dl respectively. Anemia was seen in 22 (33.8%) patients with active disease compared with 14 (21.5%) patients with LDA/remission. Statistically significant association of anemia was seen with age (p-value: 0.044) but not with gender (p-value: 0.568), duration of disease (p-value: 0.129), RA factor positivity (p-value: 0.110), Anti-CCP antibody positivity (p-value: 204) and disease severity (p-value: 0.117).

Conclusion: Anemia was seen more commonly in patients with Active Rheumatoid Arthritis.

Keywords: DAS-28 Score, Anemia, Rheumatoid Arthritis (RA), Hemoglobin Level

1. Introduction

Rheumatoid arthritis (RA) is a commonly seen inflammatory arthritis, globally occurring in up to 1% of the population [1]. RA, primarily a joint disease, can have extra-articular features and abnormal immune responses. Due to chronic inflammation, abnormalities in composition and quality of circulating blood cells can cause lymhopenia with raised neutrophils, thrombocytosis and normochromic anemia, [2] which are useful as markers of inflammation [3]. 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 [4]. Furthermore, various

non-inflammatory factors such as gender, anemia, fibrinogen levels, plasma viscosity and hypergammaglobulinemia, confound the use of these markers [5]. 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. [6]

Wilson *et al*. [7] reported anemia in as many as 60% of patients with Rheumatoid Arthritis. Furthermore, patients with Rheumatoid Arthritis who had anemia were more likely to have severe disease and with treatment of anemia the joint disease responded better to DMARD therapy. [7] Chen *et al*. [8] reported anemia to present in 47% of patients with Rheumatoid Arthritis and with increase of anemia, the disease activity, structural damage, and dysfunction of joints increased significantly. Zlateva *et al*. [9] demonstrated that arthritis patients who had concomitant anemia faced a longer hospital stay, underwent more procedures and had higher hospitalization costs as compared to patients without anemia in France. CBC is routinely done in RA patients to monitor adverse effects of medicines and other disease associated abnormalities. However, the link of anemia and disease severity in chronic arthritis is not strongly established. Thus, the purpose of the present study was to document alterations in anemia with disease severity in Rheumatoid Arthritis.

2. Material and methods

Table 1: 2010 ACR Diagnostic Criteria for Rheumatoid Arthritis

2010 ACR Diagnostic Criteria for Rheumatoid Arthritis	
Clinical Parameters	Score
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
More than 10 joints (at least 1 small joint)	5
B. Serology	
Negative RA Factor and negative Anti-CCP Antibody	0
Low-positive RA Factor or low-positive Anti-CCP Antibody	2
High-positive RA Factor or high-positive Anti-CCP Antibody	3
C. Acute-phase reactants	
Normal CRP and normal ESR	0
High CRP or high ESR	1
D. Duration of symptoms	
Less than 6 weeks	0
More than 6 weeks	1
Interpretation: Add score of categories A–D. A score of 6 or more is diagnostic for Rheumatoid Arthritis.	

This cross-sectional study was done at Department of Medicine & 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 shown in Table 1. [10] Disease severity of RA was determined according to DAS-28 score shown in Table 2. [11] Anemia was defined as hemoglobin level less than 12 g/dl in females and less than 13 g/dl in males. Keeping margin of error of 5% and confidence interval of 95% a sample size of 130 participants was required, with 65 participants each in active disease group (DAS-28 score $\geq$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 were excluded from the study.

Approval from institutional ethical review board was taken and 130 patients aged 21 to 80 years, of both genders, 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 then divided in two groups with 65 participants each. In active disease group, patients having DAS-28 score $\geq$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. All clinical parameters of DAS-28 score and CBC report including hemoglobin level of each participant were assessed and recorded. Standard treatment as per hospital protocol was given to all patients. Statistical Package for the social sciences (SPSS) version 20.0 was used for data entry and analysis. For numerical quantitative variables, mean and standard deviation were calculated. For qualitative variables, frequency and percentage were calculated. By taking $p \leq 0.05$ significant Chi Square test applied.

Table 2: DAS-28 Score to assess disease severity in Rheumatoid Arthritis

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/h Patient global assessment (VAS): 0-10
Interpretation: Remission: $\leq$2.6 Low Disease Activity: 2.7 to 3.2 Moderate Disease Activity: 3.3 to 5.1 High Disease Activity: More than 5.1

3. Results

Out of the 130 patients enrolled in our study, 108 (83.1%) were females and 22 (16.9%) male having mean age 42.8$\pm$14.4 years. Sixty (46.2%) patients were younger than 40 years old, 53 (40.8%) were aged 41-60 years and 17 (13.1%) were older than 61 years. Mean duration of disease was 8.3$\pm$6.9 years with 92 (70.8%) having duration of disease greater than 3 years. Mean ESR was 32.0$\pm$23.1 mm/hr. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 3.8$\pm$2.9, 4.2$\pm$4.0, 2.2$\pm$2.6 and 4.0$\pm$1.6 respectively. RA Factor was positive in 96 (73.8%) and Anti-CCP antibody was seen in 80 (61.5%). Mean platelet count and TLC were 356.4$\pm$99.3 $\times 10^9$/L and 9.0$\pm$2.8 $\times 10^9$/L respectively. Mean Hemoglobin level was 12.2$\pm$1.5 g/dl and anemia were found in 36 (27.7%) patients. Comparison of clinical parameters with regards to disease severity group of Rheumatoid Arthritis is shown in Table 3 and no statistically significant association of disease severity was seen with age (p-value: 0.356), gender (p-value: 0.349),

duration of disease (p-value: 0.123) and RA factor positivity (p-value: 0.231) and Anti-CCP antibody positivity (p-value: 0.071).

On stratification, mean Hemoglobin level in LDA/remission group and active disease group were 12.6±1.8 g/dl and 11.8±1.1 g/dl respectively. Anemia was seen in 22 (33.8%) patients with active disease compared with 14 (21.5%) patients with LDA/remission. Statistically significant association of anemia was seen with age (p-value: 0.044) but not with gender (p-value: 0.568), duration of disease (p-value: 0.129), RA factor positivity (p-value: 0.110), Anti-CCP antibody positivity (p-value: 204) and disease severity (p-value: 0.117) as shown in Table 4. Among the 65 patients with active disease, 56 (86.2%) were females and 09 (13.8%) male having mean age 40.3±13.1 years. Thirty-four (52.3%) patients were younger than 40 years old, 24 (36.9%) were aged 41-60 years and 07 (10.8%) were older than 60 years. Mean duration of disease was 8.1±6.1 years with 50 (76.9%) patients having duration of disease greater than 3 years. Mean ESR was 48.4±22.5 mm/hr. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 6.3±1.5, 7.2±3.6, 4.2±2.3 and 5.4±0.9 respectively. RA Factor was positive in 45 (69.2%) and Anti-CCP antibody was seen in 35 (53.8%). Mean TLC and platelet count were 8.8±2.3 $\times 10^9$/L and 375.1±84.9 $\times 10^9$/L respectively.

Table 3: Comparison of clinical parameters according to Disease Severity group of Rheumatoid Arthritis

Clinical Parameters	Group Assigned according to Disease Activity	
	LDA/Remission	Active Disease
Mean age (years)	44.5±15.5	40.3±13.1
Mean Duration of disease (years)	8.5±7.7	8.1±6.1
Mean ESR (mm/hr)	15.5±4.7	48.4±22.5
Mean VAS score	1.2±1.2	6.3±1.5
Mean Tender joint count	1.1±1.1	7.2±3.6
Mean Swollen joint count	0.3±0.8	4.2±2.3
Mean DAS-28 score	2.5±0.5	5.4±0.9
Mean Hemoglobin (g/dl)	12.6±1.8	11.8±1.1
Mean TLC ($\times 10^9$/L)	9.0±3.3	8.8±2.3
Mean Platelet Count ($\times 10^9$/L)	337.8±109.4	375.1±84.9
Age Groups:		
<40 years	26 (40.0%)	34 (52.3%)
40-60 years	29 (44.6%)	24 (36.9%)
>60 years	10 (15.4%)	07 (10.8%)
Sex:		
Female	52 (80.0%)	56 (86.2%)
Male	13 (20.0%)	09 (13.8%)
Duration of disease:		
≤3 years	23 (35.4%)	15 (23.1%)
>3 years	42 (64.6%)	50 (76.9%)
RA Factor status:		
Positive	51 (78.5%)	45 (69.2%)
Negative	14 (21.5%)	20 (30.8%)
Anti-CCP Antibody status:		
Positive	45 (69.2%)	35 (53.8%)
Negative	20 (30.8%)	30 (46.2%)
Anemia:		
Present	14 (21.5%)	22 (33.8%)
Absent	51 (78.5%)	43 (66.2%)

Among the 65 patients with LDA/remission, 52 (80.0%) were females and 13 (20.0%) male having mean age 45.2±15.3 years. Twenty-six (40.0%) patients were younger than 40 years old, 29 (44.6%) were aged 41-60 years and 10 (15.4%) were older than 60 years. Mean duration of disease in years was 8.5±7.7 with 42 (64.6%) patients having duration of disease greater than 3 years. Mean ESR was 15.5±4.7 mm/hr. Mean VAS score, tender joint count, swollen joint count and DAS-28 score were 1.2±1.2, 1.1±1.1, 0.3±0.8 and 2.5±0.5 respectively. RA Factor was positive in 51 (78.5%) and Anti-CCP antibody was seen in 45 (69.2%). Mean TLC and platelet count were 9.0±3.3 $\times 10^9$/L and 337.8±109.4 $\times 10^9$/L respectively. In the LDA/Remission group, 22 (33.8%) patients were being treated with methotrexate alone, 14 (21.5%) with leflunomide alone, 13 (20.0%) with methotrexate and hydroxychloroquine combination, 07 (10.8%) with methotrexate and leflunomide combination, 05 (7.7%) with sulfsalazine alone and 04 (6.2%) with methotrexare and sulfasalazine combination.

Table 4: Comparison of qualitative clinical parameters according to Anemia

Clinical Parameters	Anemia		p-value
	Present	Absent	
Gender:			
Female	31 (28.7%)	77 (71.3%)	0.568
Male	05 (22.7%)	17 (77.3%)	
Age:			
≤40 years	14 (23.3%)	46 (76.7%)	0.044
41-60 years	13 (24.5%)	40 (75.5%)	
≥61 years	09 (52.9%)	08 (47.1%)	
Duration of disease:			
≤3 years	07 (18.4%)	31 (81.6%)	0.129
>3 years	29 (31.5%)	63 (68.5%)	
RA Factor status:			
Positive	23 (24.0%)	73 (76.0%)	0.110
Negative	13 (38.2%)	21 (61.8%)	
Anti-CCP Antibody status:			
Positive	19 (23.8%)	61 (76.2%)	0.204
Negative	17 (34.0%)	33 (66.0%)	
Disease Severity:			
LDA/Remission	14 (21.5%)	51 (78.5%)	0.117
Active Disease	22 (33.8%)	43 (66.2%)	

4. Discussion

In the present study, anemia was seen in 22 (33.8%) patients with active disease compared with 14 (21.5%) patients with LDA/remission. The mean Hemoglobin level in LDA/remission group and active disease group were 12.6±1.8 g/dl and 11.8±1.1 g/dl respectively in the present study. Wilson *et al.* [7] reported anemia in as many as 60% of patients with Rheumatoid Arthritis and patients with anemia were more likely to have severe disease. Treatment of anemia resulted in better response of joint disease to DMARD therapy. Furthermore, clinical parameters assessed by Wilson *et al.* [7] including swollen, painful, and tender joints, pain, muscle strength, and energy levels demonstrated a positive correlation with successful treatment of anemia. Chen *et al.* [8] reported anemia to present in 47% of patients with Rheumatoid Arthritis and with increase of anemia, the disease activity, structural damage, and dysfunction of joints increased significantly. Zlateva *et al.* [9] demonstrated that arthritis patients who had concomitant anemia faced a longer hospital stay, underwent more procedures and had higher hospitalization costs as compared to patients without anemia in France. Ganna *et al.* [12] reported anemia in 46% of rheumatoid arthritis patients with severe disease patients having severe anemia. Wolfe *et al.* [13] evaluated 2120 patients of rheumatoid arthritis and found anemia in 31.5%. In the present study, statistically significant association of anemia was seen with age of the patients (p-value: 0.044). Out of the 36 patients with anemia, 14 (38.8%) were younger than 40 years, 13 (36.2%) were aged 40-60 years and 09 (25.0%) were older than 60 years. However, no association of anemia was seen with gender (p-value: 0.568), duration of disease (p-value: 0.129), RA factor positivity (p-value: 0.110), Anti-CCP antibody positivity (p-value: 204) and disease severity (p-value: 0.117).

Rheumatoid arthritis (RA), 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. [14] Due to chronic inflammation, abnormalities in composition and quantity of circulating blood cells leads to lymphopenia with raised neutrophils, thrombocytosis and normochromic anemia.[2] Various cytokines that affect granulopoiesis, anemia and neutrophil homeostasis including granulocyte colony-stimulating factor, IL-17 and IL-23 are raised in active RA and correlate with disease activity. [15] In addition, many active RA patients have leucocytosis and thrombocytosis. Data on time-integrated anemia in RA and radiologic progression is scarce and subsequently more studies are required to elaborate this. In conclusion, the present study shows anemia to be more common in patients with active rheumatoid arthritis. Thus, hemoglobin level, being an easily available, objective, inexpensive and readily reproducible clinical marker, should be considered in management of RA. The current study has some limitations as well which need to be considered. Based in a single center, the present study had a relatively small sample size and enrolled outpatient care patients 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 anemia and RA.

5. Conclusion

Our study demonstrates that anemia was seen more commonly in patients with active rheumatoid arthritis as opposed to patients with LDA/remission. We recommend that hemoglobin level, an economical and easily available clinical marker, may be used in co-relation with disease activity in RA, so that treatment may be modified accordingly to control and reduce disease morbidity and disability.

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