Original Article

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Evolution of Ferritin/ C-Reactive Protein (CRP) Ratio Inpatients of Iron Deficiency Anemia With or Without Systemic Inflammation

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ABSTRACT

Background: *The diagnosis of Iron Deficiency Anemia (IDA) is complicated by inflammation, which causes ferritin, a crucial iron-storage indicator, to increase as an acute-phase reactant, obscuring the actual iron status. Simultaneously, inflammatory cytokines inhibit iron uptake and recycling. This results in "Functional iron deficiency" insufficient iron availability despite adequate reserves. To compare Ferritin/ CRP ratio among the patients with raised CRP and low CRP levels.*

Materials and methods: *This Cross-sectional analytical study was conducted in the Department of Biochemistry, IAHS. The study was conducted from January 2024 to March 2025. 90 patients with Iron Deficiency Anemia (IDA) were selected by non-purposive sampling method. It includes 45 IDA patients with high CRP and 45 IDA patients with low CRP. Important variable of this study were Ferritin, CRP, Ferritin/CRP ratio, Hb, Transferrin saturation.*

Results: *Systemic inflammation severely disrupts iron metabolism, causing functional iron deficiency characterized by low available iron and transferrin saturation despite suppressed ferritin, while increasing total iron-binding capacity. The Ferritin/CRP ratio strongly reflects this inflammation-driven iron dysregulation, showing meaningful positive links to improved iron availability, transferrin saturation and hemoglobin levels, alongside a negative association with TIBC. This ratio effectively identifies functional iron deficiency, outperforming ferritin alone by incorporating inflammatory status, demonstrating clinically useful diagnostic performance for distinguishing it from absolute deficiency. Therefore, the Ferritin/CRP ratio serves as a valuable integrated marker of inflammation-mediated iron blockade and its resulting anemia.*

Conclusion: *The Ferritin/CRP ratio serves a substantial clinical benefit by clarifying the diagnostic uncertainty related to impact of inflammation on iron status. It accurately diagnoses functional iron insufficiency, allowing more precise therapeutic targeting than relying solely on ferritin.*

Key words: C-reactive potein; Ferritin; Iron deficiency anemia.

Introduction

Iron deficiency (ID) the predominant cause of anemia, results in Iron-Deficiency Anemia (IDA) succeeded by inflammation that causes anemia of inflammation, sometimes referred to as anemia of chronic disease.[1] IDA is the most common form of anemia worldwide, impacting children, pregnant and nonpregnant premenopausal women and individuals in low- and middle-income nations.[2] Surrogate markers are required in ordinary clinical practice because of the intrusive nature of determining iron storage depletion by the use of stainable iron in bone marrow. Detecting absolute IDA in the general population with a threshold of 30 µg/dl in the absence of inflammatory illness can be accomplished with the help of Serum Ferritin (SF) which is a biomarker that is both very effective and convenient.[3] IDA can be absolute or functional.[4] Absolute IDA is due to low or depleted total body iron stores that causes iron deficient erythropoiesis.[4] In addition to inhibiting the formation of hepcidin and the degradation of ferroportin, absolute ID also increases the amount of iron that is absorbed at the gastroduodenal junction through the use of divalent meta-transporter 1 and the amount of iron that is exported from macrophages and hepatocytes into the circulation.[2,4] A diagnosis of absolute IDA is made when the serum ferritin level is low (≤30 ng/ml) and The Serum Transferrin Saturation (TSAT) level is low (<20%).[5] There is a diagnostic threshold of serum ferritin (≤30 ng/ml) that has a sensitivity of 92% and a specificity of 98% when it comes to diagnosing IDA.[5]

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Functional ID is an imbalance between iron demand and availability despite adequate total body stores that causes iron-restricted erythropoiesis.[2,3,4,5] The etiologies of this condition include inflammation and/or infection that causes anemia of chronic disease or inflammation. These conditions include cancer, autoimmune disease, Chronic kidney disease (CKD), congestive heart failure (CHF), chronic lung disease, Inflammatory bowel disease (IBD) and obesity.[5] Functional IDA is diagnosed at a TSAT < 20% and serum ferritin level <100 mg/ml, the former being more important.[1,2,4,6]

The Kidney Disease Improving Global Outcomes Guideline suggests that patients with chronic kidney disease (CKD) should consider iron therapy when their ferritin level is equal to or less than 500 µg/L and their total serum uric acid (TSAT) level is equal to or less than 30%. However, in recent clinical trials conducted on patients with CKD who were undergoing dialysis, a ferritin level of less than 200 µg/L or a TSAT level of less than 20% was considered to be an indication for iron therapy.[6]

Systemic inflammation has a well-established impact on iron status biomarkers.[7] Studies have shown a correlation between C-reactive protein (CRP) levels and ferritin levels.[8] However, few studies have examined the changes in ferritin and transferrin saturation levels in the presence of both inflammation and ID.[9] Ferritin/CRP ratio is a more accurate depiction of iron status in individuals with iron deficiency anemia, particularly when inflammation is present. This is especially true in cases where treatment is being administered. During times of systemic inflammation, the rise of ferritin, which is an acute-phase reactant, can have the effect of concealing an underlying iron deficit. It is possible to differentiate between functional and absolute iron shortage by adjusting ferritin measurements using the CRP ratio. This allows for more accurate diagnosis and treatment. The purpose of the study is to compare Ferritin / CRP ratio between IDA with raised CRP and low CRP group patients.

Materials and methods

This cross-sectional analytical study was conducted in the Department of Biochemistry of Institute of Applied Health Sciences (IAHS). Duration of the study was from January 2024 to March 2025. After conducting non-probability purposive sampling methods, 90 patients with iron deficiency anemia (IDA) were selected. It includes 45 IDA patients with high CRP and 45 IDA patients with low CRP levels.

Inclusion criteria

- Age >18 years.
- Patients with evidence of IDA.

Exclusion criteria

- Age < 18 years.
- Any history of Malignancy and recent operation.
- Blood transfusion within 3 months.
- Patient on any iron therapy.

Data were entered into Microsoft Excel data sheet to generate a master sheet. After completion of the data entry, the master sheet was fed into Statistical package for social science (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) for processing and analysis.' Mean difference was tested by independent sample t test. Correlation was seen by Pearson's correlation test Sensitivity and specificity was observed by ROC curve analysis.

Results

Table I Comparism of attributes between two groups of respondents (n=90)

Variable	CRP > 10 mg/L (n=45)	CRP ≤ 10 mg/L (n=45)	p-value
Age (years)	45.47±12.23	47.52±15.50	0.49
Serum Iron(µg/dL)	20.84±3.89	36.09±8.01	0.01
TIBC(µg/dL)	478.27±16.69	272.16±87.91	0.01
Transferrin Saturation (TSAT)%	4.73+0.98	13.89+3.07	0.0001
Ferritin (ng/ml)	9.24+2.94	350.59+153.37	0.0006
CRP (mg/L)	3.99+2.52	53.46+31.35	0.0005
Hemoglobin (g/dl)	9.36+1.24	12.02+0.98	0.03
Ferritin/CRP ratio	4.08+3.36	7.73+2.91	0.0001

$p < 0.05$ considered significant and $p < 0.01$ considered highly significant.

Table I shows Systemic inflammation (CRP >10 mg/L) drives a distinct iron deficiency pattern characterized by severely restricted iron availability and utilization, despite paradoxically low ferritin levels. This inflammation-mediated iron blockade manifests as profoundly low circulating iron and transferrin saturation, alongside elevated iron-binding capacity (TIBC), confirming functional iron sequestration (Anemia of Inflammation). The resulting functional iron deficiency directly contributes to anemia, highlighted by significantly lower hemoglobin and reflected in the suppressed Ferritin/CRP ratio. Age variation between two groups was not significant (p 0.49), But all other alterations depict significant and highly significant variations.

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Table II Correlation between serum ferritin and covariates for CRP <10 mg/L

Variable	r
Ferritin/CRP ratio vs iron	0.687**
Ferritin/CRP ratio vs Transferrin saturation	0.712**
Ferritin/CRP ratio vs TIBC	- 0.534**
Ferritin/CRP ratio vs Hb	- 0.053
Ferritin/CRP ratio vs Age	- 0.087

**Correlation is significant at 0.01 level

These correlations strongly validate the Ferritin/CRP ratio as a marker specifically tied to the interplay between inflammation (CRP) and iron metabolism (Iron, TSAT, TIBC). Its lack of correlation with Hb suggests it reflects the underlying dysregulation causing anemia (Functional iron deficiency) rather than the anemia severity itself.

Table III Correlation between serum ferritin and covariates for CRP >10 mg/L

Variable	r
Ferritin/CRP ratio vs iron	0.473**
Ferritin/CRP ratio vs Transferrin saturation	0.501**
Ferritin/CRP ratio vs TIBC	- 0.323**
Ferritin/CRP ratio vs Hb	0.356**
Ferritin/CRP ratio vs Age	0.045

**Correlation is significant at 0.01 level

The Ferritin/CRP ratio demonstrates significant positive correlations with key iron status indicators, moderately associating with higher Serum Iron (r=0.473) and stronger association with higher Transferrin Saturation (r=0.501), confirming its link to improved iron availability. It also shows a significant positive correlation with Hemoglobin (r=0.356), suggesting a meaningful relationship with better anemia status. Conversely, the ratio has a significant negative correlation with TIBC (r=-0.323), aligning with the expected pattern where lower TIBC is associated with a higher ratio. No significant correlation exists with Age (r=0.045), indicating the ratio's associations are independent of this factor. These results validate the Ferritin/CRP ratio as a useful marker reflecting both inflammation-modulated iron metabolism and clinical hemoglobin levels. Iron and Transferrin saturation with Ferritin/CRP ratio reflected positive correlation. But TIBC, Hb and age had negative correlation with the ratio.

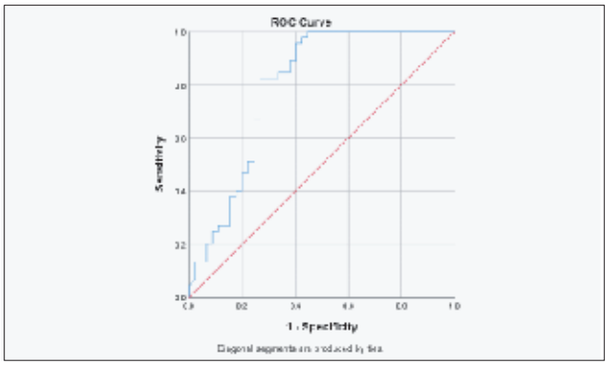

Figure 1 ROC curve analysis

Area Under the Curve				
Test Result Variable(s):				
Area	Std. Error	Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.793	0.050	0.000	0.696	0.891

The Ferritin/CRP ratio demonstrates in functional iron deficiency (FID) at a cutoff of 5.28, with high sensitivity (88.9%). While its moderate specificity (62.2%) indicates some false positives, this ratio outperforms isolated ferritin in distinguishing FID from absolute iron deficiency (AID) by integrating inflammatory status. This supports its clinical utility as a screening tool for inflammation-driven iron dysregulation. The test shows statistically significant and clinically useful diagnostic performance with an AUC of 0.793 (95%CI 0.696- 0.891), meaning it can reasonably distinguish between functional iron deficiency and absolute deficiency.

Discussion

This cross-sectional analytical study is carried out for to observe the Ferritin/CRP ratio as an emerging marker for assessing iron status in the presence of inflammation. It may helps differentiate between true iron deficiency and inflammation-induced changes in ferritin levels.

That elevated CRP (>10 mg/L) signifies significant systemic inflammation and is strongly associated with functional iron deficiency anemia. Despite much lower ferritin (9.24 vs 350.59 ng/mL), the high-CRP group exhibits severe iron deficiency markers, significantly reduced serum iron (20.84 vs 36.09 µg/dL), critically low transferrin saturation (4.73% vs 13.89%) and elevated TIBC (478.27 vs 272.16 µg/dL). This confirms inflammation-driven iron sequestration (Anemia of Inflammation), further evidenced by lower hemoglobin (9.36 vs 12.02 g/dL) and a significantly reduced ferritin/CRP ratio (4.08 vs 7.73). (Table I).

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During inflammatory situations, increased cytokines such as IL-6, IL-1β, IL-10, TNF-α and IFN-γ significantly affect iron homeostasis. IL-6 and IL-1β, in conjunction with bacterial components such as LPS, induce hepatic synthesis of hepcidin—a principal regulator that destroys ferroportin, the iron export protein. This results in diminished gastrointestinal iron absorption and heightened sequestration of iron inside macrophages of the Reticuloendothelial System (RES). Consequently, despite sufficient or increased total body iron, its accessibility for erythropoiesis is limited, leading to functional iron deficiency and anemia of inflammation.[5,13,14]

The findings in (Table II) validate the Ferritin/CRP ratio as a reliable biomarker reflecting the intricate relationship between systemic inflammation and iron metabolism. A notable positive correlation exists between serum iron and transferrin saturation (TSAT), while a negative correlation with TIBC suggests that increasing inflammation-adjusted ferritin levels enhance iron availability, underscoring the ratio's sensitivity to functional iron status rather than solely to confounding inflammatory influences. The comparatively smaller link with hemoglobin indicates that the Ferritin/CRP ratio more accurately represents the pathophysiological mechanisms underlying iron dysregulation, including hepcidin-mediated sequestration and limited iron use, rather than the severity of anemia itself. Fronseca et al. found that anemia was prevalent at 67% and independently correlated with a markedly elevated risk of hospitalization-related mortality (RR 1.82). Iron deficiency (ID) constituted the predominant type (58%), exhibiting a substantial correlation with female gender, heart failure and chronic kidney disease (CKD), whereas anemia was associated with advanced age (• 65 years), active malignancy and mild CKD.[9]

This difference could be attributed to their definitions of functional ID, which had higher thresholds for serum ferritin and Transferrin saturation. In their study, higher cut-offs were used for patients with active cancer, chronic kidney disease and heart failure.

The Ferritin/CRP ratio indicates improved iron status and reduced anemia severity, positively associating with key markers of iron availability and hemoglobin. It aligns inversely with TIBC, reflecting expected iron metabolism patterns, while demonstrating no meaningful relationship with age (Table III).

Weiss, G and Goodnough L T. found progress in comprehending the pathogenesis of Anemia of Chronic Disease (ACD), characterized by iron dysregulation and diminished erythropoiesis.[12]

The Ferritin/CRP ratio, with a cutoff of 5.28, shows high sensitivity (88.9%) and moderate specificity (62.2%) in detecting functional iron deficiency (FID). It outperforms ferritin alone by accounting for inflammation, aiding differentiation from absolute iron deficiency (AID). With an AUC of 0.793 (Figure 1).

The serum ferritin and C-reactive protein showed a linear relationship in elderly patients, with the median age of the training cohort being 76 years. The SF/CRP ratio demonstrated high diagnostic accuracy for predicting iron deficiency (ID) across multiple definitions, with Receiver Operating Characteristic–Area Under the Curve (ROC-AUC) values ranging from 0.85 to 0.92. The optimal ratio threshold of ≤6 provided the best diagnostic performance, as indicated by the Youden index being 0.61. The ratio's diagnostic power was confirmed by validation in a separate cohort with a median age of 72 years. The ROC-AUC was 0.88, with a 95% confidence interval ranging from 0.85 to 0.90. Patients who were at or below the ≤6 threshold had 37.9 times higher chances of having ID, with the 95% confidence interval ranging from 20.3 to 68.9.[13]

Limitation

- **Moderate Specificity:** The ratio's specificity (62.2%) is only moderate, meaning it incorrectly identifies a significant number of individuals without Functional Iron Deficiency (FID) as having false positives.
- **Limited Generalizability/Precision:** The diagnostic performance (AUC 0.793) and its confidence interval indicate the ratio is useful but not definitive. Its accuracy may vary significantly depending on the specific patient population, underlying causes of inflammation, or comorbidities, limiting its broad applicability without further validation.

The Ferritin/CRP ratio, while may be limited by its lack of specificity in the presence of other inflammatory or chronic diseases (e.g. Infections, malignancies, autoimmune disorders, anemia with chronic disease).

Conclusion

The significant difference between the groups with high C-reactive protein and those with low C-reactive protein demonstrates the significant inflammatory impact on conventional iron indicators, particularly ferritin. Even though ferritin levels were much lower in the high-CRP group (9.24 ng/mL vs. 350.59 ng/mL) functional iron shortage was more severe in that group, with lower serum iron, critically low TSAT, higher TIBC and lower Hb. In order to diagnose iron dysregulation effectively, a measure like the Ferritin/CRP ratio is needed to account for inflammation. Inflammation elevates ferritin, which covers true iron status, but it also causes functional iron insufficiency via hepcidin-mediated sequestration.

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Recommendations

Avoid over-reliance on a single moderately specific marker. Secondary tests can exclude false positives (e.g. Absolute iron deficiency or non-iron-related anemias). Inflammatory drivers (e.g. Acute vs. chronic, IL-6 levels) may differentially affect ferritin/CRP, subgroup analysis can improve utility.

Disclosure

The authors declare no conflict of interest.

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