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Serum Ferritin in Inflammatory Bowel Disease: Determinants, Variations, and the Association With Inflammation

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Abstract

Background and aim: Serum ferritin is the first-line marker of iron stores, but it is also an acute-phase reactant. In inflammatory bowel disease (IBD), where iron deficiency and inflammation frequently coexist, the interpretation of ferritin is therefore challenging. The primary objective of this study was to describe the distribution and the clinical and biological determinants of serum ferritin in patients with IBD, and to characterize the association between ferritin and inflammation assessed by C-reactive protein (CRP). Secondary objectives were to evaluate ferritin variations according to CRP both across patients and within patients over time, and to compare the prevalence of suspected iron deficiency according to different guideline-based classification criteria. The analysis of CRP thresholds above which the inflammatory association with ferritin becomes most prominent was an exploratory objective.

Methods: We conducted a retrospective study at the Laboratory of Biochemistry of Mohammed VI University Hospital, Oujda, Morocco, including 150 laboratory panels with simultaneous ferritin and CRP from 119 patients with IBD. Ferritin was measured by chemiluminescent microparticle immunoassay and CRP by immunoturbidimetry. Ferritin levels were compared across clinical and biological subgroups and CRP categories; correlations were stratified by CRP levels, and determinants of log-transformed ferritin were assessed using multivariable linear regression. A patient-level sensitivity analysis restricted to one panel per patient confirmed the primary associations.

Results: Median ferritin was 37.1 ng/mL (interquartile range: 13.8-94.3). Ferritin was lower in women (22.5 vs. 52.3 ng/mL; p=0.006) and in anemic patients (19.9 vs. 42.4 ng/mL; p=0.006), and higher in endoscopically active disease (44.7 vs. 25.7 ng/mL; p=0.049). Ferritin concentrations increased with CRP, from 28.4 ng/mL with CRP ⩽5 mg/L to 110.9 ng/mL with CRP >50 mg/L (p=0.001). Ferritin concentration was ⩾100 ng/mL in 50.0% of panels, compared with CRP >20 mg/L in 18.9% of panels (p<0.001). When CRP was ⩽5 mg/L, ferritin was unrelated to CRP (Spearman's rank correlation coefficient {ρ}=0.03) and correlated with hemoglobin (ρ=0.49; p<0.001); when CRP was >5 mg/L, ferritin correlated with CRP (ρ=0.39; p=0.001) and the relationship with hemoglobin was attenuated (ρ=0.09; p=0.48). In multivariable analysis, CRP, hemoglobin, and endoscopic activity were independent determinants of ferritin. Consequently, 32.5% of inflamed panels had ferritin 30-99 ng/mL, a range that may conceal iron deficiency according to European Crohn's and Colitis Organisation (ECCO) criteria.

Conclusions: In IBD, higher CRP concentrations are associated with higher ferritin values and an attenuation of the relationship between ferritin and iron-related erythropoiesis, particularly when CRP exceeds 10 mg/L (an exploratory finding requiring prospective validation). Ferritin should always be interpreted together with CRP and complemented by markers less influenced by inflammation when CRP is elevated.

Categories: Hematology, Pathology, Internal Medicine
Keywords: acute-phase reactant, c-reactive protein, crohn's disease, ferritin, inflammation, inflammatory bowel disease, iron deficiency, ulcerative colitis

Introduction

Iron deficiency is the most common cause of anemia in inflammatory bowel disease (IBD), and iron deficiency without anemia is even more frequent [1,2]. It results from chronic intestinal blood loss, reduced dietary intake, and impaired duodenal absorption, and its early detection and treatment are recommended in all patients with IBD [3,4]. Serum ferritin is the first-line laboratory test for this purpose because, in the absence of inflammation, its concentration is proportional to body iron stores, and a value below 30 ng/mL is highly specific for iron deficiency [5,6].

Ferritin is, however, also an acute-phase reactant. Interleukin-1, interleukin-6, and tumor necrosis factor-alpha increase ferritin synthesis at the transcriptional and translational levels, independent of iron status [7,8], and serum ferritin may also rise through release from damaged cells [9]. In parallel, interleukin-6 induces hepatic hepcidin, which blocks ferroportin, inhibits intestinal iron absorption, and sequesters iron in macrophages [10,11]. As a result, ferritin reflects both iron stores and inflammation, and a normal value in an inflamed patient does not exclude iron deficiency [5,6].

Guidelines take this effect into account in different ways. The European Crohn's and Colitis Organisation (ECCO) recommends a ferritin threshold of 30 ng/mL in the absence of inflammation and of 100 ng/mL in the presence of inflammation [3]; the World Health Organization (WHO) 2020 guideline proposes thresholds of 15 and 70 ng/mL, respectively [6], and the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project adjusts ferritin continuously according to C-reactive protein (CRP) [12-14]. These recommendations are mostly based on population surveys, and the magnitude of the inflammatory association with ferritin, the CRP levels at which it becomes clinically relevant, and its impact on the relationship between ferritin and erythropoiesis have rarely been described in IBD [15,16].

Materials And Methods

Study design and population

This retrospective, descriptive, and analytical study was conducted at the Laboratory of Biochemistry of Mohammed VI University Hospital, Oujda, Morocco, among patients followed for IBD between July 2021 and August 2023. We included all laboratory panels in which serum ferritin and CRP were measured on the same sample. All IBD patients with at least one simultaneous ferritin and CRP measurement during the study period were eligible, minimizing selection bias. A patient could contribute several panels obtained on different dates. Demographic data, IBD subtype (Crohn's disease {CD} or ulcerative colitis {UC}), complete blood count, and clinical and endoscopic activity were retrieved from laboratory and medical records. Patients with unclassified IBD or an unspecified subtype were included in the overall analysis but not in subtype analyses. Part of this cohort has been included in a separate study evaluating CRP as a marker of endoscopic activity, which is currently under review; the present analysis addresses a distinct question, namely the determinants of serum ferritin and the association between inflammation and its interpretation.

Laboratory methods

Serum ferritin was measured by a chemiluminescent microparticle immunoassay (CMIA) on the Alinity i analyzer of the Alinity ci system (Abbott Park, IL: Abbott Laboratories) and expressed in ng/mL. Serum CRP was measured by a particle-enhanced (latex) immunoturbidimetric assay on the ARCHITECT c-series clinical chemistry analyzer (Abbott Park, IL: Abbott Laboratories) and expressed in mg/L. The complete blood count, including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocyte count, and platelet count, was performed on an automated hematology analyzer (Kobe, Japan: Sysmex Corporation) using ethylenediaminetetraacetic acid (EDTA) whole blood. All assays were performed according to the manufacturers' instructions under routine internal quality control.

Definitions

Ferritin was analyzed as a continuous variable and in the following five categories: <15, 15-29, 30-99, 100-299, and ⩾300 ng/mL. Inflammation was defined as CRP >5 mg/L, and CRP was further categorized as ⩽5, >5-10, >10-50, and >50 mg/L; thresholds of 10 and 20 mg/L were also examined. Anemia was defined according to WHO criteria as Hb <12 g/dL in women and <13 g/dL in men, and microcytosis as MCV <80 fL [17].

To illustrate the consequences of the inflammatory association, iron deficiency was classified by the following four criteria: (1) unadjusted ferritin <30 ng/mL; (2) ECCO criteria (ferritin <30 ng/mL if CRP ⩽5 mg/L, or <100 ng/mL if CRP >5 mg/L) [3]; (3) WHO 2020 criteria (ferritin <15 ng/mL if CRP ⩽5 mg/L, or <70 ng/mL if CRP >5 mg/L) [6]; and (4) Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) regression-adjusted ferritin <30 ng/mL [13]. For the BRINDA approach, ferritin concentrations were adjusted using the following formula:

$$\text{Adjusted } \ln(\text{ferritin}) = \ln(\text{ferritin}) - \beta \times [\ln(\text{CRP}) - \ln(\text{CRP}_{\text{ref}})]$$

Here, β (0.256) represents the regression coefficient of ln(ferritin) on ln(CRP) in the study population, and CRP (0.69 mg/L) represents the CRP reference value, defined as the lowest decile of CRP in the study population. This adjustment was applied only to ferritin measurements for which CRP exceeded the reference value [13].

"Suspected iron deficiency" (referred to as "masked iron deficiency" in some previous reports) was defined for exploratory purposes as ferritin 30-99 ng/mL with CRP >5 mg/L - a range considered normal without accounting for inflammation but compatible with iron deficiency according to ECCO criteria [3]. This designation reflects guideline-based classification and should not be equated with independently confirmed iron deficiency, as no reference-standard iron-status markers were available (Limitations).

Disease activity

Clinical activity was assessed using the Harvey-Bradshaw Index (HBI) in CD and the partial Mayo score in UC [18,19]; clinical remission was defined as HBI ⩽4 or partial Mayo score ⩽1 [20]. Endoscopic activity was assessed using the Crohn's Disease Endoscopic Index of Severity (CDEIS) in CD and the Mayo endoscopic subscore in UC; endoscopic remission was defined as CDEIS <3 or Mayo endoscopic subscore 0-1 [19,21]. Clinical scores were collected at the time of laboratory sampling. Endoscopic assessments were retrieved from the most recent available record and were not necessarily performed on the same day as laboratory sampling.

Statistical analysis

Quantitative variables are expressed as median (interquartile range {IQR}) and categorical variables as numbers and percentages. Groups were compared with the Mann-Whitney U test or the Kruskal-Wallis test. Proportions were compared with Pearson's chi-squared test, reported as χ^2 (degrees of freedom, N), p-value, and effect size (Cramér's V or ϕ). When more than 20% of expected cell counts were below 5, a Monte Carlo exact p-value based on 20,000 permutations was also calculated. Correlations were assessed with Spearman's rank correlation coefficient (ρ) in all panels and after stratification by CRP (⩽5, >5, and >10 mg/L). Differences between Spearman's correlations across strata were formally assessed using Fisher's z-transformation to test whether the relationships between ferritin and hemoglobin or MCV differed significantly between inflamed and non-inflamed panels.

Determinants of ferritin were assessed by multivariable linear regression of natural log-transformed ferritin on natural log-transformed CRP, Hb, sex, and age (model 1), with endoscopic activity added in the subset with endoscopic assessment (model 2) and IBD subtype added in a third model; coefficients were back-transformed into percentage changes in ferritin. An interaction term between ln(CRP) and Hb was tested to formally evaluate whether the association between CRP and ferritin differed according to hemoglobin. Regression model diagnostics (residual plots, Cook's distance) were performed to verify that no single observation or small cluster of patients unduly influenced the results. A restricted cubic spline of ln(CRP) on ln(ferritin) was fitted to characterize the shape of their relationship and to evaluate the plausibility of threshold effects; the 10 mg/L CRP threshold reported in the Results section should be regarded as an exploratory, data-derived observation that requires prospective validation in an independent cohort.

The primary analysis was conducted on all 150 panels. A patient-level sensitivity analysis restricted to each patient's first available panel (n=119) was performed to verify that the main associations hold when statistical independence of observations is ensured. Because some patients contributed multiple panels, we additionally report the multivariable regression with heteroskedasticity-consistent standard errors clustered by patient (HC3 estimator). A random-intercept mixed-effects model with patient as the grouping variable was fitted as a supplementary analysis; given the small number of patients with three or more panels, random-effect estimates should be interpreted with caution.

Within-patient variations were analyzed in patients with at least two panels by comparing the first and last panels as follows: the change in ln(ferritin) was correlated with the change in ln(CRP), and ferritin changes were described in patients whose CRP increased at least two-fold, decreased at least two-fold, or remained within this range. Prevalence of suspected iron deficiency according to the definitions was compared with the continuity-corrected McNemar chi-squared test, with the absolute difference in prevalence as effect size.

No correction for multiple comparisons was applied; the numerous subgroup analyses and comparisons should be considered exploratory, and findings from these analyses require independent replication. A $p<0.05$ was considered statistically significant for the primary analyses. Analyses were performed with Python version 3.13 (Wilmington, DE: Python Software Foundation). Missing data arose primarily from absent endoscopic (n=49 panels) or clinical (n=14 panels) assessments; laboratory data were complete. An available-case approach was used, and each analysis is reported with its effective sample size.

Results

Characteristics of the study population

The study included 150 panels from 119 patients. A total of 31 patients contributed more than one panel (range: 2-4; median: 1). The median age of patients was 35 years (IQR: 27.5-44; range: 15-74 years), and 63 patients (52.9%) were women. Crohn's disease (CD) accounted for 82 (68.9%) patients, ulcerative colitis (UC) for 28 (23.5%) patients, and unclassified or unspecified IBD for nine (7.6%) patients. CRP was >5 mg/L in 77 (51.3%) panels, anemia was present in 58/147 (39.5%), and microcytosis in 30/147 (20.4%) panels. An endoscopic assessment was available for 101 panels (44 active) and a clinical assessment for 136 panels (33 active) (Table *1*).

Parameters	Value
Ferritin (ng/mL), median (IQR)	37.1 (13.8-94.3)
Ferritin <15 (ng/mL), n/N (%)	40/150 (26.7)
Ferritin 15-29 (ng/mL), n/N (%)	27/150 (18.0)
Ferritin 30-99 (ng/mL), n/N (%)	46/150 (30.7)
Ferritin 100-299 (ng/mL), n/N (%)	31/150 (20.7)
Ferritin ≥300 (ng/mL), n/N (%)	6/150 (4.0)
CRP (mg/L), median (IQR)	5.29 (1.89-12.74)
CRP >5 mg/L, n/N (%)	77/150 (51.3)
Hb (g/dL), median (IQR)	12.6 (11.7-14.4)
Anemia, n/N (%)	58/147 (39.5)
MCV (fL), median (IQR)	86.3 (81.5-90.0)
Microcytosis (MCV <80 fL), n/N (%)	30/147 (20.4)
MCHC (g/dL), median (IQR)	32.5 (31.4-33.5)
Platelets (×10⁹/L), median (IQR)	275 (230-338)

TABLE 1: Biological characteristics of the 150 panels.

Data are presented as median (IQR) or n/N (%).

Hb: hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration

Distribution and determinants of ferritin

Ferritin was widely dispersed, ranging from 1.95 to 1061.9 ng/mL, with a right-skewed distribution (mean: 78.8 ng/mL; geometric mean: 34.3 ng/mL). Overall, 67 panels (44.7%) had ferritin <30 ng/mL, and 37 (24.7%) had ferritin ⩾100 ng/mL (Table *1*). Ferritin was lower in women than in men (22.5 vs. 52.3 ng/mL; p=0.006) and differed according to the age group, with the lowest values in patients aged 30-45 years (p=0.028). It was lower in anemic than in non-anemic patients (19.9 vs. 42.4 ng/mL; p=0.006) and higher in endoscopically active than in inactive disease (44.7 vs. 25.7 ng/mL; p=0.049). Ferritin did not differ between CD and UC (p=0.62) or according to clinical activity (p=0.86) (Table *2*).

Variables		n	Ferritin (ng/mL)	p-Value
Gender, median (IQR)	Women	73	22.5 (9.0-53.1)	0.006
	Men	77	52.3 (20.6-118.9)	
Age, median (IQR)	Age <30 years	52	38.4 (16.2-110.3)	0.028
	Age 30-45 years	65	24.6 (8.9-81.5)	
	Age >45 years	33	50.5 (25.7-113.6)	
Disease type, median (IQR)	CD	104	33.6 (13.4-104.8)	0.62
	UC	36	42.0 (18.0-90.1)	
Clinical disease activity, median (IQR)	Clinically inactive	103	37.1 (16.0-97.9)	0.86
	Clinically active	33	41.7 (12.5-93.8)	
Endoscopic disease activity, median (IQR)	Endoscopically inactive	57	25.7 (13.6-70.8)	0.049
	Endoscopically active	44	44.7 (18.5-99.3)	
Anemia status, median (IQR)	No anemia	89	42.4 (20.6-104.2)	0.006
	Anemia	58	19.9 (6.2-77.9)	

TABLE 2: Serum ferritin according to clinical and biological characteristics.

Hb: hemoglobin; CD: Crohn's disease; UC: ulcerative colitis

Ferritin concentrations according to CRP

Ferritin was positively associated with CRP (ρ=0.27; p=0.001). Median ferritin was 28.4 ng/mL with CRP ⩽5 mg/L and 21.5 ng/mL with CRP >5-10 mg/L, then increased to 67.0 ng/mL with CRP >10-50 mg/L and 110.9 ng/mL with CRP >50 mg/L (Kruskal-Wallis p=0.001) (Table *3*, Figure *1*, panel A). The distribution of ferritin categories differed across CRP categories (χ^2 {12, N=150}=23.05, p=0.027, Cramér's V=0.23; Monte Carlo exact p=0.026) - the proportion of panels with ferritin ⩾100 ng/mL was 19.2% with CRP ⩽5 mg/L, 17.6% with CRP >5-10 mg/L, 33.3% with CRP >10-50 mg/L, and 60.0% with CRP >50 mg/L. The proportion with ferritin <30 ng/mL decreased from 52.1% to 10.0% across the same categories.

CRP (mg/L)	n	Ferritin (ng/mL), median (IQR)	Ferritin <30 ng/mL (%)	Ferritin ≥100 ng/mL (%)
≤5	73	28.4 (7.2-81.0)	52.1	19.2
>5-10	34	21.5 (12.7-58.8)	58.8	17.6
>10-50	33	67.0 (31.3-119.3)	24.2	33.3
>50	10	110.9 (60.5-137.2)	10.0	60.0
p-Value (categories)	-	0.001	-	$\chi^2(12)=23.05$, p=0.027, V=0.23 (all ferritin categories)
>5 vs. ≤5	77 vs. 73	50.0 (18.0-113.6) vs. 28.4 (7.2-81.0), p=0.024	37.7 vs. 52.1	29.9 vs. 19.2; $\chi^2(1)=2.31$, p=0.13, φ=0.12
>10 vs. ≤10	43 vs. 107	85.1 (37.5-123.2) vs. 25.7 (9.6-69.2), p<0.001	20.9 vs. 54.2	39.5 vs. 18.7; $\chi^2(1)=7.17$, p=0.007, φ=0.22
>20 vs. ≤20	28 vs. 122	98.3 (50.0-134.9) vs. 28.3 (12.7-72.6), p<0.001	14.3 vs. 51.6	50.0 vs. 18.9; $\chi^2(1)=11.89$, p<0.001, φ=0.28

TABLE 3: Serum ferritin according to CRP category and CRP threshold.

P-values compare ferritin (Kruskal-Wallis or Mann-Whitney test) and the proportion of ferritin ≥100 ng/mL (Pearson's chi-squared test, with Cramér's V or φ as effect size) across groups.

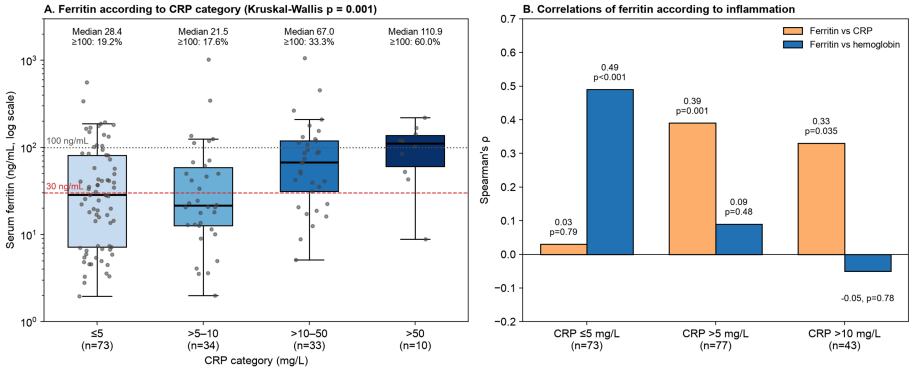


FIGURE 1: Effect of inflammation on serum ferritin.

(A) Serum ferritin according to CRP category (log scale; boxes show median and IQR, whiskers extend to 1.5 × IQR, dots represent individual panels). Dashed and dotted lines indicate ferritin thresholds of 30 and 100 ng/mL. (B) Spearman's correlation coefficients for ferritin with CRP and hemoglobin according to CRP stratum.

The association between CRP and ferritin strengthened with higher CRP levels. Panels with CRP >5 mg/L had higher ferritin than those with CRP ⩽5 mg/L (50.0 vs. 28.4 ng/mL; p=0.024), but the proportion with ferritin ⩾100 ng/mL did not differ significantly (29.9% vs. 19.2%; $\chi^2\{1, N=150\}=2.31$, p=0.13, $\phi=0.12$). With a threshold of 10 mg/L, median ferritin was more than three times higher (85.1 vs. 25.7 ng/mL; p<0.001), and ferritin ⩾100 ng/mL was twice as frequent (39.5% vs. 18.7%; $\chi^2\{1, N=150\}=7.17$, p=0.007, $\phi=0.22$). With a threshold of 20 mg/L, half of the panels had ferritin ⩾100 ng/mL (50.0% vs. 18.9%; $\chi^2\{1, N=150\}=11.89$, p<0.001, $\phi=0.28$) (Table *3*). These observations are consistent with a more pronounced inflammatory association at higher CRP values; the 10 mg/L threshold should be interpreted as an exploratory, data-derived finding (Methods).

Attenuation of the relationship between ferritin and erythrocyte indices by inflammation

In all panels, ferritin was positively associated with Hb ($\rho=0.29$; p<0.001), mean corpuscular volume (MCV) ($\rho=0.23$; p=0.005), and mean corpuscular hemoglobin concentration (MCHC) ($\rho=0.26$; p=0.002). Stratification by CRP revealed two distinct patterns (Table *4*, Figure *1*, panel B). In panels without

inflammation (CRP ⩽5 mg/L), ferritin was not related to CRP (ρ=0.03; p=0.79) but was strongly associated with Hb (ρ=0.49; p<0.001), MCV (ρ=0.24; p=0.046), and MCHC (ρ=0.35; p=0.003). In inflamed panels (CRP >5 mg/L), ferritin was associated with CRP (ρ=0.39; p=0.001) and the relationship with Hb was attenuated and non-significant (ρ=0.09; p=0.48); MCV remained marginally associated (ρ=0.26; p=0.028). With CRP >10 mg/L, ferritin remained associated with CRP (ρ=0.33; p=0.035) but was unrelated to Hb, MCV, or MCHC. Formal Fisher's z-tests confirmed that the Spearman's correlation between ferritin and Hb differed significantly between the CRP ⩽5 and CRP >5 mg/L strata (z=2.94; p=0.003), and between the CRP ⩽5 and CRP >10 mg/L strata (z=3.35; p<0.001).

Stratum	n	CRP, Spearman's ρ (p-Value)	Hb, Spearman's ρ (p-Value)	MCV, Spearman's ρ (p-Value)	MCHC, Spearman's ρ (p-Value)
All panels	150	0.27 (0.001)	0.29 (<0.001)	0.23 (0.005)	0.26 (0.002)
CRP ≤5 mg/L	73	0.03 (0.79)	0.49 (<0.001)	0.24 (0.046)	0.35 (0.003)
CRP >5 mg/L	77	0.39 (0.001)	0.09 (0.48)	0.26 (0.028)	0.22 (0.07)
CRP >10 mg/L	43	0.33 (0.035)	-0.05 (0.78)	0.04 (0.83)	0.14 (0.39)

TABLE 4: Spearman's correlations of serum ferritin according to CRP.

Hb: hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration

The same pattern was observed in anemic panels. Among the 29 anemic panels with CRP ⩽5 mg/L, median ferritin was 7.4 ng/mL (IQR: 5.0-37.1), 20 (69.0%) had ferritin <30 ng/mL, and three (10.3%) had ferritin ⩾100 ng/mL. Among the 29 anemic panels with CRP >5 mg/L, median ferritin was 41.0 ng/mL (IQR: 11.6-118.9; p=0.026), 13 (44.8%) had ferritin <30 ng/mL, and eight (27.6%) had ferritin ⩾100 ng/mL. Similarly, in microcytic panels, median ferritin was 4.5 ng/mL with CRP ⩽5 mg/L (n=12) and 19.1 ng/mL with CRP >5 mg/L (n=18), and ferritin was ⩾30 ng/mL in 4/12 and 8/18 panels, respectively.

Multivariable analysis

In multivariable analysis (model 1; n=147; R^2=0.18), ln(CRP) and Hb were independently associated with ferritin as follows: each doubling of CRP was associated with a 19.4% higher ferritin (95% CI: 8.6-31.4; p<0.001), and each 1 g/dL increase in Hb with a 15.1% higher ferritin (95% CI: 5.4-25.7; p=0.002). After adjustment, sex and age were no longer significantly associated with ferritin. In panels with endoscopic assessment (model 2; n=99; R^2=0.23), endoscopically active disease was associated with a two-fold higher ferritin (+101.1%; 95% CI: 20.9-234.7; p=0.007), independently of CRP (+17.7% per doubling; p=0.005) and Hb (+17.3% per g/dL; p=0.005) (Table *5*). IBD subtype was not associated with ferritin (-14.0%; p=0.55). The interaction term between ln(CRP) and Hb was not statistically significant (p=0.18), suggesting that the data do not provide strong evidence for effect modification, although the study may be underpowered to detect a modest interaction. The models explained 18-23% of ferritin variability, indicating that substantial unexplained variability remains. Results of the patient-level sensitivity analysis (n=119, one panel per patient) and the multivariable regression with cluster-robust standard errors were consistent with the primary analysis; the direction, magnitude, and statistical significance of the associations were preserved (data not shown in detail; data are available upon reasonable request from the corresponding author).

Variables	Model 1 (n=147)	p-Value	Model 2 (n=99)	p-Value
CRP (per doubling), percentage change in ferritin (95% CI)	+19.4 (8.6-31.4)	<0.001	+17.7 (5.0-31.8)	0.005
Hb (per 1 g/dL), percentage change in ferritin (95% CI)	+15.1 (5.4-25.7)	0.002	+17.3 (5.0-31.0)	0.005
Male sex, percentage change in ferritin (95% CI)	+25.3 (-18.4 to 92.5)	0.30	+23.2 (-26.9 to 107.7)	0.43
Age (per year), percentage change in ferritin (95% CI)	+1.2 (-0.5 to 2.9)	0.17	+1.0 (-0.9 to 3.0)	0.30
Endoscopically active disease, percentage change in ferritin (95% CI)	-	-	+101.1 (20.9-234.7)	0.007
R^2	0.18	-	0.23	-

TABLE 5: Multivariable linear regression of log-transformed serum ferritin.

Conclusions for this subgroup should be interpreted with caution given the limited sample size (n=10).

Hb: hemoglobin

Within-patient variations (exploratory analysis)

A total of 23 patients had at least two panels (54 panels). Between the first and last panels, the change in ln(ferritin) tended to correlate with the change in ln(CRP) (ρ=0.41; p=0.056), whereas it was not correlated with the change in Hb (ρ=0.17; p=0.46). This analysis is exploratory and did not reach statistical significance; its results may be explained by sampling variability, unrecorded treatment changes, or both. In five patients whose CRP increased at least two-fold, median ferritin increased by 93.6% (from 33.8 to 73.2 ng/mL). In six patients whose CRP decreased at least two-fold, median ferritin decreased by 74.7% (from 64.9 to 10.3 ng/mL). In 12 patients with stable CRP, the median change in ferritin was +19.8%.

Consequences for the classification of iron deficiency

Among the 77 inflamed panels, 29 (37.7%) had ferritin <30 ng/mL, 25 (32.5%) had ferritin 30-99 ng/mL, and 23 (29.9%) had ferritin ⩾100 ng/mL. The 25 panels with ferritin 30-99 ng/mL represent "suspected iron deficiency" according to ECCO criteria (Definitions). The estimated prevalence of suspected iron deficiency was 44.7% with unadjusted ferritin <30 ng/mL, 47.3% with the WHO 2020 criteria, 61.3% with the ECCO criteria, and 62.7% with BRINDA-adjusted ferritin. Compared with unadjusted ferritin, the ECCO criteria reclassified 25 panels as suspected iron deficient, and none in the opposite direction (McNemar χ^2{1, N=150}=23.04, p<0.001; absolute difference 16.7 percentage points), and BRINDA adjustment reclassified 27 panels (McNemar χ^2{1, N=150}=25.04, p<0.001; difference 18.0 points). These differences reflect changes in classification criteria, not independently confirmed iron deficiency diagnoses.

Unadjusted suspected iron deficiency appeared less frequent in endoscopically active than inactive disease (31.8% vs. 56.1%; χ^2{1, N=101}=5.92, p=0.015, ϕ=0.24), but this difference was no longer observed after ECCO adjustment (54.5% vs. 68.4%; χ^2{1, N=101}=2.04, p=0.15, ϕ=0.14). Suspected iron deficiency (ferritin 30-99 ng/mL with CRP >5 mg/L) was more frequent in UC than in CD (10/36, 27.8% vs. 13/104, 12.5%; χ^2{1, N=140}=4.55, p=0.033, ϕ=0.18). Among anemic panels, the proportion classified as suspected iron deficient increased from 56.9% to 70.7% with the ECCO criteria.

Discussion

This study shows that serum ferritin in IBD is associated with both iron status and inflammatory activity, and that inflammation becomes the dominant determinant once CRP is elevated. Ferritin concentrations increased with CRP, especially above 10 mg/L (an exploratory observation), and inflammation attenuated the relationship between ferritin and hemoglobin and erythrocyte indices. The association was independent of Hb and disease activity in multivariable analysis and was also suggested within patients over time in an exploratory analysis. As a consequence, about one-third of inflamed panels had ferritin values that appeared normal by unadjusted criteria but were consistent with iron deficiency according to ECCO thresholds.

Ferritin as an acute-phase reactant in IBD

The four-fold difference in median ferritin between the lowest and highest CRP categories illustrates the acute-phase behavior of ferritin in IBD. Ferritin synthesis is upregulated by interleukin-1, interleukin-6, and tumor necrosis factor-alpha through transcriptional and translational mechanisms independent of iron [7,8], while hepcidin traps iron in macrophages and hepatocytes, where it is stored as ferritin [10,11]. In addition, serum ferritin may partly derive from cellular damage, which further dissociates it from iron stores in inflammatory states [9]. In our multivariable model, each doubling of CRP was associated with

approximately 19% higher ferritin, corresponding to an approximately 80% increase for a 10-fold rise in CRP (e.g., from 5 to 50 mg/L). The BRINDA project has shown that the inflammatory association with ferritin is substantial and should be estimated in each population; our data quantify this association in a cohort of patients with IBD and are consistent with a dose-dependent effect of inflammation on ferritin levels [13].

CRP and the relationship with ferritin: an exploratory threshold observation

An exploratory finding of this study is that the association between CRP and ferritin appeared non-linear. Ferritin concentrations were similar in panels with CRP ⩽5 mg/L and >5-10 mg/L, and increased more markedly above 10 mg/L, with more than one-third of panels exceeding 100 ng/mL above this threshold and half above 20 mg/L. This pattern is consistent with the dose-dependent induction of ferritin by cytokines and with BRINDA data showing that the inflammatory association with ferritin increases with the degree of inflammation [7,13,14]. However, the 10 mg/L threshold was not predefined and emerged from the data; it should not be applied clinically without prospective validation in an independent cohort. In practice, the results suggest that mild CRP elevations may coexist with ferritin values that still partly reflect iron stores, whereas ferritin values obtained with CRP >10 mg/L may warrant more cautious interpretation. The ECCO threshold of 100 ng/mL is applied as soon as CRP exceeds 5 mg/L; our data are consistent with this recommendation being of greatest clinical relevance in patients with moderate to high CRP [3].

Attenuation of the relationship between ferritin and erythropoiesis

The stratified correlations provide the most direct evidence of the confounding of ferritin by inflammation. In the absence of inflammation, ferritin behaved as an iron-store marker as follows: it was independent of CRP and strongly associated with Hb, MCV, and MCHC. In inflamed panels, ferritin was associated with CRP and the relationship with Hb was attenuated and no longer statistically significant; with CRP >10 mg/L it was unrelated to any erythrocyte index. Fisher's z-tests confirmed that the correlation between ferritin and Hb differed significantly between inflamed and non-inflamed strata. Ferritin was therefore less reflective of the iron available for erythropoiesis in inflamed patients [4,5]. This was also apparent in anemic patients: anemic panels without inflammation had a median ferritin of 7.4 ng/mL, typical of iron deficiency anemia, whereas anemic panels with inflammation had a median ferritin of 41.0 ng/mL, and more than one-quarter had ferritin ⩾100 ng/mL. This profile is consistent with the mixed picture of iron deficiency and anemia of inflammation frequently described in IBD, in which ferritin alone cannot distinguish between absolute and functional iron deficiency [10,16,22,23].

Disease activity, sex, and within-patient variations

Ferritin was higher in endoscopically active disease, and this association persisted after adjustment for CRP and Hb, with a two-fold higher ferritin in active disease. This suggests that mucosal inflammation may be associated with higher ferritin beyond what is captured by CRP, possibly through local cytokine production or through inflammatory processes poorly reflected by CRP in some patients, particularly with UC [15,16]. Paradoxically, patients with active disease, who have the greatest blood losses and most impaired iron absorption, had higher ferritin values and therefore an apparently lower prevalence of unadjusted suspected iron deficiency [2,3]. In contrast, clinical activity was not associated with ferritin, consistent with the poor correlation between symptoms and mucosal inflammation.

Women had lower ferritin than men, consistent with menstrual losses and previous reports, but this difference was no longer significant after adjustment for CRP, Hb, and age, suggesting that it was partly explained by these factors, although the limited sample size may also have reduced statistical power [1,23].

The within-patient analysis, although limited to 23 patients and exploratory ($p=0.056$ for the correlation between changes in ln{CRP} and ln{ferritin}), is consistent with a directional association as follows: ferritin nearly doubled when CRP increased and fell by three-quarters when CRP decreased. These observations should not be interpreted causally - iron supplementation, treatment changes, and other factors were not recorded and may have contributed to these variations. They are best regarded as hypothesis-generating and warrant prospective evaluation.

Consequences for clinical and laboratory practice

Because higher CRP concentrations are associated with higher ferritin, a substantial proportion of inflamed patients had ferritin values in the apparently normal range despite possible iron deficiency, and the estimated prevalence of suspected iron deficiency increased from 44.7% to more than 60% when inflammation was taken into account. These results support the systematic co-measurement of CRP with ferritin in IBD [3,15]. From a laboratory perspective, ferritin results could be accompanied by an interpretive comment indicating that values up to 100 ng/mL may be consistent with iron deficiency when CRP is elevated, particularly above 10 mg/L (exploratory threshold). In inflamed patients, markers less influenced by inflammation, such as transferrin saturation or soluble transferrin receptor, should complement ferritin [3,24], and intravenous iron should be considered because hepcidin reduces oral iron absorption [3,25]. Conversely, ferritin measured during a flare should be repeated after the resolution of inflammation.

Limitations

This study has several limitations. Its retrospective, single-center design may limit the generalizability of the findings to other populations and healthcare settings, and unmeasured case-mix differences cannot be excluded. Because 31 patients contributed more than one panel, observations were not fully independent; although the patient-level sensitivity analysis (n=119), the regression with cluster-robust standard errors, and the random-intercept mixed-effects model yielded consistent results, within-patient correlation may have influenced some p-values in the exploratory subgroup analyses. Reference-standard iron-status markers (transferrin saturation, soluble transferrin receptor, hepcidin, and bone-marrow iron) were not available; therefore, the true iron status of each patient could not be established. All iron-deficiency estimates reflect classification according to guideline-defined ferritin thresholds, and suspected iron deficiency as defined here may include patients who are not truly iron deficient. In addition, iron supplementation (particularly intravenous iron, which acutely increases ferritin), blood transfusions, IBD-directed treatments (corticosteroids, immunomodulators, and biologics), concurrent infections, hepatic comorbidities, disease location, and dietary intake were not systematically recorded, and their influence on ferritin concentrations, particularly in the within-patient analysis, cannot be excluded.

Several analyses were also limited by sample size. The CRP >50 mg/L subgroup comprised only 10 panels, and point estimates in this stratum should be interpreted with particular caution. The within-patient analysis included only 23 patients, and the correlation between changes in CRP and ferritin did not reach statistical significance (ρ=0.41; p=0.056); these results are exploratory and do not allow causal inference. No correction for multiple comparisons was applied, and some statistically significant results among the numerous subgroup and stratified analyses may represent false-positive findings. The multivariable models explained only 18%-23% of ferritin variability, indicating that factors not captured by the available covariates substantially influence ferritin concentrations. Finally, the CRP threshold of 10 mg/L, above which the inflammatory association appeared more pronounced, was not predefined and emerged from exploratory analyses; it should not be adopted as a clinical cutoff without prospective validation. These findings should therefore be replicated in larger prospective studies with independent observations and comprehensive iron-status assessment.

Conclusions

In patients with IBD, serum ferritin is associated with both iron status and inflammation. Higher CRP concentrations are associated with higher ferritin values, particularly above 10 mg/L, an exploratory threshold requiring prospective validation, independently of hemoglobin and disease activity; inflammation attenuates the relationship between ferritin and hemoglobin and erythrocyte indices. As a result, apparently normal ferritin values in inflamed patients may be consistent with iron deficiency according to guideline-based criteria. Ferritin should always be interpreted together with CRP, with particular caution when CRP is elevated, and should be complemented by markers less influenced by inflammation, such as transferrin saturation or soluble transferrin receptor. Prospective studies including transferrin saturation, soluble transferrin receptor, and hepcidin are needed to define inflammation-adjusted ferritin thresholds and to confirm the clinical relevance of the exploratory CRP threshold reported here.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Biomedical Research Ethics Committee, Faculty of Medicine and Pharmacy of Oujda, Mohammed First University, Oujda, Morocco issued approval #2026. The study was conducted in

accordance with the Declaration of Helsinki. Data were extracted from laboratory and medical records and fully anonymized before analysis. Given the retrospective design and the use of anonymized data, the requirement for informed consent was waived. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Filmann N, Rey J, Schneeweiss S, et al.: Prevalence of anemia in inflammatory bowel diseases in european countries: a systematic review and individual patient data meta-analysis. Inflamm Bowel Dis. 2014, 20:936-45. 10.1097/01.MIB.0000442728.74340.fd
2. Gisbert JP, Gomollón F: Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol. 2008, 103:1299-307. 10.1111/j.1572-0241.2008.01846.x
3. Dignass AU, Gasche C, Bettenworth D, et al.: European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015, 9:211-22. 10.1093/ecco-jcc/jju009
4. Camaschella C: Iron-deficiency anemia. N Engl J Med. 2015, 372:1832-43. 10.1056/NEJMra1401038
5. Daru J, Colman K, Stanworth SJ, De La Salle B, Wood EM, Pasricha SR: Serum ferritin as an indicator of iron status: what do we need to know?. Am J Clin Nutr. 2017, 106:1634-9. 10.3945/ajcn.117.155960
6. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations . (2020). https://www.who.int/publications/i/item/9789240000124.
7. Torti FM, Torti SV: Regulation of ferritin genes and protein. Blood. 2002, 99:3505-16. 10.1182/blood.v99.10.3505
8. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV: Serum ferritin: past, present and future. Biochim Biophys Acta. 2010, 1800:760-9. 10.1016/j.bbagen.2010.03.011
9. Kell DB, Pretorius E: Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014, 6:748-73. 10.1039/c3mt00347g
10. Weiss G, Goodnough LT: Anemia of chronic disease. N Engl J Med. 2005, 352:1011-23. 10.1056/NEJMra041809
11. Ganz T: Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation . Blood. 2003, 102:783-8. 10.1182/blood-2003-03-0672
12. Suchdev PS, Namaste SM, Aaron GJ, Raiten DJ, Brown KH, Flores-Ayala R: Overview of the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Adv Nutr. 2016, 7:349-56. 10.3945/an.115.010215
13. Namaste SM, Rohner F, Huang J, et al.: Adjusting ferritin concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr. 2017, 106:359-71. 10.3945/ajcn.116.141762
14. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP: Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. Am J Clin Nutr. 2010, 92:546-55. 10.3945/ajcn.2010.29284
15. Stein J, Dignass AU: Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. Ann Gastroenterol. 2013, 26:104-13.
16. Gasche C, Lomer MC, Cavill I, Weiss G: Iron, anaemia, and inflammatory bowel diseases. Gut. 2004, 53:1190-7. 10.1136/gut.2003.035758
17. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity . (2011). https://iris.who.int/items/b8bdcf8f-1212-4eca-93fc-373328dce41a.
18. Harvey RF, Bradshaw JM: A simple index of Crohn's-disease activity . Lancet. 1980, 315:10.1016/s0140-6736(80)92767-1
19. Schroeder KW, Tremaine WJ, Ilstrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987, 317:1625-9. 10.1056/NEJM198712243172603
20. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P: Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clin Gastroenterol Hepatol. 2010, 8:357-63. 10.1016/j.cgh.2010.01.001
21. Mary JY, Modigliani R: Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989, 30:983-9. 10.1136/gut.30.7.983
22. Bergamaschi G, Di Sabatino A, Albertini R, et al.: Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-alpha treatment. Haematologica. 2010, 95:199-205. 10.3324/haematol.2009.009985
23. Antunes CV, Neto AE, Nascimento CR, et al.: Anemia in inflammatory bowel disease outpatients: prevalence, risk factors, and etiology. Biomed Res Int. 2015, 2015:10.1155/2015/728925
24. Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG: Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. Clin Chem. 1998, 44:45-51. 10.1093/clinchem/44.1.45
25. Kulnigg S, Gasche C: Systematic review: managing anaemia in Crohn's disease . Aliment Pharmacol Ther. 2006, 24:1507-23. 10.1111/j.1365-2036.2006.03146.x