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Frequency of Different Types of Anemia in Patients of Rheumatoid Arthritis presenting to a Tertiary Care Hospital

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ABSTRACT

Objective: To study the frequency of different types of anemia in patients of rheumatoid arthritis.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Rheumatology, Pak-Emirates Military Hospital Rawalpindi, Pakistan from Oct 2021 to Mar 2022.
Methodology: One hundred and thirty-nine individuals with Rheumatoid Arthritis were included in the study and frequency of different types of anemia was assessed. Red cell indices (RBC count, MCV, MCH, MCHC), total leucocyte count (TLC), platelet count (PLT), serum ferritin and C-reactive protein (CRP) were entered for all patients. B12 and folate was only ordered and followed up in cases with high MCV. Anemia was defined as a Hb <12 g/dL for women and <13 g/dL for men.
Results: Mean age of participants was 48.61±1 2.5 years, female majority (61.9%). Different type of anemias seen in patients with RA included Iron deficiency anemia (IDA) being the most common (43.2%), followed by anemia of chronic disease (ACD, 28.8%). Megaloblastic anemia due to vit B12/folate deficiency was observed in 11.5% of patients. In 11(7.9%) subjects, IDA combined with ACD was seen. Treatment-induced cytopenia was found in 5.8% of patients, while in 2.9% of respondents the cause of anemia was not to be found.
Conclusion: Iron Deficiency anemia was the most commonly seen anemia type (43.2%) followed by anemia of chronic disease (28.8%), megaloblastic anemia (11.5%) and combined IDA and anemia of chronic disease (7.9%) in our study.

Keywords: Anemia, Iron Deficiency Anemia, Cytopenia, Rheumatoid Arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology characterized by a symmetric polyarthritis and is most common form of chronic inflammatory arthritis.[1] Since persistently active RA often results in articular cartilage and bone destruction, it is vital to diagnose and treat this disease early and aggressively before damage ensues.[2] RA, a systemic disease, may lead to a variety of extra-articular manifestations including subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities, which must be managed accordingly.[3,4]

Anemia has been defined by the World Health Organization as Hemoglobin less than 12 g/dL in non-pregnant females and less than 13 g/dL in males.[5] There are different mechanisms of developing anemia in rheumatoid arthritis.6 Anemia of chronic disease (ACD) manifested by the development of disturbances of iron homeostasis.[6] ACD is frequently a presenting feature of RA and it resolves with the treatment of the disease itself.[7] Iron Deficiency Anemia (IDA) caused by gastrointestinal or menstrual blood loss or pregnancy. Comorbid conditions that interfere with iron absorption may also contribute including celiac disease, Helicobacter pylori infection, atrophic gastritis, malabsorption syndromes.[8,9] Megaloblastic anemia is usually mild, with a high Mean Corpuscular Volume due to either vitamin B12 or folate deficiency. Other mechanisms include hemolysis, which has been reported as an atypical feature of RA associated with Felty syndrome, a rare complication of RA featuring mild anemia, neutropenia and splenomegaly, and pure red cell aplasia (PRCA), which is also a rare complication of RA.[9] Also there can be anemia due to bone marrow suppression due to drugs.[10]

The frequency of different types of anemia in RA remains largely undocumented in our literature, and the purpose of our study was to determine this and give our practicing physicians an insight for exploring different mechanisms of anemia in RA patients.

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METHODOLOGY

This Cross-sectional study was conducted at the Department of Rheumatology, Pak Emirates Military Hospital Rawalpindi, Pakistan, from October, 2021 to March 2022 following approval from the Institutional Ethical Review Committee (A/28/EC/451).

Inclusion Criteria: Patients of either gender who were diagnosed cases of rheumatoid arthritis for at least 1 year, who also had anemia, aged between 20-70 years were included.

Exclusion Criteria: Pregnant females, patients with chronic debilitating medical conditions such as chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, diabetes mellitus and mal-absorptive conditions were excluded.

Sample size was calculated to be 139 using WHO sample size calculator keeping the prevalence of RA as 0.24%.[11] Using convenience sampling, all patients of Rheumatoid Arthritis coming to the rheumatology OPD were screened for anemia, after obtaining informed consent.

A specialized data collection tool was developed for this study. Red cell indices (RBC count, MCV, MCH, MCHC), total leucocyte count (TLC), platelet count (PLT), serum ferritin and C-reactive protein (CRP) were entered for all patients. B12 and folate was only ordered and followed up in cases with high Mean Corpuscular Volume (MCV). Anemia was defined as hemoglobin <12 g/dL for women and <13 g/dL for men. Red cell indices and other labs were interpreted,[12] as follows Table-I.

The data were summarized as mean, frequency and percentage and then analysis was carried out by Statistical Package for Social Sciences (SPSS) version 23. Chi-square test was used to check for association between different parameters, and a *p*-value <0.05 was considered statistically significant.

RESULTS

Among a total of 139 patients, 53(38.1%) were male and 86(61.9%) were female with mean age of 48.6±12.5 years. Thirty-eight (27.3%) patients had RA for 1-5 years, 59(42.4%) were diagnosed with RA for 5-10 years and 42(30.2%) had been RA patients for more than 10 years.

Seventy-three (52.5%) had hemoglobin (Hb) levels between 8.0-9.5 g/dL, while 51(36.7%) had Hb between 9.6-10.9 g/dL and 15(10.8%) had a hemoglobin level less than 8.0 g/dL. Other blood work showed that 131(94.2%) patients had normal TLC levels whereas 8(5.8%) had TLC below 4. Normal platelets counts were seen in 111(79.9%) patients, whereas 20(14.4%) had reactive thrombocytosis with platelet count of over 400 and very few 8(5.8%) had thrombocytopenia with platelet count lower than 150.

The type of anemia was analyzed on the basis of MCV levels. Most patients (51.1%) patients had low MCV with low ferritin levels representing iron deficiency anemia, whereas 37.4% had normal MCV. Sixteen patients (11.5%) had high MCV anemia representing Macrocytic anemia with low vitamin B12 (4.3%) or folate (7.2%) levels. Red cell and reticulocyte count showed 81(58.3%) patients had normal, and 58(41.7%) had low red cell count (< 3.5) whereas reticulocyte count was found to be normal in 97(69.8%) and low (< 0.5) in 42 (30.2%) patients of RA with anemia Table-II.

Duration of disease was compared with type of anemia, which revealed that iron deficiency anemia was the most common type of anemia (35.9%) followed by anemia of chronic disease (15.8%) in patients with disease less than 10 years duration, whereas IDA was found in 10(7.1%) patients and ACD in 12(8.6%) patients with disease of more 10 years duration Table-III.

Table-I: Different Types of Anemia

Type of Anemia	RBC count (x 109)	MCV (fL)	MCH (pgm)	Ferritin (ng/ml)	CRP (mg/	B12/Folate
ACD	<3.8 F <4.2 M	80-100 in most cases	24-36	>200	>6	Not relevant
IDA	<3.8 F <4.2 M	<80	<24	<15	Negative	Not relevant
Marrow suppression	<3.8 F <4.2 M	77-100	24-36	Not relevant	Not relevant	Not relevant
B12/Folate deficiency	<3.8 F <4.2 M	>100	24-36 or can be higher	Not relevant	Not relevant	Low

MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, CRP: C-Reactive Protein, IDA: Iron Deficiency Anemia, ACD: Anemia of Chronic Disease

Table-II: Parameters studied in Patients of Rheumatoid Arthritis (n=139)

		n (%)
Gender	Male	53(38.1%)
	Female	86(61.9%)
Duration of illness	1-5 years	38(27.3%)
	5-10 years	59(42.4%)
	>10 years	42(30.2%)
Hemoglobin Levels	<8.0 g/dL	15(10.8%)
	8-9.5 g/dL	73(52.5%)
	9.6-10.9g/dL	51(36.7%)
Mean Corpuscular Volume	Low (<74)	71(51.1%)
	Normal (75-100)	52(37.4%)
	High (>101)	16(11.5%)
Red Cell Count	Normal	81(58.3%)
	Low (<3.5)	58(41.7%)
Reticulocyte Count	Normal	97(69.8%)
	Low (<0.5%)	42(30.2%)
C-Reactive Protein	Normal	88(63.3%)
	High (>15mg/L)	51(36.7%)

Table-III: Associated of Disease Duration with Type of Anemia (n=139)

		Anemia						*p*-value
		IDA n(%)	ACD n(%)	Megloblastic n(%)	Treatment Induced n(%)	Others n(%)	Combo : IDA + ACD n (%)	
RA	1-5 years 38 (27.3)	25(65.7)	6(15.7)	2(5.2)	2(5.2)	1(2.6)	2(5.2)	0.011
	5 - 10 years 59 (42.4)	25(42.3)	22(37.2)	5(8.4)	1(1.6)	2(3.3)	4(6.7)	
	> 10 years 42 (30.2)	10(23.8)	12(28.5)	9(21.4)	5(11.9)	1(2.3)	5(11.9)	

RA: Rheumatoid Arthritis, IDA: Iron Deficiency Anemia, ACD: Anemia of Chronic Disease

Furthermore, C-Reactive Protein (CRP) levels were also checked in patients, which was found to be normal in 88(63.3%) patients but was raised in 51(36.7%). Iron Deficiency anemia was the most commonly seen anemia in 60(43.2%) patients of RA followed by anemia of chronic disease in 40(28.8%). Megaloblastic anemia due to vitamin B12/folate deficiency were noticed in 16(11.5%) subjects. It was also observed that in 11(7.9%) patients of RA, a combination of IDA and anemia of chronic disease was seen, as evident by CRP levels. A small number (5.8%) patients showed treatment-induced cytopenias, specifically methotrexate-induced bone marrow suppression. In very few patients 4(2.9%) the cause of anemia was not to be found Figure-1.

DISCUSSION

One hundred and thirty-nine patients of Rheumatoid Arthritis (RA) with anemia were enrolled and the type of anemia was assessed using blood tests. Anemia has a reported prevalence of 72.8% in RA in the developing world which is double as compared to the developed countries.[13,14] In our study, iron deficiency was found to be the most common of the causes (43.2%) out of which 75% were female, representing that iron deficiency anemia (IDA) is more common in female patients of younger age due to ongoing menstrual blood loss. Pakistani population has a reported iron deficiency prevalence of 45%.[15,16] It is a developing country and has yet to fight the challenges of nutritional deficiencies. Common causes of anemia include poor intake of iron in diet and increased losses as a result of gastrointestinal diseases, worm infestations, pregnancy and menstrual loss.[17] Furthermore, anemia of chronic disease (ACD) was observed in 40(28.8%) patients with 20(50%) in each gender with equal frequency of ACD. ACD is represents inadequate control of the disease, which is generally because of unintentional and intentional factors. The former includes forgetfulness due to complicated drug regimen while the latter represents patient-based factors like intolerance to the therapy or feeling well at a point in time and stopping the drugs altogether. Estimated cost of rheumatoid arthritis treatment is over $12000 which is difficult to manage in a resource constrained country.[18,19]

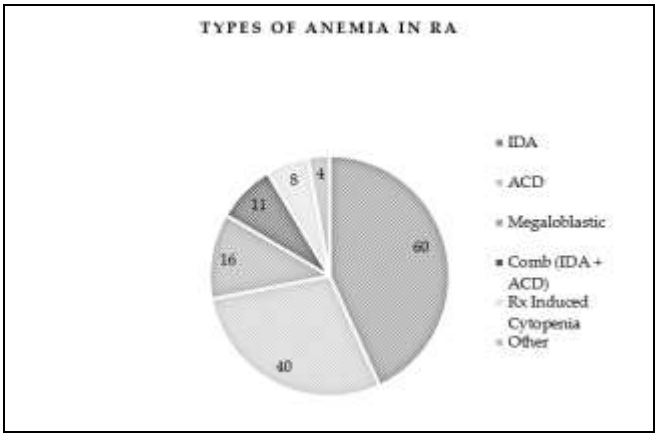

Figure-1: Types of Anemia in RA Patients
**IDA: Iron Deficiency Anemia, ACD: Anemia of Chronic Disease, Comb: Combination of IDA and ACD, Rx: Treatment*

An opposite story can be found in patients with cytopenias who take methotrexate daily instead of a weekly prescribed dose. They present with progressive dyspnea and fatigue. These patients can be treated with a daily dose of 1 mg folic acid, which can be increased upto 5 mg per day.[20]

A small proportion of patients also had a combination of iron deficiency and anemia of chronic disease, indicated by the fact that they had a low ferritin but a raised CRP. Usually ACD is normocytic but co-existing iron deficiency can lead to a low MCV.[21]

Frequency of megaloblastic anemia was found to be in 8(50%) patients in each gender Figure-2. Most of them had folate deficiency, although all patients had been co-prescribed folic acid supplements along with methotrexate. This can be attributed to dietary habits of patients and warrants further inquiry so as to ascertain if patients have adequate intake and absorption of folate.[22,23]

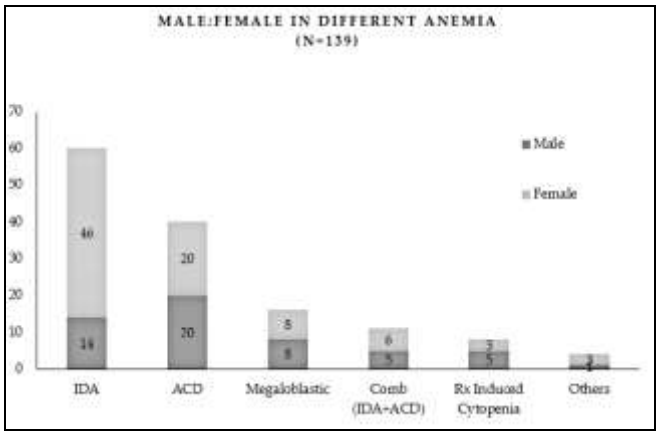

Figure-2: Female to Male Ratio in different types of Anemia (n=139)

IDA: iron deficiency Anemia, ACD: Anemia of Chronic Disease, Comb: Combination, Rx: Treatment

LIMITATIONS OF STUDY

The authors of this study are well aware of its limitations. This study was carried out in a single center, which might not reflect the actual burden of disease. Secondly, rare causes of anemia in RA were not explored in this as it adds to the cost of laboratory tests and needed larger sample set and more detailed data.

CONCLUSION

Iron Deficiency anemia was the most commonly seen anemia type (43.2%) followed by anemia of chronic disease (28.8%), megaloblastic anemia (11.5%) and combined IDA and anemia of chronic disease (7.9%) in our study.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ZUA & AF: Conception, study design, drafting the manuscript, approval of the final version to be published.

MN & HAS: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MH & MA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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