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Hematological Abnormalities and Their Association with Disease Activity in Rheumatoid Arthritis: A Cross-Sectional Study.

Dr. Md Abdul Rahman[1*], Dr. Syed Hassan[2], Dr. Moid Mir Siddiq Ali[3], Dr. Nausheen Sultana[4].

[1]Assitant Professor, Department of General Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana, India.
[2]Assistant Professor, Department of General Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana, India.
[3]Assistant Professor, Department of Respiratory Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana, India.
[4]Junior Consultant, Department of General Medicine, Femcity: Women and Children Hospital, Hyderabad, Telangana, India.

Correspondence:
Dr. Md Abdul Rahman.
Assitant Professor, Department of General Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana, India.

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Abstract

Background: Hematological abnormalities are frequent extra-articular manifestations of rheumatoid arthritis (RA), but their relationship with disease activity is often under-recognized. ***Objectives:*** To describe the hematological profile of patients with RA, estimate the prevalence and pattern of anemia, and assess associations between hematological variables, rheumatoid factor (RF) status, and Disease Activity Score in 28 joints (DAS28). ***Methods:*** This hospital-based cross-sectional study included 88 adults aged 20–60 years who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA. Clinical assessment included tender and swollen joint counts, visual analogue assessment, disease duration, and DAS28. Investigations included complete blood count, peripheral smear, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF, serum iron, total iron-binding capacity, ferritin, and routine biochemistry. ***Results:*** The mean age was 40.98 ± 9.73 years and 79.5% were women. Mean DAS28 was 4.8 ± 0.78; 52.3% had moderate and 45.5% severe disease activity. Anemia was present in 75.0% and was associated with RF positivity (p=0.0305) and higher DAS28 (5.04 ± 0.58 versus 4.32 ± 0.91; p=0.006). Among anemic patients, anemia of chronic disease (ACD) accounted for 60%, iron-deficiency anemia for 25%, and dimorphic anemia for 15%. Mean DAS28 was highest in normocytic normochromic anemia (5.38 ± 0.46). RF-positive patients had higher DAS28 than RF-negative patients (4.98 ± 0.61 versus 4.01 ± 0.53; p=0.0025). Platelet count, eosinophil count, ESR, CRP, and ferritin increased significantly across DAS28 categories. Thrombocytosis, eosinophilia, leukocytosis, and lymphopenia occurred in 31%, 27%, 29.5%, and 23%, respectively. ***Conclusion:*** Anemia, particularly ACD, was highly prevalent and closely associated with active RA. Routine interpretation of the complete blood count and iron profile alongside inflammatory markers may provide a practical adjunct to clinical assessment of disease activity.

Keywords: anemia of chronic disease; DAS28; ferritin; hematological profile; iron-deficiency anemia; rheumatoid arthritis.

INTRODUCTION

Although this cohort was recruited between 2017 and 2019, the 2010 ACR/EULAR classification criteria remain the accepted international classification criteria for established rheumatoid arthritis [1]. The 2025 EULAR/ACR criteria address identification of individuals at risk of developing rheumatoid arthritis and do not replace the 2010 classification criteria [2].

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease that primarily affects synovial joints but also produces clinically important systemic manifestations [3]. Persistent inflammation may result in progressive cartilage and bone damage, functional limitation, and extra-articular disease [4]. Hematological abnormalities are among the most frequent systemic findings and can reflect inflammatory burden, nutritional deficiency, occult blood loss, drug toxicity, immune-mediated cytopenia, or marrow dysfunction [5].

Anemia is the dominant hematological abnormality in RA [6]. Anemia of chronic disease, now frequently termed anemia of inflammation, results from cytokine-driven iron sequestration, impaired erythropoietin production or response, reduced erythroid proliferation, and shortened red-cell survival [7].

Hepcidin induction by interleukin-6 limits intestinal iron absorption and traps iron within macrophages [8]. Iron-deficiency anemia may coexist because of poor intake or gastrointestinal blood loss, particularly with prolonged non-steroidal anti-inflammatory drug exposure [9]. Distinguishing iron deficiency from anemia of inflammation is clinically important because treatment differs and serum ferritin may be elevated as an acute-phase reactant [10].

RA can also influence leukocyte and platelet counts. Leukocytosis, neutrophilia, thrombocytosis, lymphopenia, and eosinophilia may accompany active inflammation, whereas neutropenia can occur in Felty syndrome or as an adverse effect of therapy [3]. Platelet count and inflammatory markers may therefore provide additional information regarding disease activity [11].

However, data describing the combined hematological profile of Indian patients with RA and its relationship with DAS28 remain limited [5]. This study evaluated anemia and other hematological abnormalities in adults with RA and examined their association with RF status, disease duration, inflammatory markers, and DAS28.

MATERIALS AND METHODS

Study design and setting

A hospital-based cross-sectional study was conducted in the Department of General Medicine at Owaisi Hospital and Research Centre and Princess Esra Hospital, Hyderabad. The study period was approximately 18 months. Institutional ethics approval was obtained and written informed consent was taken from all participants.

Participants

Eighty-eight inpatients and outpatients with RA were enrolled. Eligible participants were 20–60 years old, had disease duration up to five years, and fulfilled the 2010 ACR/EULAR classification criteria [1]. Patients with previously diagnosed and treated anemia, unrelated bleeding disorders, overlap connective-tissue disease, known malignancy, renal failure, hemolytic anemia, or another source of chronic blood loss were excluded.

Clinical assessment

History included disease duration, medication exposure, and symptom onset. Examination documented pallor, nodules, lymphadenopathy, deformity, tender and swollen joint counts, and extra-articular manifestations. Patient global health was recorded on a 100-mm visual analogue scale.

Laboratory assessment

Complete blood count with red-cell indices, differential count, platelet indices, peripheral smear, ESR, CRP, RF, serum iron, total iron-binding capacity, ferritin, renal function, serum proteins, bleeding time, and clotting time were obtained. Anemia was defined in the thesis protocol as hemoglobin below 11 g/dL in women and below 12 g/dL in men, a threshold lower than current World Health Organization criteria [12].

Peripheral smear patterns were classified as microcytic hypochromic, normocytic normochromic, dimorphic, or normal. Iron-deficiency anemia and anemia of chronic disease were differentiated using the iron profile and ferritin, with ferritin below 50 microgram/L supporting iron deficiency in the inflammatory setting [10].

Disease activity

DAS28 was calculated from 28 tender and swollen joint counts, ESR, and patient global assessment. Scores were categorized as mild (<3.1), moderate (3.2–5.1), and severe (>5.1), as defined in the original protocol.

Statistical analysis

Data were summarized using frequency, percentage, mean, and standard deviation. Group comparisons used t test, analysis of variance, chi-square/Yates correction, or non-parametric tests as reported in the thesis. A two-sided p value below 0.05 was considered statistically significant.

RESULTS

The study included 88 patients. Women constituted 79.5% of the cohort and the mean age was 40.98 ± 9.73 years. The largest age group was 40–49 years (36.4%). Mean disease duration was 2.93 ± 1.13 years. RF was positive in 70 patients (79.5%). Mean DAS28 was 4.8 ± 0.78; only two patients had mild activity, whereas 46 had moderate and 40 had severe activity.

Table 1: Baseline demographic and disease characteristics

Characteristic	Value
Age, mean ± SD, years	40.98 ± 9.73
Female sex	70 (79.5%)
Disease duration, mean ± SD, years	2.93 ± 1.13
RF positive	70 (79.5%)
DAS28, mean ± SD	4.8 ± 0.78
Mild DAS28	2 (2.3%)
Moderate DAS28	46 (52.3%)
Severe DAS28	40 (45.5%)
Joint deformity	44 (50.0%)
Rheumatoid nodules	6 (6.8%)
Radiographic evidence of RA	54 (61.4%)

Anemia was found in 66 patients (75.0%); mean hemoglobin for the cohort was 10.67 ± 1.83 g/dL. RF positivity was more frequent among anemic than non-anemic patients, and anemia was associated with a significantly higher DAS28. Disease activity also increased with longer disease duration. Among anemic patients, ACD was the predominant pattern, followed by iron-deficiency and dimorphic anemia.

Table 2: Anemia profile and relationship with disease activity

Variable	Result	p value
Anemia prevalence	66/88 (75.0%)	–
RF positive: anemic vs non-anemic	87% vs 54%	0.0305
DAS28: anemic vs non-anemic	5.04 ± 0.58 vs 4.32 ± 0.91	0.006
Microcytic hypochromic pattern	16/88 (18.2%)	–
Normocytic normochromic pattern	40/88 (45.5%)	–
Dimorphic pattern	10/88 (11.4%)	–
ACD among anemic patients	60%	–
IDA among anemic patients	25%	–
Dimorphic anemia among anemic patients	15%	–
DAS28: ACD vs IDA	5.38 ± 0.46 vs 4.77 ± 0.35	0.0001

Clinical components of DAS28 were consistently greater in anemic patients. Compared with iron-deficiency anemia, patients with ACD had higher tender and swollen joint counts and a higher global assessment score, supporting a closer relationship between ACD and inflammatory activity.

Table 3: Selected clinical and laboratory comparisons

Parameter	Anemic	Non-anemic	p value
Tender joint count	10.4 ± 5.45	5.27 ± 3.85	0.004
Swollen joint count	6.5 ± 3.78	3.28 ± 4.82	0.006
Global assessment	66.1 ± 53.1	31.2 ± 43.3	0.005
Hemoglobin, g/dL	9.72 ± 1.43	12.49 ± 0.75	0.0001
MCV, fL	78.27 ± 8.87	86.42 ± 5.3	0.0036
MCH, pg	24.51 ± 3.63	27.92 ± 2.2	0.0033
MCHC, g/dL	31.08 ± 1.73	32.27 ± 0.81	0.0071

Other hematological abnormalities included leukocytosis in 26 patients (29.5%), neutrophilia in 72 (81.8%), lymphopenia in 20 (22.7%), eosinophilia in 24 (27.3%), and thrombocytosis in 28 (31.8%). No participant had leukopenia, thrombocytopenia, immature circulating cells, large granular lymphocytosis, abnormal bleeding time, or abnormal clotting time.

Table 4: Laboratory parameters across DAS28 categories

Parameter	Mild	Moderate	Severe	p value
Platelet count (lakh/cmm)	2.75 ± 1.35	3.49 ± 0.93	4.09 ± 0.97	0.0046
Eosinophils (%)	1.0 ± 1.4	2.39 ± 3.25	5.76 ± 6.7	0.0001
CRP	6.8 ± 5.5	23.13 ± 24.5	53.85 ± 19.9	0.0006
Ferritin	50 ± 2.3	52.73 ± 34.7	151.5 ± 88.9	0.001
ESR, mm/hour	25 ± 14.1	43.24 ± 12.2	67.25 ± 25.5	0.0001

DISCUSSION

These findings remain clinically relevant in the current treat-to-target era. Contemporary EULAR recommendations continue to emphasize regular disease activity assessment, early therapeutic optimization, and comprehensive monitoring [13]. Routine hematological parameters remain inexpensive adjunctive markers of inflammatory burden and treatment surveillance in patients with rheumatoid arthritis [5]. This study demonstrates a high burden of hematological abnormalities in relatively young adults with RA. Three-quarters of the cohort were anemic, and anemia was associated with RF positivity, longer disease duration, and greater DAS28. The predominance of women and the concentration of patients in the fourth and fifth decades are consistent with the recognized epidemiology of RA [3].

The prevalence of anemia was 75%, which is at the upper end of previously reported estimates. Earlier cohorts have reported rates of approximately 40%–76% [6]. Comparable estimates have been described in more recent cohort analyses [14]. Several factors may account for the high prevalence in the present series, including background nutritional anemia, delayed or incomplete disease control, gastrointestinal blood loss, and the use of a relatively low hemoglobin threshold in the original protocol [12]. Nevertheless, the consistent association between anemia and objective and clinical measures of activity indicates that the finding cannot be attributed solely to background iron deficiency [11].

ACD was the most frequent anemia subtype and patients with a normocytic normochromic pattern had the highest DAS28. This relationship is biologically plausible. Pro-inflammatory cytokines, particularly interleukin-6, stimulate hepcidin production, reduce iron absorption, inhibit iron release from macrophages, and limit iron availability for erythropoiesis [15]. Circulating hepcidin concentrations have been shown to track disease activity in RA [16]. Tumor necrosis factor and interleukin-1 can further suppress erythroid progenitors and blunt the erythropoietin response [10]. Oxidative stress associated with active RA may additionally shorten red-cell survival [17]. Thus, ACD often parallels inflammatory burden and may improve with effective control of RA [18].

Iron-deficiency anemia accounted for one-quarter of anemia cases, while 15% had a dimorphic pattern. In clinical practice, ACD and iron deficiency commonly overlap [9]. Ferritin is useful but must be interpreted cautiously because it rises during inflammation [19]. In patients with active RA and equivocal ferritin, transferrin saturation, soluble transferrin receptor, or the soluble transferrin receptor/log ferritin index may improve diagnostic discrimination [20]. A dimorphic picture should prompt assessment of combined iron, folate, or vitamin B12 deficiency and review of gastrointestinal blood loss and medication exposure.

Anemia was also linked to RF positivity. RF-positive patients had lower mean hemoglobin and higher DAS28 than RF-negative participants. RF positivity is often associated with more persistent and extra-articular disease [4], and the present findings support closer hematological surveillance in seropositive patients. However, because the study was cross-sectional, RF cannot be considered a direct cause of anemia. Platelet count, eosinophil count, ESR, CRP, and ferritin increased across DAS28 categories. Reactive thrombocytosis is a recognized response to inflammatory cytokines and may serve as an inexpensive adjunctive marker of active disease [5]. Eosinophilia was less common but showed a strong statistical relationship with DAS28. This association should be interpreted carefully because eosinophilia can be influenced by atopy, parasitic infection, and medications, variables not fully characterized in the thesis.

Leukocytosis and neutrophilia were common, while leukopenia was absent. The absence of leukopenia and Felty syndrome is understandable because disease duration was restricted to five years and patients with advanced or complicated disease may have been underrepresented [3]. Lymphopenia may reflect inflammatory activity or corticosteroid exposure. No clinically evident coagulation abnormality, hematologic malignancy, hyperviscosity syndrome, or large granular lymphocyte disorder was detected. The findings have direct clinical relevance. A complete blood count, peripheral smear, ESR/CRP, and targeted iron studies are inexpensive and widely available. Their combined interpretation can identify treatable nutritional deficiency, signal active inflammation, and highlight possible drug toxicity. Anemia should not be managed empirically with iron alone without defining the likely mechanism, because iron replacement is unlikely to fully correct pure ACD unless inflammatory activity is simultaneously controlled [19].

Clinical implications

The results support a structured approach to anemia in RA. First, anemia should prompt assessment of current disease activity rather than automatic prescription of iron [19]. Second, low ferritin or low transferrin saturation should lead to evaluation for dietary deficiency and gastrointestinal blood loss [9]. Third, normal or elevated ferritin in a patient with active inflammation does not exclude coexisting iron deficiency; additional tests may be required [20]. Finally, unexpected leukopenia, thrombocytopenia, or pancytopenia should trigger review of disease-modifying therapy, infection, hypersplenism, marrow disease, and large granular lymphocyte disorders [3].

Strengths and limitations

The study evaluated multiple blood-cell lineages and correlated them with a composite measure of RA activity. Important limitations include the single-centre cross-sectional design, modest sample size, non-probability recruitment, exclusion of disease lasting more than five years, and use of hemoglobin cut-offs below current World Health Organization thresholds [12]. Medication exposure, nutritional status, parasitic disease, menstrual blood loss, and gastrointestinal evaluation were not comprehensively adjusted for. Anti-cyclic citrullinated peptide antibody, hepcidin, soluble transferrin receptor, reticulocyte indices, vitamin B12, and folate were not routinely assessed [20]. Some statistical methods and units were incompletely specified in the thesis. Consequently, observed associations should be interpreted as hypothesis-generating and not causal.

CONCLUSION

Anemia was the most frequent hematological abnormality in this RA cohort and was strongly associated with seropositivity and higher disease activity. ACD was more common than iron-deficiency anemia and showed the greatest relationship with DAS28. Thrombocytosis, eosinophilia, leukocytosis, lymphopenia, ESR, CRP, and ferritin also reflected inflammatory activity. Routine hematological assessment, combined with careful evaluation of iron status and treatment exposure, should form part of comprehensive RA care.

DECLARATIONS

Ethics approval and consent to participate

Institutional ethics approval was obtained for the dissertation study, and written informed consent was obtained from participants.

Consent for publication

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

The data supporting the findings are contained in the dissertation dataset and may be made available by the corresponding author subject to institutional approval.

Author contributions

MDAR: conception of the original thesis, data collection, analysis, and drafting. SH: updating the manuscript in accordance with recent EULAR recommendations, critical scientific revision, and polishing the original 2017–2019 thesis for publication. MMSA: interpretation of data, manuscript revision, and overall scientific review. NS: contributed to patient data acquisition during her internship posting at Deccan College of Medical Sciences during the original study period (2017–2019), reviewed the manuscript, and approved the final version.

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