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"Prevalence of anemia in rheumatoid arthritis and its correlation with disease activity."

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Abstract
Background*: Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of unknown etiology affecting approximately 1% of the world population, 0.75% in India and 0.2% in Manipur. The hallmark swelling, bony erosions and synovial thickening reflect the underlying inflammatory and auto immune processes of RA. Anemiais one of the most frequent extra-articular manifestations in RA with a prevalence in RA of 33%-60% and also correlates with disease activity. Therefore, we conducted this study to determine the prevalence of anaemia in RA patients in Manipur and to correlate with disease activity.*
Methods:*This cross-sectional study was conducted at Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from 2018 to 2020. 236RA patientsabove 18 years of age who attendedRheumatology OPD,Medicine OPD or admitted in the General Medicine wards were enrolled.Complete hemogram and other related blood investigations were studied.*
Results:*The mean age of the participants was 49.1±10.4 years and majority (52.5%) were in the age group of 46-60 years. Most of them (90.3%) were females with a F:M ratio of 9.3:1. Majority (49.2%) had >5years duration of RAand among DMARDs, hydroxychloroquine was the most commonly prescribed drug in 85.6% patients. Anaemia was present in 58.9% patients. 110(79%) patients had anemia of chronic disease and 29(21%) patients had iron deficiency anemia. There was no significant association between the prevalence of anaemia and gender (p=0.123) or age (p=0.923)of the patients and duration of rheumatoid arthritis (p=0.127).There was statistically significant and very strong negative correlation between Hb level with SJC, TJC, GHA and DAS-28 (p<0.001).*
Conclusion:*Our study inferred a strong negative correlation between Hb level and disease activity and those with anemia had more severe joint disease. These results suggest thatif the anemia is successfully treated, the joint disease is likely to respond to treatment as well. Hence screening and treating for anemia is important in management of RA patients.*
Keywords*:Anemia,Autoimmune disease, DAS-28 ESR, Rheumatoid arthritis*

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I. Introduction

Rheumatoid arthritis(RA) is a chronic, symmetric, peripheral poly-arthritis of unknown etiology which if untreated, typically leads to articular cartilage and bonedestruction through a persistent inflammatory synovitis.[1]One of the most frequent extra-articular manifestations of RA is anemia[2].The prevalence of anemia in RA is between 33% and 60%.[3]

Different types of anemia can occur in rheumatoid arthritis such as anemia of chronic disease (ACD), iron deficiency anemia (IDA), aplastic anemia, macrocytic anemia, the commonest form being anemia of chronic disease(ACD)[4].More precisely,anemia of chronic disease (normocytic normochromic) anemia is present in 60% of RApatients. In the study by Arul R et al[5], microcytic hypochromic anemia suggestive of iron deficiency anemia (IDA) is present in 25% and dimorphic anemia in 15% of RA patients. Disability with reduction in quality of life occurs with RA disease progression[6]. The disease activity is usually assessed by using DAS-28, erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP)[4].

The actual pathogenesis of anemia in RA is unknown however plausible factors includes inflammatory cytokines, defective production of erythropoietin, reduced bone marrow response to erythropoietin or to defective reticulo-endothelial release of iron causing erythroblast iron deficit [7.]Davies D et al[8] showed that

inflammatory cytokines, particularly tumour necrosis factor α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) contribute to the pathogenesis of ACD, possibly by inhibiting erythropoietin (EPO) production. Iron deficiency in RA can be due to non-steroidal anti-inflammatory drugs (NSAID) induced gastrointestinal blood loss,poor intake of dietary iron.[7]. Vreugdenhil G et al[9] studied that active RA resulted in decreased iron absorption and in ACD patients, iron absorption correlated inversely with ESR and CRP.Bone marrow iron availability may be decreased due to decreased iron release by the mononuclear phagocyte system or may be due to ineffective erythropoiesis.

As theseverity of anemia corelates with the degree of inflammation, it is unknown whether anaemia itself leads to increased morbidity and/or mortality or whether it is the underlying etiology of the RAor associated co-morbidities. Nonetheless, it is plausible to suggest that anemia, potentially leading to increased cardiac output and/or local tissue hypoxia and inflammation could aggravate functional decline in the affected RA individual and thus interfere with independent living. Studies suggest that increases in haemoglobin (Hb) level is significantly associated with positive changes in quality of life in patients with RA.Although such Hb correlation with RA are established in Western Countries. There are only few data from India about the prevalence of anemia in RA in India and more so no study has been conducted in Manipur on this subject.Therefore, thisstudy evaluated the prevalence of anaemia in RA patients in RIMS, Imphal, Manipur and to correlate it with disease activity.

II. Materials and Methods

This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from September 2018 to August 2020. 236 RA patients who attended Rheumatology OPD,Medicine OPD or admitted in the General Medicine wards wereenrolled following the criteria.

Inclusion Criteria

1. All previously or newly diagnosed patients with Rheumatoid arthritis (according to 2010 American college of Rheumatology/European League against Rheumatism Classification Criteria[2].
2. Those above 18 yearsof age giving consent for participation.

Exclusion Criteria include patients diagnosed with hereditary types of anemia -hereditary spherocytosis, sickle cell anemia, those previously diagnosed anemia, those who have mixed disorder like mixed connective tissue disease, overlap syndrome and previously known malignancies, renal failure or any other chronic blood loss like haemorrhoids and those not giving consent.

Study procedure

Personal details including a detailed history of presenting symptoms, past history and personal history were recorded in proper proforma along with age, sex, body mass index (BMI),family history, disease duration, duration of treatment, doses of methotrexate, other drugs {Hydroxychloroquine (HCQ), NSAIDS, etc} and investigations like CRP,ESR, Rheumatoid factor (RF), complete hemogram (CBC). A detailed relevant clinical examination of every subject was also done.

Study tools

1.Complete hemogram (Randox auto analyser used).The World Health Organization (WHO) criteria was used for diagnosis of anemia i.e. Hb<13 g/dL in men and <12 g/dL in women.[10]

2.ESR (Westergen method used).The normal range was 0-9 mm/ 1st hr (Males) and 0-20 mm/1st hr (Females).

3.CRP (Rhelax- CRP reagent used).

4.Blood for RF using Rhelax-RF.

5. DAS28-ESR wasclassified as follows:

< 2.6 : Remission
2.6-3.1 : Mild disease activity
3.2-5.1 : Moderate disease activity
>5.1 : Severe disease activity

DAS28ESR was calculated using DAS calculator.

Statistical analysis: Study variables were expressed as frequency and percentages, mean (±SD) or median (IQR), depending on the type of distribution. The prevalence of anaemia was expressed as frequency and percentage with 95% Confidence Interval (95% CI). Chi square test, independent samples t test,Pearson correlation or Spearman correlation were used to determine association Hb value with the disease activity. A p-value of <0.05 was considered significant.

Statistical software: SPSS V21 (IBM Corp., Armonk, NY, United States) for windows were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal. (No.A/206/REB-comm(SP)/RIMS/2015/423/41/2018.)

III. Results

A total of 236 patients with RAabove 18 years of age were included in the study. The mean age of the participants was 49.1 ±10.4 years. The median age of the participants was 50 (42-56) years and majority of the participants (52.5%) were in the age group of 46-60 years. Majority (90.3%) of the participants were females with a F:M ratio of 9.3:1. More than half (53.3%) of the patients were with normal body mass index (BMI) and obesity was present in 14% of the patients.Duration of RA was more than 5 years in 49.2% of the participants while the duration was less than one year in 7.2% of the patients. Among DMARDs, HCQ and methotrexate were taken by 85.6% and 78.4% of the study subjects respectively and steroid was taken by 11.4% of the patients. ESR was elevated in 74.6% patients and CRP was positive in 48.7% of the patients. In DAS28-ESR,16patients (11%)were in remission while 66 patients (27.96%)were having high disease activity (table1). In disease activity scores, median SJC score was 4 (2-6) and the median TJC score was 2 (0-4), the median GHA score was 2 (1-6) and mean DAS28ESR score was 4.2 (±1.5)(Table2). Anemia was present in 58.9% patients(Table3).Among the types of anemia, 110(79%) patients were detected anemia of chronic disease with mean MCV of 90.8 ± 2.05fL and normocytic normochromic anemia on peripheral smear (PS).While 29 patients (21%) hadIDA with mean MCV of 75 ± 1.02fL and microcytic hypochromic on PS (Table4). There was no significant association between the prevalence of anemia with gender of the patient (p=0.123)or age(p=0.923). There was no significant association of anemia with duration of RA(p=0.127) though prevalence of anemia was higher among the patients with >5years duration of RA (Table5).There was statistically significant and very strong negative correlation between Hb level with SJC, TJC,GHA and DAS28ESR (p<0.001) (Table 6).

Table1. Baseline characteristics of the study subjects.

Parameters	**Results n(%) 236(100%)**
Age in years, median (range)	50(42-56)
Gender: Male Female	23(9.7%) 213(90.3%)
BMI(kg/m^2)	
Underweight (<18.5) Normal (18.5-22.9) Overweight (23-24.99) Obese (25 and more)	32(13.6%) 126(53.3%) 45(19.1%) 33(14%)
Duration of RA (in years) <1 1-5 >5	 17(7.2%) 103(43.6%) 116(49.2%)
Treatment /drugs **Methotrexate** **Hydroxychloroquine** **Steroids** **Others(sulfasalazine,biologicals, etc)**	 185(78.4%) 202(85.6%) 27(11.4%) 15(6.4%)
ESR Elevated Normal	 176(74.6%) 60(25.4%)
CRP Positive Negative	 115(48.7%) 121(51.3%)
DAS28-ESR score <2.6 -Remission 2.6-3.2 -Low 3.2-5.1-Moderate >5.1 -High	 16(11%) 82(34.7%) 72(30%) 66(27.96%)

Table 2. Disease activity scores of the study participants (N=236)

Statistics	**SJC**	**TJC**	**GHS**	**DAS28ESR**
Mean (±SD)	4.6 (3.1)	2.2 (2.3)	3.3 (2.5)	4.2 (1.5)
Median (IQR)	4 (2-6)	2 (0-4)	2 (1-6)	4.2 (2.8-5.6)

Table 3. Prevalence of anemia among the patients with rheumatoid arthritis (N=236)

Anaemia	**Frequency (n)**	**Percentage (95% CI)**
Yes	139	58.9 (52.3-65.2)
No	97	41.1 (34.8-47.7)

Table 4. Comparison of Types of anemia among the Patients with Rheumatoid Arthritis (n=139)

	Anemia of Chronic Disease	Iron deficiency Anemia
No of anemic patients	110 (79%)	29 (21%)
Mean MCV (80-100 fl)	90.8 ± 2.05	75 ± 1.02
Peripheral blood smear	Normocytic normochromic anemia	Microcytic hypochromic

Table 5. Association of anemia and duration of rheumatoid arthritis (N=236)

Duration of RA (years)	Anemia		p-value
	Yes n (%)	No n (%)	
<1	9 (52.4)	8 (47.1)	0.127
1-5	54 (52.4)	49 (47.6)	
>5	76 (65.5)	40 (34.5)	

Table 6. Correlation between the Hb level and the disease activity score (N=236)

Disease activity score	Anemia (Mean±SD)	Nonanemic (Mean±SD)	Correlation p-value
SJC	6.17±4.27	2.91±2.52	**<0.001**
TJC	3.71±3.21	0.12±0.1	**<0.001**
DAS	4.71±1.25	1.14±1.15	**<0.001**

IV. Discussion

The mean and median age of the study population was 49.1 ±10.1 years and 50(42-56) respectively. Agarwal et al[11]reported mean age of 43.9±11.83 yearswhereas Arul R et al[5]found mean age of 47±7.2 years. Our study found 213(90.7%)patients to be female and 23(9.7%) patients to be male giving a M: F value of 9.3:1similar to a study by Eshmurzaeva et al[11]. The present study showed more than half (53.3%) of the participants had BMI within normal limit and obesity was seen in 14% of participants. 116 (49.2%) patients suffered RA for duration of more than 5 years. Although the prevalence of anemia was found to be higher among these patients, it was not statistically significant(p=0.127). There was no statistically significant difference between gender or age of the patients with the Hb level. In terms of drugs used for its treatment, HCQ was the most commonly prescribed drugs (85.6%), followed by methotrexate (78.4 %) and steroid (11.4%) (table 1). However,Singh et al[12]reported higher percentage of usage of methotrexate (92.16%)followed by HCQ (74.51%) and sulfasalazine (27.45%) as many of our patients have problems for regular monitoring of CBC, liver function test (LFT) etc,HCQ was preferred. Combination of two DMARDs in moderate to high disease activity have a better outcome .[13]

Our criteria of anemiawere defined as a haemoglobin level < 13 g/dl in men and < 12 g/dl in women[10]. Out of 236 patients ,139 patients (58.9%) were found to be anemic similar to studies by Agrawal et al[7].Peeters HR et al[14]and Ganna S etal[15]found the prevalence of anemia to be 64%.Wilson et al[16] found the prevalence of anemia between 33% and 60%.Arul R et al[5] did a random sampling of Hb in RA patients and found a prevalence of anemia of 75%.

Regarding the types of anemia, ACD was the most common type of anemia found in 79% of our patients followed by IDA in 21% of anemic patient which draws similarity to that of the studyby Peeters HR et al[14]. In a study conducted by Agarwal et al[7]ACD was found in 51.6% whereas IDAwas found in 48.4% of anemic patients and disease activity was higher in the anemic patients. The mean MCV was 90.8±2.5 fLinACD whereas it was 75±1.02 fL in IDA.

Disability determinants were swollen joint count(SJC), tender joint count(TJC), global health assessment(GHA)and joint deformities.In our study, statistically significant and very strong negative correlation between Hb level and SJC, TJC, GHA and DAS28ESR (p<0.001)were found.The severity of anemia was found to be related with disease activity and inflammation. The present study showed a significant correlation of DAS28 score, TJC, SJC in RA patients with anemia and is comparable to other studies as shown in table 7. Similar result was mentioned by GannaS et al[15] where lower Hb level was significantly correlated to disability, articular damage and disease activity. Disease activity was assessed by DAS28-ESR scores. Most of our patients (138,58.46%) had moderate to high disease activity. Low disease activity was seen in 34.7%(82 patients).Elevated ESR was found in 176 (74.6%) of study participants and CRP was positive in 115 patients(48.7%).Comparison of various studies with the present study is shown in table 7.

It is clear that anemia was the most common comorbid condition in RA patients [12] and disease activity was high in anemic patients. Low Hb leads to disability, increased disease activity, articular damage and

prolongs disease duration[17]. Functionality is impaired by low Hb level.Anemia should be screened in all RA patients and its treatment should be incorporated in RA management[14].

Table 7:Comparison of various studies with the present study.

Authors	Disease variable	Anemic group	Non-anemic group	p- value
Taziet al[17]	TJC	5.37±6.32	2.23±4.27	<0.001
	DAS28 score	5.45± 1.55	4.7±1.69	<0.001
Agarwalet al[7]	SJC	8.81±8.08	3.82±5.77	<0.001
	TJC	17.4±5.45	8.27±5.87	0.0002
	DAS 28 score	5.19±1.50	3.82±1.36	<0.001
Borah et al[18]	SJC	9.75±3.78	4.09±2.66	0.0001
	TJC	31.42 ± 10.07	18.52 ± 11.28	0.001
	DAS 28 score	1.41±0.44	0.7±0.25	0.001
GannaS et al[15]	SJC	28.67 ± 9.01	16.53 ± 8.27	0.002
	TJC	5.43±4.27	1.88±1.13	0.025
	DAS 28 score	5.2 ± 1.3	2.8 ± 1.1	0.001
Present study	SJC	6.17 ±4.27	2.91±2.52	$p \leq 0.001$
	TJC	3.71±3.21	0.123±0.1	$p < 0.001$
	DAS 28 score	4.71±1.25	1.14±1.5	$p \leq 0.001$

V. Conclusion

The study showed a strong negative correlation between Hb level and disease activity in RA ($p \leq 0.01$) and also with SJC,TJC, GHA and DAS28-ESR. These results suggest that patients with RA who have anemia are more likely to have more severe joint diseaseand more disability is likely to respond to treatment as well.Hence, screening and treating for anemia is important in management of RA patients.However, further studies including a larger number of patients with long term follow up are needed for conclusive results.

Declarations:
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Conflict of Interest: None declared
Approval of research ethics board**:** Taken

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