

## ORIGINAL ARTICLE

# Anaemia in Newly Diagnosed Patients of Rheumatoid Arthritis and its Correlation with Disease Activity

Laxmikant Goyal<sup>1</sup>, Pujan J Shah<sup>2</sup>, RN Yadav<sup>3\*</sup>, Renu Saigal<sup>4</sup>, Abhishek Agarwal<sup>3</sup>, S Banerjee<sup>5</sup>

## Abstract

**Aim:** To detect frequency of anemia in patients of Rheumatoid arthritis (RA) and to establish relationship between hemoglobin level and disease activity in RA.

**Method:** Fifty nine patients of RA fulfilling 2010 ACR/EULAR criteria of RA having disease duration less than two years were included in the study. Haemoglobin (Hb) levels were measured. Disease activity was assessed by DAS-28 score.

**Results:** Among 40/59 (67.80%) anemic cases, 22/40 (55%) patients had anaemia of chronic disease (ACD), 11/40 (27.50%) patients had Iron deficiency anemia (IDA), 3/40 (7.5%) patients had vitamin B<sub>12</sub> deficiency, 1/40 (2.50%) patient had folate deficiency and 3/40 (7.50%) patients had combined IDA and vitamin B<sub>12</sub> deficiency. Duration of disease, rheumatoid factor positivity and occurrence of erosive disease were not significantly different among anaemic and nonanaemic patients ( $p > 0.05$  for each). Mean ESR ( $p > 0.02$ ) and DAS-28 ( $p > 0.001$ ) were statistically significantly different among anaemic and nonanaemic patients.

Haemoglobin level had significant negative correlation with disease activity (DAS28) in RA cases ( $r = -0.5533$ ,  $p < 0.0001$ ).

**Conclusion:** Anemia was seen in higher frequency in RA patients. Haemoglobin had significantly negative correlation with disease activity (DAS 28) in RA.

## Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory, auto-immune disease of unknown origin with characteristic persistent symmetric polyarthritis (synovitis) and extra articular involvement of skin, heart, lungs and eye. Anaemia is a common feature of RA. Garrod first noted the association of RA with anaemia.<sup>1</sup> Prevalence of anaemia in RA ranges from 30-70% in different studies.<sup>2-4</sup>

Overall anaemia of chronic disease and iron deficiency anaemia are frequent causes of anaemia in RA patients,<sup>5</sup> but in developing countries like India, nutritional deficiency may also be a major associated problem adding to the etiology in genesis of anaemia in RA patients.

Although in RA anaemia is usually not very severe, it has been found to be associated with a higher degree of disease activity. Anaemia is associated

with a negative impact on both RA symptoms and quality of life.<sup>3,5-7</sup>

Since there had been no reported studies on anaemia in RA from northern India, here we endeavored this study to estimate the frequency of anaemia in recent onset RA patients and to observe any relation of disease activity with haemoglobin level in patients of RA.

## Material and Methods

This hospital based observation study was conducted among 59 patients of RA (diagnosed as per 2010 ACR/EULAR Classification Criteria<sup>8</sup>) having disease duration less than two years, who attended the Rheumatology clinic, at a tertiary hospital in north India, during May 2012 to April 2013, after approval by the Research Review Board/Institutional Ethics Committee. All patients gave informed consent

before enrolling in to the study. Patients of RA with disease duration more than two years, who were on DMARD, with active apparent bleeding from any site of the body, suffering from concomitant illnesses that can cause anaemia (e.g. chronic kidney disease, chronic liver disease) or who failed to give consent were excluded from this study.

Complete history was taken and every patient was subjected to complete rheumatological assessment. From each patient blood sample sent for complete blood count, erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF), C-reactive protein (CRP), serum Iron, serum ferritin, Total Iron binding Capacity (TIBC), serum folate and serum vitamin B<sub>12</sub> level estimation.

The radiographs of both hands (postero-anterior view) were reported for presence of erosions by experienced radiologist who was blinded to the study. Upper GI endoscopy was done by a trained gastroenterologist, blinded to the study, to see if any gastritis/duodenal disease present. Stool examination was done by microscopy of stool specimen of patient by trained microbiologist blinded to the study, to rule out any occult bleeding from GIT or presence of any parasitic ova/ cyst.

Disease activity was assessed according to disease activity score (DAS-28).<sup>9</sup> DAS-28 score  $> 5.1$ -indicate high disease activity,  $> 3.2$ - $< 5.1$ -moderate disease activity,  $< 3.2$ -low disease activity, and  $< 2.6$ -remission. The 28 joints assessed for both tenderness and swelling were ten proximal interphalangeal joints, ten metacarpophalangeal joints, two wrists, two elbows, two shoulders and two knees.

Anaemia<sup>3</sup> was defined as Hb $< 13$ gm%

<sup>1</sup>Assistant Professor, Geriatric Medicine, <sup>2</sup>Senior Resident, Department of Cardiology, SGPGL, Lucknow, Uttar Pradesh; <sup>3</sup>Professor, <sup>4</sup>Former Senior Professor, <sup>5</sup>Senior Professor, Department of Medicine, SMS Medical College, Jaipur, Rajasthan; \*Corresponding Author  
Received: 16.11.2015; Revised: 13.05.2016; Accepted: 10.08.2017

for males and Hb<12gm% for females. Iron deficiency anemia (IDA)<sup>10</sup> was diagnosed when low serum iron (<60 µg/dL) with low serum ferritin (<30 µg/dL) with raised iron binding capacity(>360 µg/dL) were present. Anaemia of chronic disease (ACD)<sup>10</sup> was considered when low serum iron (<60 µg/dL) with high serum ferritin (30-200 µg/dL) with normal or decreased iron binding capacity (<300 µg/dL) was found. Patients with serum vitamin B<sub>12</sub> (<193pg/dL) were labeled as vitamin B<sub>12</sub> deficiency anaemia. Anemia with serum folate level (<3ng/dL) was label as folate deficiency anaemia. As serum ferritin levels can differentiate between IDA and ACD in RA patients and its correct estimation eliminates the need for bone marrow examination to diagnose type of anaemia,<sup>11-13</sup> so bone marrow examination was not performed.

**Statistical analysis**

Microsoft Excel® and SPSS® 17.0 for Windows® were used for data storage and analysis. Continuous variables were expressed as mean ± standard

deviation. Student’s t test and Chi-Square test were used to determine statistical difference between variables. Pearson’s coefficient was used to investigate the correlation between the two variables. Statistical significance was set at P value ≤ 0.05.

**Results**

Out of 59 patients enrolled in our study, 40(67.80%) were found to be anaemic. Anaemic and non-anaemic group did not differ significantly with respect to age and sex (p >0.05 for each). So age and sex were not confounding factors in our study.

Duration of disease, rheumatoid factor positivity and occurrence of erosive disease were not significantly different among anaemic and nonanaemic patients (p>0.05 for each). However statistically significant difference was observed in mean ESR (p>0.02) and DAS-28 (p>0.001) among anaemic and nonanaemic patients (Table 1).

In this study, among 40/59 (67.80%)

anemic cases, 22/40(55%) patients had ACD, 11/40(27.50%) patients had IDA, 3/40(7.5%) patients had vitamin B<sub>12</sub> deficiency, 1/40(2.50%) patient had folate deficiency and 3/40(7.50%) patients had combined IDA and vitamin B<sub>12</sub> deficiency (Figure 1). None of the patient had ACD and IDA together in current study.

Haemoglobin level had significant negative correlation with disease activity (DAS28) in RA cases (r -0.5533, p <0.0001) (Figure 2).

**Discussion**

Anemia is not considered a major problem in rheumatoid arthritis (RA) by the vast majority of physicians. This statement is based on the fact that studies on anemia in RA are sparse, and with few systemic reviews. This study evaluated anemia in RA.

*Type of anaemia (Figure 1):*

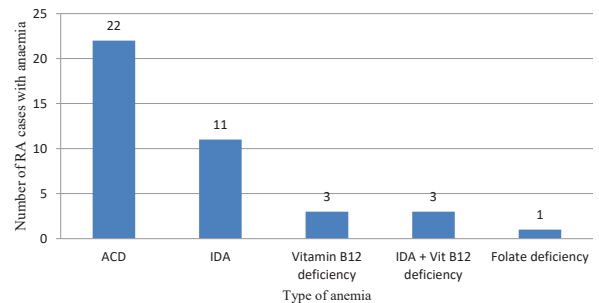
In this study, 40/59 (67.80%) RA cases were found to be anemic. Anemia of chronic disease (22/40, 55.00%) was the commonest type of anemia observed in this study, Iron deficiency

**Table 1: Demographic, clinical and bio-chemical characteristics of Rheumatoid arthritis patients**

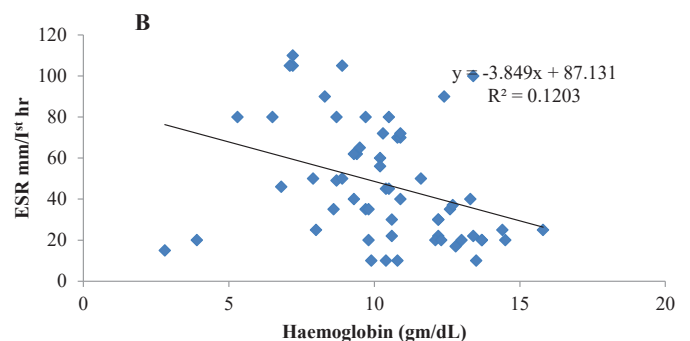
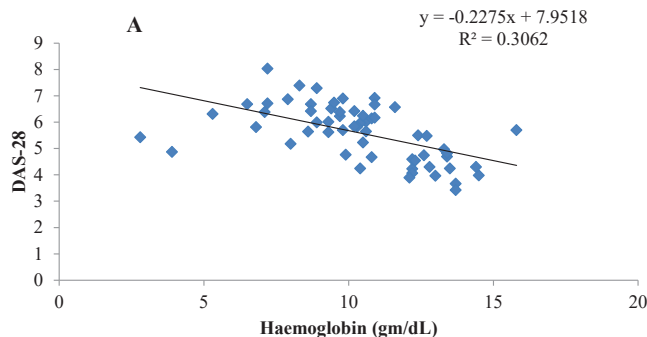
	Anaemic	Non-anaemic	P	Sig
Number of patients	40 (67.80 %)	19 (32.20 %)		
Sex Male/female	7/33	4/15	>0.05	NS
Age (in years)	38.05±14.50	41.47±12.06	>0.05	NS
Duration of disease (in months)	10.46±3.27	10.95±4.64	>0.05	NS
RF positivity (number of RA cases)	32 (80.00 %)	12 (63.15 %)	>0.05	NS
Erosions (number of RA cases)	10(25%)	2(10.53%)	>0.05	NS
Haemoglobin (gm/dl)	9.02 ± 1.95	13.17 ± 0.97	<0.0001	HS
ESR (mm/l <sup>st</sup> hr)	52.76 + 28.77	32.18 + 24.09	<0.02	Sig
TJC	12.98 + 4.21	5.82 + 2.10	< .001	HS
SJC	9.17 + 3.82	2.35 + 0.93	<0.001	HS
VAS	40.95 + 12.26	27.94 + 11.33	< .001	HS
DAS-28	6.0312 + 0.8712	4.5218 + 0.6461	< .001	HS
DAS 28 Moderate (3.2-5.1)	4 (6.78)	16 (27.12)	<0.001	HS
High (>5.1)	36 (61.02)	3 (5.08)		

**Table 2: Mean serum haemoglobin levels (gm/dL) and disease activity**

DAS-28	n	Serum haemoglobin (gm/dL)	P	Sig
Moderate (DAS 3.2-5.1)	20	12.215 ± 2.305	<0.0001	HS
High (DAS >5.1)	39	9.403 ± 2.185		



**Fig. 1: Type of anemia in RA cases**



**Fig. 2: Correlation of haemoglobin and disease activity parameters. (A) Correlation of haemoglobin and DAS28 score (r - 0.5533, P< 0.0001); (B) Correlation of haemoglobin and ESR (r - 0.3467, P<0.007)**

anemia (11/40, 27.50%) was the next common type. This study finds a higher occurrence of ACD than IDA in RA patients. Similar results were obtained in a study done in 2006 in which ACD was seen in 51.6% and IDA in 48.4% anemic RA cases.<sup>2</sup> In the study by Adriana Sabau et al<sup>7</sup> 70.4% patients were anaemic in which IDA was present in 47.36% patients and the rest of 52.63% patients had ACD. Helen A. et al<sup>5</sup> had observed 57.5% RA patients anaemic out of which 37.5% patients had ACD and 20% patients had IDA. In various other cross-sectional studies, ACD has been reported to be present in 30% to 70% of patients with RA,<sup>2-4</sup> as confirmed by the data from Wolfe.<sup>14</sup> These findings support the notion that ACD is the most frequent cause of anemia in RA;<sup>15</sup> however, iron deficiency or a combination of both should be considered in patients with RA developing anemia.

#### *Anaemia (Hb) and disease activity in RA*

The patients with anemia had higher levels of mean DAS28 score and ESR. Furthermore, these patients had more joints involvement and higher VAS (Table 1). Patients with higher disease activity also had lower mean hemoglobin levels (Table 2). Also in previous studies significant relation in DAS28 and anemia was found.<sup>2,5,6,16</sup> Since both ESR and DAS28 are indicators of disease activity, presence of anemia also indicates active disease. ESR is a marker of chronic inflammation and anemia is the result of inflammation. So raised ESR is significantly related to the presence of anemia.

The well established relationship between inflammation and anaemia, as found in a cohort study,<sup>6</sup> was also confirmed in this study by significant inverse correlation between haemoglobin and DAS28, and haemoglobin and ESR. ACD in RA may be caused by a shortened red blood cell life span, pathologic iron homeostasis induced by hepcidin, and blunted response to erythropoietin.<sup>17</sup> Interestingly, erythropoietin treatment reduced disease activity in RA patients.<sup>18</sup> Our results are consistent with anaemia as an indicator of deficient anti-inflammatory properties of erythropoietin.<sup>19</sup> Hepcidin may trigger functional iron deficiency upon induction by TNF- $\alpha$ , interleukin-6, and other inflammatory stimuli,<sup>17</sup> resulting in reduced intestinal iron uptake at the

mucosal barrier, and iron retention in the reticulo-endothelial system via internalization of the same exclusive cellular iron exporter ferroportin on both cell types.

In this study, haemoglobin level had statistically significant negative correlation with DAS-28 score ( $r$  -0.553,  $p < 0.05$ ) and ESR (Figure 2), as reported in previous studies.<sup>2,7</sup> This observation supports that anemia is associated with a negative impact on DAS-28 which is a marker of disease activity.

#### *Anemia and erosive disease*

In this study RF positivity was found in 32/40 (80%) anaemic RA patients and in 12/19 (63.15%) non-anaemic patients. Although RF positivity was higher in anaemic than non-anaemic patients but association between RF and anaemia was not statistically significant ( $p > 0.05$ ). Helen A. Papadaki et al<sup>5</sup> and D J Borah et al<sup>16</sup> also reported statistically insignificant higher frequency of RF positivity in anaemic patients. Due to limitation of resources, we could not measure quantitative value of RF in our patients which might have given a better idea of correlation between RF and level of haemoglobin.

Although anaemic patients had higher frequency of erosive disease (10, 25% v/s 2, 10.53%) at presentation in this study, statistically there was no significance difference in anaemic and nonanaemic patients for the presence of erosions ( $p > 0.05$ ). This might be due to study design and small sample size. Previous studies reported significant association of anaemia with joint erosion in RA.<sup>20</sup>

In early RA, small erosions (in the absence of clinically detectable inflammation) are not picked up on plain radiographs and are better detected on ultrasound and MRI,<sup>21</sup> this might be the reason for the dissociation of disease activity from radiographic outcome.<sup>22</sup> In a large observational study<sup>6</sup>, mean joint damage progression rates were significantly lower in clinical remission than in active disease and anaemia-related progression of joint damage was not restricted to the patients with clinically active disease. Thus, anaemia may be a useful surrogate marker for subclinical RA disease activity.

The association between anaemia and erosions was not observed in a smaller patient population in this study as in a previous small sample

study,<sup>23</sup> but in the large ERAS inception cohort, anaemic patients underwent a more aggressive course of joint destruction.<sup>20,24</sup>

In summary, these results indicate that anaemia may serve as predictor of disease activity in RA patients. This report may add clinical background to recent discoveries at the nexus of inflammation, haematopoiesis, and iron metabolism,<sup>19</sup> and highlights the clinical implications of anaemia in RA. Diagnosis of anaemia in RA should prompt a thorough search for subclinical disease activity, after exclusion of other frequent causes.

#### **Conclusion**

Anemia was seen in higher frequency among RA patients. Haemoglobin had significantly negative correlation with disease activity (DAS-28) in RA.

#### **Conflict of Interest**

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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