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Research Article

A Cross-Sectional Study of Plasma C-Reactive Protein and Serum Ferritin Levels in Rheumatoid Arthritis Patients

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disorder in which persistent synovial inflammation is accompanied by measurable changes in circulating acute-phase reactants. C-reactive Protein (CRP) is routinely used to quantify inflammatory activity, whereas ferritin is influenced by both iron stores and inflammation and may therefore provide complementary information. **Objective:** To assess plasma CRP and serum ferritin levels in patients with RA and determine their relationship with clinical disease activity. **Methods:** This hospital-based cross-sectional study included 74 adults with RA attending Medinirai Medical College and Hospital, Palamu, during a 1-year period. Demographic and clinical data were recorded, disease activity was assessed using DAS28-ESR and plasma CRP, serum ferritin, Erythrocyte Sedimentation Rate (ESR) and hemoglobin were measured. **Results:** The mean age was 48.6±11.2 years and 54 (73.0%) participants were women. Mean DAS28-ESR was 4.61±1.18. Mean CRP and ferritin levels were 18.7±14.9 mg/L and 186.4±124.6 ng/mL, respectively. CRP increased from 6.8±4.7 mg/L in remission/low disease activity to 33.0±15.2 mg/L in high disease activity ($p<0.001$). Ferritin similarly increased from 111.5±71.4 to 274.8±138.6 ng/mL ($p<0.001$). CRP correlated strongly with DAS28-ESR ($r = 0.69$, $p<0.001$), while ferritin showed a moderate positive correlation ($r = 0.46$, $p<0.001$). CRP and ferritin were also positively correlated ($r = 0.41$, $p<0.001$). **Conclusion:** Higher CRP and ferritin levels were associated with greater RA disease activity. CRP demonstrated the stronger relationship, while ferritin may serve as a useful adjunctive marker when interpreted alongside inflammatory and hematologic indices.

Keywords: Rheumatoid Arthritis, C-Reactive Protein, Ferritin, Disease Activity, DAS28, Inflammation

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease characterized by persistent synovitis, autoantibody production, progressive cartilage and bone damage and a broad spectrum of systemic manifestations. Its consequences extend beyond joint pain and deformity to fatigue, anemia, cardiovascular disease, pulmonary involvement, disability and premature mortality. Contemporary global estimates demonstrate a substantial and increasing burden of RA, with millions of people affected worldwide and further growth anticipated as populations age [1]. Epidemiological patterns vary by sex, age, geography, ancestry, smoking exposure, socioeconomic conditions and access to specialist care, but women are consistently affected more often than men [2].

The inflammatory process in RA is driven by interacting innate and adaptive immune pathways. Activated macrophages, fibroblast-like synoviocytes, T cells, B cells and osteoclasts generate a cytokine-rich synovial microenvironment in which tumor necrosis factor, interleukin (IL)-6, IL-1, granulocyte-macrophage colony-stimulating factor and other mediators sustain tissue inflammation and structural damage [3]. Because the degree of systemic inflammation is clinically meaningful, acute-phase reactants are incorporated into routine assessment and even into the 2010 American College of Rheumatology/European League Against Rheumatism classification framework for RA [4].

C-reactive protein is synthesized predominantly by hepatocytes in response to IL-6 and related inflammatory signaling. Its relatively rapid rise and fall make it useful for monitoring changes in systemic inflammation. In RA, CRP contributes to composite disease activity measures, helps identify patients with ongoing inflammatory activity and has

also been associated with systemic comorbidity risk [5]. Nevertheless, clinical joint activity and acute-phase responses are not perfectly concordant; some patients with clinically active disease may have normal inflammatory markers, while others may retain elevated CRP despite apparently controlled joint counts [6]. Thus, interpretation is strengthened when CRP is considered together with clinical findings and additional laboratory measures. Persistent CRP elevation in RA has also been documented in patients with low apparent clinical activity, underscoring the possibility of residual systemic inflammation [7].

Ferritin is best known as the major intracellular iron-storage protein, but circulating ferritin is also an acute-phase reactant. In inflammatory states, cytokine-driven iron sequestration, hepatocellular responses, macrophage activation and altered iron handling can increase serum ferritin independently of total body iron stores. An earlier study in RA reported significant relationships between ferritin and markers of disease activation, suggesting that ferritin can reflect inflammatory burden in at least a subset of patients [8]. Current understanding also recognizes ferritin as an immunometabolic protein whose concentration may change across infection, autoimmunity, tissue injury and other inflammatory conditions [9].

Iron metabolism in RA is particularly complex because inflammatory iron restriction and absolute iron deficiency may coexist. High disease activity can be accompanied by abnormalities in transferrin, ferritin, hepcidin and soluble transferrin receptor concentrations [10]. Rheumatoid anemia commonly reflects inflammation-mediated iron sequestration and impaired erythropoiesis, with IL-6-hepcidin signaling playing a central mechanistic role [11]. These processes create an important interpretive challenge: a normal or elevated ferritin value does not necessarily exclude functional iron restriction and a low ferritin value may still identify depleted iron stores despite inflammation.

In resource-constrained tertiary-care settings, inexpensive and widely available biomarkers that complement clinical examination may support more consistent assessment of inflammatory burden. However, locally generated data on the combined behavior of plasma CRP and serum ferritin in RA are limited. The present study was therefore designed to assess plasma CRP and serum ferritin levels among patients with RA attending a tertiary care hospital in Palamu and to examine their relationships with disease activity and selected hematological and inflammatory parameters.

METHODS

Study Design and Setting

A hospital-based cross-sectional study was conducted over a period of 1 year at Medinirai Medical College and Hospital, Palamu, Jharkhand, India. Patients were recruited from adult medicine/rheumatology services using consecutive sampling until the required sample size of 74 participants was achieved.

Study Population

Adults aged 18 years or older with a clinical diagnosis of rheumatoid arthritis fulfilling the 2010 ACR/EULAR classification criteria were eligible. Patients were included irrespective of sex, disease duration, or use of conventional disease-modifying antirheumatic drugs, provided they were clinically stable enough to undergo assessment and blood sampling. Exclusion criteria were acute febrile illness or documented infection during the preceding 4 weeks, active malignancy, major surgery or trauma within the preceding 3 months, known chronic liver failure, end-stage kidney disease, hereditary iron-overload disorder, pregnancy, recent blood transfusion and conditions likely to cause major non-RA-related distortion of ferritin or CRP values. Patients receiving iron therapy were recorded and those who had started parenteral iron within the preceding 3 months were excluded.

Clinical Assessment

A structured case record form was used to document age, sex, disease duration, current treatment, smoking status, relevant comorbidities and serological status where available. Tender and swollen joint counts were performed for 28 joints. Disease activity was quantified using DAS28-ESR, incorporating 28-joint tender count, 28-joint swollen count, ESR and patient global health assessment. For analysis, participants were grouped as remission/low disease activity (DAS28 ≤3.2), moderate disease activity (DAS28 >3.2 to ≤5.1) and high disease activity (DAS28 >5.1).

Laboratory Measurements

Venous blood was collected under standard aseptic precautions during the same clinical visit. Plasma CRP was measured by a quantitative immunoturbidimetric method and expressed in mg/L. Serum ferritin was measured by a chemiluminescent immunoassay and expressed in ng/mL. ESR was determined by the Westergren method and complete blood count parameters including hemoglobin were obtained using an automated hematology analyzer. Internal laboratory quality-control procedures were followed for all assays. Because ferritin is influenced by inflammation as well as iron status, ferritin values were interpreted in conjunction with CRP, ESR and hemoglobin rather than as an isolated measure of iron stores.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables are presented as mean±standard deviation and categorical variables as frequency and percentage. Differences across disease-activity categories were assessed using one-way analysis of variance with post-hoc pairwise comparison where appropriate. Categorical variables were compared using the chi-square test or Fisher exact test. Pearson correlation coefficients were calculated for relationships among CRP, ferritin, DAS28-ESR, ESR and hemoglobin. An exploratory multivariable logistic regression model was used to examine whether CRP and ferritin were independently associated with high disease activity after adjustment for age, sex and disease duration. A two-sided p-value<0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed by the Institutional Ethics Committee of Medinirai Medical College and Hospital, Palamu (approval number to be inserted from the study record). Written informed consent was obtained from all participants. Patient identifiers were not used in the analysis dataset.

RESULTS

A total of 74 patients with RA were included. The mean age was 48.6±11.2 years and 54 (73.0%) were women. Mean disease duration was 6.4±4.3 years. Rheumatoid factor positivity was documented in 59 (79.7%) patients and anti-cyclic citrullinated peptide antibody positivity in 61 (82.4%). Thirty-one patients (41.9%) met the study definition of anemia. The mean DAS28-ESR was 4.61±1.18, indicating that moderate-to-high inflammatory activity was common in the study population. Twenty-one patients (28.4%) were in remission/low activity, 32 (43.2%) had moderate activity and 21 (28.4%) had high activity (Table 1).

The overall mean plasma CRP concentration was 18.7±14.9 mg/L, while mean serum ferritin was 186.4±124.6 ng/mL. Both biomarkers showed a graded increase across disease-activity categories. Mean CRP was 6.8±4.7 mg/L in the remission/low group, 17.3±9.6 mg/L in the moderate group and 33.0±15.2 mg/L in the high-activity group (p<0.001). Mean ferritin increased from 111.5±71.4 ng/mL to 177.8±103.9 ng/mL and 274.8±138.6 ng/mL across the same categories (p<0.001). ESR showed a similar pattern, while hemoglobin decreased with increasing disease activity (Table 2).

Correlation analysis demonstrated a strong positive relationship between CRP and DAS28-ESR (r = 0.69, p<0.001) and a moderate positive relationship between ferritin and DAS28-ESR (r = 0.46, p<0.001). CRP and ferritin were positively correlated with each other (r = 0.41, p<0.001). CRP also correlated with ESR (r = 0.62, p<0.001), while ferritin had a weaker but significant correlation with ESR (r = 0.37, p = 0.001). Hemoglobin was inversely related to disease activity (r = -0.34, p = 0.003) and showed a modest inverse association with ferritin (r = -0.24, p = 0.041). In the exploratory adjusted model, CRP (adjusted OR 1.08 per 1 mg/L increase, 95% CI 1.03-1.14; p = 0.002) and ferritin (adjusted OR 1.006 per 1 ng/mL increase, 95% CI 1.002-1.010; p = 0.004) remained independently associated with high disease activity (Table 3).

Table 1: Baseline Demographic, Clinical and Laboratory Characteristics (n = 74)

Variable	Value
Age, years	48.6±11.2
Female sex	54 (73.0%)
Male sex	20 (27.0%)
Disease duration, years	6.4±4.3
Rheumatoid factor positive	59 (79.7%)
Anti-CCP positive	61 (82.4%)
Hemoglobin, g/dL	11.5±1.6
Anemia	31 (41.9%)
ESR, mm/hour	43.7±20.4
DAS28-ESR	4.61±1.18
Remission/low activity	21 (28.4%)
Moderate activity	32 (43.2%)
High activity	21 (28.4%)
Plasma CRP, mg/L	18.7±14.9
Serum ferritin, ng/mL	186.4±124.6

Table 2: Laboratory Parameters According to Rheumatoid Arthritis Disease Activity

Parameter	Remission/low (n = 21)	Moderate (n = 32)	High (n = 21)	p-value
Plasma CRP, mg/L	6.8±4.7	17.3±9.6	33.0±15.2	<0.001
Serum ferritin, ng/mL	111.5±71.4	177.8±103.9	274.8±138.6	<0.001
ESR, mm/hour	25.8±11.2	42.4±14.8	63.6±18.1	<0.001
Hemoglobin, g/dL	12.3±1.4	11.5±1.5	10.8±1.6	0.003

Values are mean±SD. p-values are from one-way ANOVA across the three disease-activity categories

Table 3: Correlations Among Inflammatory, Iron-Related and Disease-Activity Variables

Variable pair	Correlation coefficient (r)	p-value	Interpretation
CRP vs DAS28-ESR	0.69	<0.001	Strong positive
Ferritin vs DAS28-ESR	0.46	<0.001	Moderate positive
CRP vs ferritin	0.41	<0.001	Moderate positive
CRP vs ESR	0.62	<0.001	Strong positive
Ferritin vs ESR	0.37	0.001	Moderate positive
Hemoglobin vs DAS28-ESR	-0.34	0.003	Inverse
Ferritin vs hemoglobin	-0.24	0.041	Weak inverse

Correlation coefficients are Pearson r values. Statistical significance was set at $p<0.05$

DISCUSSION

The present cross-sectional study evaluated two widely available laboratory markers in 74 patients with RA at a tertiary care hospital in Palamu. Three principal observations emerged. First, both plasma CRP and serum ferritin increased progressively across categories of disease activity. Second, CRP had a stronger correlation with DAS28-ESR than ferritin, supporting its established role as a direct marker of systemic inflammatory activity. Third, ferritin showed a statistically significant but more moderate relationship with disease activity, consistent with its dual biological role as an iron-storage protein and an acute-phase reactant. These findings support a complementary rather than interchangeable role for the two biomarkers.

The strong relationship between CRP and DAS28-ESR is biologically plausible and clinically expected. IL-6-driven hepatic CRP synthesis responds rapidly to inflammatory signaling generated by active synovitis and CRP is embedded in routine RA monitoring strategies. Pope and Choy emphasized that CRP is not merely a laboratory indicator but is linked to multiple inflammatory pathways and comorbidities in RA [5]. Kay and colleagues demonstrated that acute-phase reactant levels and clinical disease activity may be discordant in some patients, yet they also found that acute-phase reactants contribute information that is not completely captured by clinical examination [6]. The current finding of r=0.69 between CRP and DAS28-ESR therefore fits with the broader evidence that CRP is clinically useful while still requiring contextual interpretation.

The magnitude of CRP elevation also deserves attention. Patients with high disease activity had mean CRP values approximately five times those observed in the remission/low-activity group. Graf *et al*. previously reported that clinically relevant CRP elevation can persist even in patients whose RA appears controlled by joint counts or composite disease measures [7]. Persistent systemic inflammation is important because RA is associated with non-articular complications, particularly cardiovascular morbidity. Although the present study did not evaluate cardiovascular outcomes, the observation reinforces the value of identifying substantial inflammatory activity rather than relying solely on symptom burden.

Serum ferritin behaved differently from CRP but still showed a clear activity gradient. Seyhan *et al*. reported that ferritin in RA was associated with acute-phase parameters and disease activation [8]. The current results extend that concept by demonstrating higher mean ferritin across clinically defined disease-activity categories and a moderate correlation with DAS28-ESR. However, ferritin should not be interpreted as a pure inflammatory marker. Mahroum reviewed the broader role of ferritin across iron metabolism, inflammation and autoimmunity, highlighting its complex behavior in immune-mediated disease [9]. Kell and Pretorius similarly argued that circulating ferritin can reflect cellular stress and damage in addition to conventional iron storage [15].

The interaction between inflammation and iron handling is particularly relevant in RA. Tański *et al*. documented frequent iron deficiency in RA and demonstrated relationships between iron-metabolism indices and disease activity [10]. Rheumatoid anemia often represents anemia of inflammation, in which IL-6 induces hepatic hepcidin, limits iron export through ferroportin, reduces intestinal iron absorption and sequesters iron within macrophages and hepatocytes [11]. Consequently, serum iron availability may fall despite normal or elevated ferritin. In a study of RA patients, Khalaf *et al*. found anemia of chronic disease, isolated iron deficiency anemia and mixed patterns, with hepcidin strongly related to ferritin [12]. Nita *et al*. likewise demonstrated that hepcidin is linked simultaneously to inflammation, iron metabolism and erythropoietic variables in RA [13].

These mechanisms explain why the ferritin-DAS28 correlation in the present study was weaker than the CRP-DAS28 correlation. Ferritin is influenced not only by inflammatory intensity but also by baseline iron stores, sex, nutritional status, occult blood loss, liver function, metabolic factors and treatment history. In inflammatory settings, standard ferritin thresholds may therefore misclassify iron status. Dignass *et al*. emphasized that ferritin can be substantially elevated during inflammation and that interpretation of iron deficiency may require additional measures such as transferrin saturation [16]. Similarly, the soluble transferrin receptor can improve detection of iron depletion in selected highly inflammatory RA patients, although its incremental value is not uniform across all patients [14]. Thus, an elevated ferritin concentration in active RA should not automatically be considered evidence of adequate iron stores.

The inverse relationship between hemoglobin and disease activity in the present analysis is also consistent with an inflammatory effect on erythropoiesis. The high-activity group had lower mean hemoglobin and ferritin showed a

modest inverse relationship with hemoglobin. This pattern is compatible with functional iron sequestration, but the cross-sectional design cannot distinguish anemia of inflammation from absolute iron deficiency without a complete iron profile, reticulocyte indices, and, where necessary, soluble transferrin receptor measurement. Ferritin therefore appears most useful when interpreted as part of a panel rather than as a stand-alone test.

From a practical perspective, simultaneous CRP and ferritin measurement may be useful in tertiary-care clinics where clinicians frequently evaluate both inflammatory activity and anemia. A markedly elevated CRP with rising ferritin may strengthen suspicion of active systemic inflammation, whereas low or borderline ferritin despite elevated CRP should raise concern for depleted iron stores. Conversely, disproportionately high ferritin requires consideration of alternative causes such as infection, liver disease, malignancy, or other hyperferritinemic inflammatory syndromes. Clinical context remains essential.

The study has several limitations. Its cross-sectional design identifies associations but cannot establish temporal or causal relationships. The sample was drawn from a single tertiary care hospital and may not represent community-based RA populations. Medication exposure, including glucocorticoids and disease-modifying antirheumatic drugs, can alter inflammatory markers and was not analyzed in treatment-specific subgroups. Ferritin was not accompanied by a complete iron profile in the main analysis, limiting discrimination between absolute and functional iron deficiency. Finally, DAS28-ESR itself contains an acute-phase measure, which may partly strengthen correlations with inflammatory biomarkers. Prospective studies with serial measurements, complete iron indices, hepcidin and treatment-response data would help define whether ferritin adds clinically meaningful predictive information beyond CRP and standard disease-activity scoring.

CONCLUSIONS

Among patients with rheumatoid arthritis attending a tertiary care hospital in Palamu, higher plasma CRP and serum ferritin levels were associated with greater clinical disease activity. CRP showed the strongest relationship with DAS28-ESR, while ferritin demonstrated a moderate association and should be interpreted in the context of inflammation, hemoglobin and iron status. Combined assessment of these readily available biomarkers may support clinical evaluation, but ferritin should not be used in isolation to infer either RA activity or iron sufficiency.

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