Jurnal Media Penelitian dan Pengembangan Kesehatan

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

The role of serum ferritin as a biomarker of iron and inflammation in anemia: a systematic literature review

Peran Serum Ferritin sebagai Biomarker Besi dan Inflamasi pada Anemia: Systematic Literature Review

Rafi Andyah Arum Kedaton[1*], Nabila Sinta Devi[1], Kusworini Kusworini[2], Diadjeng Setya Wardani[3]

[1]Program Studi Magister Kebidanan, Fakultas Kedokteran, Universitas Brawijaya, Malang, Indonesia

[2]Departemen Patologi Klinik, Fakultas Kedokteran, Universitas Brawijaya, Malang, Indonesia

[3]Departemen Kebidanan, Fakultas Kedokteran, Universitas Brawijaya, Malang, Indonesia

*Email: rafiandyah@student.ub.ac.id

ABSTRACT

***Background**: Anemia remains a major global health concern, particularly in low- and middle-income countries where distinguishing Iron Deficiency Anemia (IDA)[1] from Anemia of Inflamation (AI)[2] remains diagnostically challenging. Hemoglobin alone cannot differentiate these conditions, necessitating more specific biomarkers. Serum ferritin, the primary iron-storage protein, reflects body iron reserves but is also elevated during inflammation through interleukin-6-mediated hepcidin induction.*

***Objective:** This review examines the dual role of ferritin as an iron biomarker and an inflammatory marker.*

***Methods:** A literature search was conducted in PubMed, ScienceDirect, SpringerLink, and the Cochrane Library with a ten-year publication limit. Of the 89 articles identified, only eight studies met the inclusion criteria and directly evaluated the relationship between ferritin, iron status, and inflammatory processes.*

***Results:** Ferritin remains a key indicator of iron reserves, but its interpretation needs to take into account the inflammatory status.*

***Conclusion:** The combination of ferritin with inflammatory biomarkers such as C-Reactive Protein (CRP)[3] and Alpha-1-acid glycoprotein (AGP)[4] improves the diagnostic accuracy for anemia related to both iron deficiency and inflammation.*

***Keywords**: anemia, biomarker, ferritin serum, hepcidin, inflammation,*

ABSTRAK

Latar belakang: Anemia merupakan masalah kesehatan global yang penting, terutama di negara berpendapatan rendah dan menengah, di mana pembedaan antara anemia defisiensi besi dan anemia akibat inflamasi sering menjadi tantangan. Pemeriksaan hemoglobin tidak mampu membedakan kedua kondisi tersebut sehingga diperlukan biomarker yang lebih spesifik. Serum feritin, sebagai protein penyimpan besi utama,

[1] IDA = *Iron deficiency anemia*, a condition caused by insufficient iron stores leading to reduced hemoglobin production and impaired oxygen transport

[2] AI = *Anemia of inflammation* (also referred to as anemia of chronic disease), a form of anemia caused by inflammatory processes that increase hepcidin production and reduce iron availability for erythropoiesis

[3] CRP = *C-reactive protein*, an acute-phase protein that rises in response to inflammation and is widely used to detect inflammatory activity in clinical and nutritional assessments

[4] AGP = *Alpha-1-acid glycoprotein*, an acute-phase protein that increases during inflammation and is commonly used as a biomarker to assess inflammatory status, especially in nutritional and iron-status studies

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

mencerminkan cadangan besi tubuh, tetapi kadarnya dapat meningkat pada kondisi inflamasi melalui aktivasi interleukin-6 (IL-6) dan peningkatan produksi hepcidin.
Tujuan: Penelitian ini meninjau peran ferritin sebagai biomarker besi sekaligus penanda inflamasi. Telaah literatur dilakukan melalui PubMed, ScienceDirect, SpringerLink, dan Cochrane Library dengan batasan publikasi sepuluh tahun terakhir. Dari 89 artikel yang teridentifikasi, hanya 8 studi yang memenuhi kriteria inklusi dan secara langsung mengevaluasi hubungan ferritin dengan status besi serta proses inflamasi.
Hasil: Ferritin tetap menjadi indikator utama cadangan zat besi, tetapi interpretasinya perlu memperhitungkan status inflamasi.
Kesimpulan: Kombinasi feritin dengan biomarker inflamasi seperti CRP dan AGP meningkatkan akurasi diagnostik untuk anemia yang terkait dengan kekurangan zat besi dan peradangan.

Kata kunci: anemia, biomarker, hepcidin, inflamasi, serum ferritin

INTRODUCTION

Anemia remains a global health problem affecting both children and adults, with high prevalence in low- and middle-income countries and an increasing burden in developed nations. Iron deficiency is the leading cause, but anemia of chronic disease and inflammation also contribute significantly [1], [2]. Serum ferritin has long been used as the primary biomarker for assessing iron stores, as it is sensitive in detecting iron depletion before hemoglobin declines. However, ferritin levels are influenced by adiposity and inflammatory status, which further complicates their interpretation[3].

In clinical practice, ferritin levels have been shown to increase in parallel with improvements in iron status following supplementation, whether with lactoferrin or alternative iron formulations, confirming its reliability as a monitoring tool [4], [5]. Nevertheless, in patients with critical illness, burns, or chronic inflammation, ferritin often rises as part of the acute-phase response, thereby masking underlying iron deficiency [6]. For this reason, ferritin alone is insufficient for accurate diagnosis. Recent studies recommend correcting ferritin concentrations using inflammatory markers such as CRP and albumin or combining ferritin with other biomarkers like sTfR[5] to enhance diagnostic accuracy [7]. These findings reinforce the dual role of ferritin as both an iron biomarker and an inflammatory marker.

Furthermore, genetic evidence has revealed associations between iron status and autoimmune inflammatory diseases. Mendelian randomization analyses indicate that genetically, elevated ferritin levels are linked to a reduced risk of rheumatoid arthritis but an increased risk of systemic lupus erythematosus [8], [9]. Research on chronic anemia in patients with recessive dystrophic epidermolysis bullosa (RDEB) also identified close interplay between the inflammation–hepcidin axis and ferritin levels [10]. Therefore, ferritin should not be regarded solely as a marker of iron stores but also as a mediator in immune responses and disease pathogenesis. This study aimed to comprehensively review the role of serum ferritin as a biomarker of iron status and inflammation in anemia, and to explore its clinical and methodological implications.

METHODS

Study design

This study was a Systematic Literature Review (SLR) with a descriptive qualitative design using a secondary data analysis approach, conducted in August 2025.

[5] sTfR = *Soluble Transferrin Receptor*, a biomarker reflecting cellular iron demand

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

Data source and search strategy

A systematic literature search was performed following the framework of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), using databases including PubMed, ScienceDirect, Wiley Online Library, Taylor & Francis, Directory of Open Access Journals (DOAJ), and the Cochrane Library. The search strategy employed the following string: ("serum ferritin" OR ferritin OR "plasma ferritin") AND (anemia OR anaemia OR "iron deficiency anemia" OR IDA OR "anemia of chronic disease" OR ACD OR "anemia of inflammation") AND ("iron biomarker" OR "iron status" OR "iron stores" OR "serum iron" OR "transferrin saturation" OR TIBC OR sTfR) AND (inflammation OR "inflammatory marker" OR "acute phase reactant" OR "C-reactive protein" OR CRP OR IL-6 OR hepcidin).

Eligibility criteria

The search was limited to articles published within the last ten years, written in English or Indonesian, and available in full text, with inclusion criteria consisting of original research and review articles that examined the relationship between serum ferritin, iron status, and inflammation. Exclusion criteria included articles with incomplete methodology, non-scientific publications (such as editorials, commentaries, or opinion papers), and studies in which ferritin biomarkers were not involved as study variables.

Study selection process

Article selection was carried out in several stages, including identification, title and abstract screening, and full-text review, with the results presented in a PRISMA flow diagram.

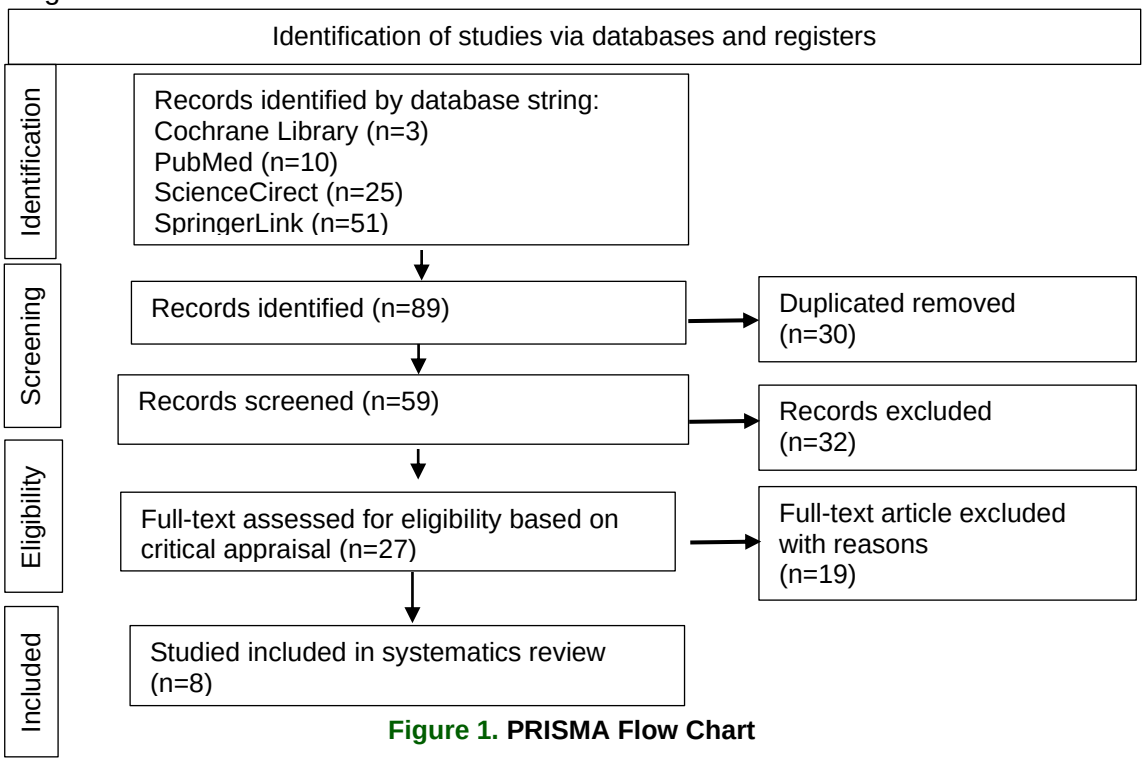

Figure 1. PRISMA Flow Chart

This diagram summarizes the study selection process. From 88 records identified, 30 duplicates were removed, 59 were screened, 27 full-texts assessed, and 8 studies were finally included in the review (Figure 1).

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

Quality assessment

Eligible studies were then assessed for methodological quality using the Joanna Briggs Institute (JBI) Critical Appraisal Tools according to the study design, evaluating validity, risk of bias, and clarity of reporting.

Data extraction

The most important information taken from each article was the author, year, study design, sample size, analyzed variables, and main findings. The study framework was organized using the PICOT approach, as presented in Table 1.

Table 1. PICOT Framework for the Study

Component	Description
Population (P)	Patients with anemia (adults and children, with various etiologies: iron deficiency, anemia of chronic disease, inflammation, infection, cancer, autoimmune disorders)
Intervention (I)	Serum ferritin assessment
Comparison (C)	Comparison with additional parameters for assessing iron status (such as serum iron, TIBC[6], TS[7], and sTfR)
Outcome (O)	Diagnostic accuracy, clinical interpretation, and therapeutic implications in the management of anemia
Time (T)	Articles published within the last 10 years (2015-2025)

RESULTS

Eight studies were included in this review, encompassing diverse populations and research designs ranging from randomized clinical trials, observational surveys, and case-control studies to retrospective cohorts and genetic analyses. The studies addressed different determinants of iron status, including supplementation, inflammation, adiposity, and genetic predisposition. Collectively, they provided evidence on clinical outcomes as well as mechanistic insights. The results are summarized below.

A randomized clinical trial in children with inflammatory bowel disease and iron deficiency anemia compared lactoferrin with ferrous sulfate [4]. Lactoferrin was more effective in increasing hemoglobin, serum iron, transferrin saturation, and ferritin levels. It also significantly reduced inflammatory markers, including interleukin-6 and hepcidin. Gastrointestinal side effects were less frequent in the lactoferrin group compared with ferrous sulfate. This suggests lactoferrin as a promising alternative therapy for pediatric iron deficiency anemia.

A population-based biomarker study conducted in India investigated 979 women of reproductive age [1]. The prevalence of anemia was 41.5%, and iron deficiency anemia was 30%. After adjusting ferritin levels for inflammation, the prevalence of iron deficiency increased to 61.5%. Rural women were found to have a higher prevalence compared with urban women. These findings highlight the importance of adjusting for inflammation when assessing iron status.

Data from the UK National Diet and Nutrition Survey between 2008 and 2019 were analyzed to examine adiposity and iron status [5]. Among 1,098 women of reproductive age, central adiposity measures such as waist-to-height and waist-to-hip ratios were associated with anemia. Higher levels of adiposity were also linked with both iron deficiency and iron deficiency anemia. Ferritin levels were influenced by inflammation, complicating the interpretation of iron status. This study emphasizes the interaction between obesity and iron metabolism in women.

[6] TIBC = Total Iron-Binding Capacity, an indirect measure of transferrin levels and iron-binding availability

[7] TS = Transferrin Saturation, the percentage of transferrin that is bound to iron

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

A crossover randomized trial evaluated iron-enriched Aspergillus oryzae compared with ferrous sulfate in young women with low ferritin levels [3]. Supplementation with Aspergillus oryzae iron resulted in lower non-transferrin-bound iron levels. Participants reported fewer gastrointestinal side effects compared to ferrous sulfate. Both supplements were similarly effective in improving markers of iron status. These results indicate that fungal-derived iron may be safer and equally efficacious as conventional supplementation. A case-control study focused on erythroferrone and hepcidin levels in children with iron deficiency anemia [11]. The study compared 26 children with anemia to 26 healthy controls. Results showed lower hemoglobin, serum iron, ferritin levels, and hepcidin levels in the anemia group. After one month of iron therapy, ferritin levels and hepcidin levels significantly increased while erythroferrone did not change. A strong positive correlation between ferritin levels and hepcidin levels was observed. A retrospective cohort of 60 burn patients examined iron status using updated postoperative guidelines [6]. Iron deficiency was identified in 31% of patients, and reduced iron availability in 83%. Despite this high prevalence, intravenous iron was underutilized. Patients with iron deficiency often went untreated, indicating under-recognition of the condition. This highlights the complexity of managing anemia in critical illness.

An equivalence randomized clinical trial evaluated iron supplementation with or without vitamin C in 440 adults with iron deficiency anemia [3]. Both groups showed comparable improvements in hemoglobin levels. Serum ferritin also increased similarly in both groups. No significant differences in adverse events were observed between regimens. These findings indicate that vitamin C does not provide additional benefit when combined with oral iron therapy. A Mendelian randomization study explored genetic associations between iron status and rheumatoid arthritis [8]. Data from more than 250,000 individuals were analyzed for ferritin, serum iron, total iron-binding capacity, and transferrin saturation. Genetically higher ferritin and serum iron were associated with a lower risk of rheumatoid arthritis. No significant associations were observed for total iron-binding capacity or transferrin saturation. This suggests that overall iron levels may have a protective role in autoimmune disease.

Table 2. Study Characteristics

No	Title, Researcher & Year	Method	Main Findings	Risk Bias
1	S. El Amrousy, M. El-Afify, and A. El-Azab, "Lactoferrin For Iron-Deficiency Anemia In Children With Inflammatory Bowel Disease: A Clinical Trial," Italian Journal Of Pediatrics, vol. 48, no. 1, p. 161, 2022.	**Design**: RCT **Sample**: 80 children with IBD (5–18 yrs) randomized to ferrous sulfate or lactoferrin for 3 months **Instrument**: Hb, ferritin, IL-6, hepcidin (ELISA) **Analysis**: t-test, χ^2, $p<0.05$.	• Both groups improved significantly in Hb and iron markers ($p < 0.001$), but lactoferrin produced greater increases than ferrous sulfate ($p = 0.01–0.006$). • Lactoferrin also reduced IL-6 and hepcidin ($p < 0.001$) and caused far fewer side effects (2.5% vs. 46.2%).	• This RCT demonstrated low risk of bias overall, with appropriate randomization, comparable baseline groups, and valid outcome measurements.

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

No	Title, Researcher & Year	Method	Main Findings	Risk Bias
2	J. L. Finkelstein et al., "Iron Status And Inflammation In Women Of Reproductive Age: A Population-Based Biomarker Survey And Clinical Study," Clin. Nutr. ESPEN, vol. 49, pp. 483-494, 2022.	**Design**: Cross-sectional biomarker survey. **Sample**: 979 women of reproductive age (15–40 years) in Southern India, observed over one year. **Instrument**: Hemoglobin (Hb), serum ferritin (SF), soluble transferrin receptor (sTfR), C-reactive protein (CRP), α-1-acid glycoprotein (AGP), with BRINDA[8] inflammation adjustment. **Analysis**: Chi-square test and one-way ANOVA with significance level $p < 0.05$.	• Anemia prevalence was 41.5%, IDA 30%, and inflammation-adjusted iron deficiency rose to 61.5%. • Rural women had significantly higher rates of anemia and iron deficiency ($p < 0.05$).	Overall low risk of bias, with standardized biomarker methods; minor concerns include residual confounding and single time-point measurements.
3	A. E. Bries, C. Wang, I. Agbemafle, B. Wels, and M. B. Reddy, "Assessment of Acute Serum Iron, Non-Transferrin-Bound Iron, and Gastrointestinal Symptoms With 3-Week Consumption Of Iron-Enriched Aspergillus Oryzae Compared With Ferrous Sulfate," Current Developments in Nutrition, vol. 3, no. 12, article nzz127, 2019.	**Design**: RCT. **Sample**: 16 young women with serum ferritin < 40 µg/L, consuming 65 mg Fe/day from ferrous sulfate or iron-enriched Aspergillus oryzae for 3 weeks. **Instrument**: Serum iron (SI), transferrin saturation (TS%), non-transferrin-bound iron (NTBI), and gastrointestinal side-effect questionnaire. **Analysis**: Repeated-measures regression / ANOVA (SAS v9.4), significance level $p < 0.05$.	• A.oryzae iron produced similar increases in serum iron and transferrin saturation as ferrous sulfate, but resulted in significantly lower NTBI levels ($p < 0.05$). • Gastrointestinal side effects were notably higher with ferrous sulfate, while A. oryzae showed substantially better tolerability.	Randomization and outcome measurements were appropriate, but the very small sample size and short duration limit generalizability.
4	S. P. Demirdjian, M. A. Kerr, M. S. Mulhern, P. D. Thompson, M. Ledwidge, and M. T. McCann, "Association between	**Design**: Cross-sectional analysis using the NDNS 2008–2019 dataset. **Sample**: 1,909 women aged 19–49 years, selected through stratified random sampling.	• Central adiposity was strongly associated with lower ferritin and higher rates of anemia, iron deficiency, and IDA ($p <$ 0.05–0.001), even after adjusting for age,	Minor concerns include residual confounding and cross-sectional design, which limit causal interpretation.

[8] BRINDA = Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia, an international model for adjusting iron biomarkers for inflammation

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

No	Title, Researcher & Year	Method	Main Findings	Risk Bias
	Adiposity and Iron Status in Women of Reproductive Age: Data from the UK National Diet and Nutrition Survey (NDNS) 2008-2019," The Journal of Nutrition, vol. 154, no. 10, pp. 3048-3059, 2024.	**Instrument**: BMI[9], waist circumference, serum ferritin, hemoglobin, CRP, and dietary iron intake. **Analysis**: Multivariable linear regression and logistic regression adjusted for age, inflammation, and socioeconomic factors.	socioeconomic factors, diet, and inflammation (significant AOR). • CRP increased with adiposity and significantly reduced ferritin in regression models ($p < 0.001$), while overweight/obese women had higher odds of anemia and IDA than normal-weight women ($p < 0.05$).	
5	M. Dulkadir, E. Karacan, and H. S. Gürsoy, "Erythroferrone And Hepcidin Levels In Children With Iron Deficiency Anemia," BMC Pediatrics, vol. 24, no. 1, p. 259, 2024.	**Design**: Case–control study. **Sample**: 26 children with iron deficiency anemia and 26 healthy controls, assessed over one month at Kırşehir Ahi Evran University Hospital. **Instrument**: Hb, MCV, MCH, MCHC, serum iron, TIBC, ferritin, hepcidin, and erythroferrone (measured using ELISA). **Analysis**: Group comparisons (including pre–post treatment changes) and correlation analysis between ERFE, ferritin, hepcidin, and hematologic indices.	• Children with IDA had significantly lower Hb, serum iron, ferritin, and hepcidin compared with controls ($p < 0.001$). • Post-treatment, ferritin and hepcidin increased significantly ($p < 0.05$), while erythroferrone (ERFE) showed no significant change ($p > 0.05$). • A strong positive correlation was observed between ferritin and hepcidin (e.g., $r > 0.6$, $p < 0.01$), indicating disrupted iron–hepcidin regulation in IDA.	• Moderate risk of bias due to small sample size (26 vs. 26) and potential selection bias inherent to case–control designs. • Measurement bias is low because ferritin, hepcidin, and ERFE were assessed using standardized ELISA methods. • Temporal relationship cannot be established, limiting causal interpretation.
6	N. Betar, J. Rea, and G. M. Wood, "Iron Status in Patients With Burn Anaemia," Burns, vol. 49, no. 3, pp. 701–706, 2023.	**Design**: Retrospective cohort study. **Sample**: 60 burn patients (≥15% TBSA), assessed over one year in a single burn center using retrospective record-based sampling. **Instrument**: Hemoglobin (Hb), serum iron, number of transfusion units, total	• Burn patients had a high burden of iron deficiency (31%), and low iron availability (83%), and Hb did not improve without targeted therapy; greater TBSA% and more surgeries were linked to poorer iron status ($p < 0.05$).	• Moderate risk of bias due to the retrospective design and reliance on medical record completeness. • Potential selection bias, as the sample came from a single burn center with record-based inclusion.

[9] BMI = *Body Mass Index,* a screening measure of weight status (kg/m²)

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

No	Title, Researcher & Year	Method	Main Findings	Risk Bias
		burn surface area (TBSA), and number of surgical interventions. **Analysis**: Linear mixed-effects regression to evaluate Hb trends over time and the hematologic response to intravenous iron therapy.	• IV iron significantly improved Hb ($p < 0.05$), yet iron deficiency often remained unrecognized and inadequately treated.	
7	N. Li, G. Zhao, W. Wu et al., "The Efficacy and Safety of Vitamin C for Iron Supplementation in Adult Patients With Iron Deficiency Anemia: A Randomized Clinical Trial," JAMA Network Open, vol. 3, no. 11, e2023644, 2020.	**Design**: RCT with a 3-month follow-up. **Sample**: 440 adults with newly diagnosed iron deficiency anemia (IDA), randomized equally (220 vs. 220) to oral iron + vitamin C or oral iron alone. **Instrument**: Hemoglobin change at 2 weeks (primary outcome), reticulocyte percentage, hemoglobin at 4 weeks, serum ferritin at 8 weeks, and monitoring of adverse events. **Analysis**: Equivalence testing with a predefined margin of ±1 g/dL for hemoglobin, supported by t-tests, chi-square tests, 95% confidence intervals, and intention-to-treat analysis.	• Hemoglobin improvement was equivalent between iron + vitamin C and iron alone (~+2.0 g/dL at 2 weeks, within the ±1 g/dL equivalence margin), with no significant differences in reticulocyte %, Hb at 4 weeks, or ferritin at 8 weeks ($p > 0.05$). • Vitamin C provided no additional therapeutic benefit, and adverse events were similar between groups, indicating comparable efficacy and safety.	Low risk of bias overall, due to proper randomization, allocation concealment, and intention-to-treat analysis.
8	B. Wu, "Genetically Predicted Iron Status Is a Causal Risk of Rheumatoid Arthritis: A Mendelian Randomization Study," Glob. Med. Genet., vol. 11, no. 4, pp. 270–277, 2024.	Two-sample Mendelian randomization study, genetic data from 257,953 individuals for iron traits and summary-level data from 5,427 rheumatoid arthritis cases and 479,171 controls, instrumental variables: SNPs for ferritin, serum iron, TIBC, transferrin saturation; analysis: inverse-variance weighted (IVW) method with random effects, MR-Egger, weighted median/mode, leave-	• Genetically higher serum ferritin and serum iron levels were associated with a significantly lower risk of rheumatoid arthritis (RA) (IVW method, $p \leq 0.014$). • No significant causal association was found for TIBC or transferrin saturation with RA risk ($p > 0.05$). • Sensitivity analyses (MR-Egger, weighted median/mode, leave-one-out) showed consistent results, supporting robustness.	Low risk of bias, strengthened by strong genetic instruments (SNPs) and multiple sensitivity analyses.

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

No	Title, Researcher & Year	Method	Main Findings	Risk Bias
		one-out sensitivity (p≤0.014 for significant exposures).	• No evidence of horizontal pleiotropy, indicating the biological validity of the instrumental variables.	

DISCUSSION

Serum Ferritin as an Inflammatory Marker in Anemia

Serum ferritin serves a dual role as an indicator of iron stores and as an acute-phase protein that rises during inflammation. In pure iron deficiency anemia, ferritin levels decline, reflecting depleted body iron reserves [4]. In contrast, during chronic inflammation such as autoimmune disease, infection, or obesity, ferritin often increases despite reduced iron stores [1], [5]. This elevation is largely driven by proinflammatory cytokines, particularly interleukin-6, which stimulates hepatic hepcidin production [3]. Therefore, the interpretation of ferritin in anemia with an inflammatory component requires contextual consideration.

In anemia of chronic disease, elevated ferritin reflects inflammatory activity rather than adequate iron storage [6], [11]. Inflammation-induced hepcidin suppresses ferroportin, thereby inhibiting iron release from macrophages and intestinal absorption [3]. This reduces iron availability for erythropoiesis even when serum ferritin appears normal or elevated. Pediatric studies have shown a strong correlation between ferritin and hepcidin in IDA, while erythroferrone did not change after iron therapy [8]. These findings highlight ferritin's role as a biomarker that is strongly influenced by inflammation [2], [10].

Several studies emphasize the importance of adjusting ferritin cut-off values in inflammatory conditions. A population-based study in India demonstrated that the prevalence of iron deficiency nearly doubled after correcting ferritin values for inflammation [9]. Analysis of the UK National Diet and Nutrition Survey also showed that central adiposity was associated with a higher risk of IDA through inflammatory pathways [12]. In pregnancy, elevated maternal adiposity caused ferritin to be less accurate as a predictor of iron deficiency due to inflammation [13]. Even in apparently healthy populations, higher ferritin cut-offs (30–45 ng/mL) were more sensitive for detecting deficiency, yet the risk of misclassification due to inflammation remained [14].

Ferritin also plays a role in oxidative stress and ferroptosis. Through ferritinophagy, ferritin degradation releases free iron, which promotes reactive oxygen species formation and lipid peroxidation [15], [16], [17]. This process has been implicated in the pathogenesis of rheumatoid arthritis, lupus, neurodegenerative disorders, and cancer [18], [19]. At the same time, ferritin has a protective role by binding excess iron to prevent oxidative injury [14], [20], [21], [22]. Genetic analyses have shown that higher ferritin levels are associated with reduced risk of rheumatoid arthritis but increased risk of asthma and lupus [8], [19], [23]. Thus, ferritin functions as a central mediator between inflammation, iron metabolism, and oxidative stress.

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

In pregnancy and neonatal contexts, ferritin demonstrates complex interactions with inflammation. Cord blood studies reported an inverse relationship between ferritin and hemoglobin that was not explained by CRP or IL-6 [24]. Placental iron regulation has also been shown to be only partially aligned with maternal and neonatal ferritin concentrations [13]. Ferritin is also elevated in chronic inflammatory conditions such as atopic dermatitis and periodontitis, reinforcing its role as an inflammatory biomarker [25], [26]. Moreover, in COVID-19, elevated ferritin has been identified as a marker of systemic inflammation and poor prognosis [14].

Serum Ferritin as a Biomarker of Iron Status

Serum ferritin is the most widely used biomarker for assessing body iron stores. In conditions of pure iron deficiency, ferritin levels decrease in proportion to depleted iron reserves, making it a highly specific marker of deficiency [1]. Several community and clinical studies consistently show that low ferritin strongly correlates with anemia prevalence among adolescents, women of reproductive age, and children [10]. In randomized trials of iron supplementation, increases in serum ferritin paralleled rises in hemoglobin and reductions in anemia prevalence, confirming its reliability for monitoring intervention impact [5], [27]. Thus, serum ferritin remains the gold standard biomarker for iron status in both research and clinical practice[28], [20].

Despite its strengths, serum ferritin is influenced by age, sex, and physiological status. Large surveys indicate that ferritin concentrations vary between adolescents, adults, and pregnant women, with lower cut-offs required for accurate detection in specific groups [3], [11], [27]. Ethnic differences also affect baseline ferritin levels, with East Asians generally showing higher ferritin than Europeans or South Asians, even at comparable hemoglobin concentrations [29], [30]. The WHO guidelines, therefore, recommend population-specific cut-offs, such as <15 µg/L for adults and <12 µg/L for children, while adjustments are advised in the presence of inflammation [20], [31]. These recommendations emphasize the need for contextual interpretation of ferritin values across diverse populations [29].

Advances in molecular biology have deepened understanding of ferritin's role in iron storage. Structurally, ferritin is a nanocage protein capable of storing up to 4500 iron atoms, with heavy (H) and light (L) subunits playing distinct roles in iron oxidation and storage [26]. Recent studies highlight the contribution of ferritinophagy, a lysosomal degradation pathway, to the regulation of intracellular iron release [25]. Furthermore, ferritin is expressed in different cellular compartments, including mitochondria, where it contributes to iron buffering and oxidative stress protection [24]. These findings indicate that serum ferritin is not only a passive marker but part of dynamic iron homeostasis [1]

Clinical guidelines increasingly incorporate ferritin into diagnostic algorithms alongside other iron markers. In the presence of chronic disease, ferritin alone may not distinguish true deficiency from inflammation-associated anemia, necessitating its combined use with soluble transferrin receptor or hepcidin levels [7], [32], [33]. Nevertheless, ferritin remains the earliest indicator of declining iron stores, becoming abnormal before hemoglobin or hematocrit levels decrease [34]. In surgical and obstetric populations, measurement of ferritin levels has been shown to predict transfusion needs and maternal anemia risk more effectively than hemoglobin alone [31]. Therefore, its integration into routine clinical screening is critical for timely intervention.

Ferritin also serves as an essential metric for evaluating public health interventions. Large-scale supplementation and fortification trials demonstrated that ferritin is responsive to changes in dietary iron intake and accurately reflects improvements in iron status at the population level. A cluster-randomized trial in India, for example, showed that iron-fortified foods significantly increased ferritin concentrations and reduced the

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

prevalence of iron deficiency anemia [4], [5]. Similarly, ferritin-based surveillance has been used to estimate the burden of iron deficiency among undernourished children, guiding targeted nutritional policies [35]. While ferritin interpretation requires caution in inflammatory states, its sensitivity, specificity, and responsiveness to interventions confirm its central role as a biomarker of iron status.

This review provides a comprehensive overview of the role of serum ferritin as both a biomarker of iron status and an indicator of inflammation. However, several limitations should be acknowledged, including heterogeneity of the populations and study designs analyzed, variations in ferritin measurement methods, and the influence of inflammatory conditions that may affect result interpretation. Although ferritin remains an early indicator of iron stores, its interpretation cannot be separated from the clinical and physiological context of the patient. The findings highlight the need to adjust ferritin cut-off values based on population characteristics and inflammatory status, as well as to integrate other markers, such as hepcidin or soluble transferrin receptor, to improve diagnostic accuracy. Implicatively, the results of this review may inform more targeted clinical strategies and public health policies, particularly in the early detection of anemia, planning of nutritional interventions, and monitoring the effectiveness of iron supplementation across diverse population groups.

CONCLUSION

Serum ferritin remains a reliable biomarker for assessing iron status due to its high sensitivity and specificity in detecting early iron deficiency, and it has been validated in epidemiological studies, supplementation trials, and public health surveillance. Its levels are influenced by physiological factors such as age, sex, pregnancy, and ethnicity, requiring context-specific cut-offs and careful interpretation. Additionally, ferritin functions as an acute-phase protein that increases in response to inflammation, so elevations in chronic disease, infection, or obesity may reflect inflammatory activity rather than adequate iron stores. Integrating ferritin with additional biomarkers such as CRP, AGP, or soluble transferrin receptor is important to distinguish iron deficiency from anemia of inflammation, reinforcing its role as a hybrid biomarker at the intersection of iron metabolism and inflammation.

Future research should also incorporate improved screening protocols such as routinely pairing ferritin with CRP/AGP, integrating sTfR or Ret-He in high-inflammation settings, and applying standardized adjustment models like BRINDA to enhance diagnostic precision. Targeted treatment strategies based on combined biomarker profiles, including personalized iron supplementation and early referral for patients showing functional iron deficiency, can further strengthen clinical decision-making and public health interventions.

REFERENCES

[1] J. L. Finkelstein *et al.*, “Iron status and inflammation in women of reproductive age: A population-based biomarker survey and clinical study,” *Clin. Nutr. ESPEN*, vol. 49, pp. 483–494, 2022, doi: 10.1016/j.clnesp.2022.02.123.

[2] G. Weiss, T. Ganz, and L. T. Goodnough, “Anemia of in fl ammation,” *Am. Soc. Hematol.*, vol. 133, no. 1, 2019, doi: 10.1182/blood-2018-06-856500.

[3] Q. S. P. Demirdjian *et al.*, “Maternal Adiposity and Inflammation : Risk Factors for Iron Deficiency in Human Pregnancy,” *J. Nutr.*, no. xxxx, doi: 10.1016/j.tjnut.2025.08.022.

[4] D. El Amrousy, D. El-Afify, A. Elsawy, M. Elsheikh, A. Donia, and M. Nassar, “Lactoferrin for iron-deficiency anemia in children with inflammatory bowel disease: a clinical trial,” *Pediatr. Res.*, vol. 92, no. 3, pp. 762–766, 2022, doi: 10.1038/s41390-022-02136-2.

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

[5] A. E. Bries, C. Wang, I. Agbemafle, B. Wels, and M. B. Reddy, "Assessment of Acute Serum Iron, Non-Transferrin-Bound Iron, and Gastrointestinal Symptoms with 3-Week Consumption of Iron-Enriched Aspergillus oryzae Compared with Ferrous Sulfate," *Curr. Dev. Nutr.*, vol. 3, no. 12, p. nzz127, 2019, doi: 10.1093/cdn/nzz127.

[6] N. Betar *et al.*, "Iron status in patients with burn anaemia," *Burns*, vol. 49, no. 3, pp. 701–706, 2023, doi: 10.1016/j.burns.2022.05.014.

[7] S. T. Mcsorley, A. Tham, I. Jones, D. Talwar, and D. C. Mcmillan, "Regression Correction Equation to Adjust Serum Iron and Ferritin Concentrations Based on C-Reactive Protein and Albumin in Patients Receiving Primary and Secondary Care," *J. Nutr.*, vol. 149, no. 5, pp. 877–883, 2019, doi: 10.1093/jn/nxz008.

[8] B. Wu, "Genetically Predicted Iron Status Is a Causal Risk of Rheumatoid Arthritis: A Mendelian Randomization Study," *Glob. Med. Genet.*, vol. 11, no. 04, pp. 270–277, 2024, doi: 10.1055/s-0044-1789259.

[9] D. Ye *et al.*, "Associated with Altered Risk of Systemic Lupus Erythematosus among European Populations," *J. Nutr.*, vol. 151, no. 6, pp. 1473–1478, 2021, doi: 10.1093/jn/nxab015.

[10] L. Quintana-castanedo *et al.*, "Interplay between iron metabolism , in fl ammation , and EPO-ERFE- hepcidin axis in RDEB-associated chronic anemia," *Blood Adv.*, vol. 9, no. 9, 2025, doi: 10.1182/bloodadvances.2024015271.

[11] R. Dulkadir, G. Turna Saltoğlu, and A. Güneş, "Erythroferrone and hepcidin levels in children with iron deficiency anemia," *BMC Pediatr.*, vol. 24, no. 1, pp. 1–6, 2024, doi: 10.1186/s12887-024-04594-5.

[12] J. Wu, Z. Zheng, J. Wang, and W. Xiao, "Iron Status and Risk of Periodontitis and Dental Caries : A Mendelian Randomization Study," *Int. Dent. J.*, vol. 75, no. 2, pp. 1441–1449, 2024, doi: 10.1016/j.identj.2024.11.018.

[13] K. M. Delaney *et al.*, "Placental Erythroferrone and Erythropoietin mRNA Expression is not Associated with Maternal or Neonatal Iron Status in Adolescents Carrying Singletons and Adult Women Carrying Multiples," *J. Nutr.*, vol. 153, no. 7, pp. 1950–1958, 2023, doi: 10.1016/j.tjnut.2023.05.023.

[14] A. L. Hanson *et al.*, "Iron dysregulation and inflammatory stress erythropoiesis associates with long-term outcome of COVID-19," *Nat. Immunol.*, vol. 25, no. 3, pp. 471–482, 2024, doi: 10.1038/s41590-024-01754-8.

[15] C. Ricci *et al.*, "Ferritin at different iron loading: From biological to nanotechnological applications," *Int. J. Biol. Macromol.*, vol. 276, no. July, 2024, doi: 10.1016/j.ijbiomac.2024.133812.

[16] N. K. Lee, S. Cho, and I. Kim, "Ferritin – a multifaceted protein scaffold for biotherapeutics," *Nat. Med.*, vol. 1, no. October, pp. 1–6, 2022, doi: 10.1038/s12276-022-00859-0.

[17] S. Dutt, I. Hamza, and T. B. Bartnikas, "Molecular Mechanisms of Iron and Heme Metabolism," *Annu. Rev. Nutr.*, vol. 42, pp. 311–335, 2022, doi: 10.1146/annurev-nutr-062320-112625.

[18] L. Rochette, G. Dogon, E. Rigal, M. Zeller, and Y. Cottin, "Lipid Peroxidation and Iron Metabolism : Two Corner Stones in the Homeostasis Control of Ferroptosis," *Int. J. Mol. Sci.*, vol. 24, no. 449, pp. 1–17, 2024.

[19] P. Arosio, G. Cairo, and F. Bou-abdallah, "A Brief History of Ferritin , an Ancient and Versatile Protein," *Int. J. Mol. Sci.*, vol. 26, no. 206, pp. 1–24, 2025.

[20] WHO, *WHO Guideline on Use of Ferritin Concentrations to Assess Iron Status in Individuals and Populations*. 2020.

[21] J. Chifman, R. Laubenbacher, and S. V. Torti, "A systems biology approach to iron metabolism," *Adv. Exp. Med. Biol.*, vol. 844, pp. 201–225, 2014, doi: 10.1007/978-1-

https://doi.org/10.34011/jmp2k.v36i1.4137

Vol 36 No 1, Maret 2026
e-ISSN: 2579-8103
p-ISSN:1979-8253

4939-2095-2_10.

[22] E. Piskin, D. Cianciosi, S. Gulec, M. Tomas, and E. Capanoglu, "Iron Absorption: Factors, Limitations, and Improvement Methods," *ACS Omega*, vol. 7, no. 24, pp. 20441–20456, 2022, doi: 10.1021/acsomega.2c01833.

[23] P. Arosio, "New Advances in Iron Metabolism, Ferritin and Hepcidin Research," *Int. J. Mol. Sci.*, vol. 23, no. 23, pp. 2–5, 2022, doi: 10.3390/ijms232314700.

[24] J. Daru, K. Colman, S. J. Stanworth, B. De La Salle, E. M. Wood, and S. R. Pasricha, "Serum ferritin as an indicator of iron status: What do we need to know?," *Am. J. Clin. Nutr.*, vol. 106, pp. 1634S-1639S, 2017, doi: 10.3945/ajcn.117.155960.

[25] J. A. J. Fischer, A. M. Cherian, J. N. Bone, and C. D. Karakochuk, "The effects of oral ferrous bisglycinate supplementation on hemoglobin and ferritin concentrations in adults and children: a systematic review and meta-analysis of randomized controlled trials," *Nutr. Rev.*, vol. 81, no. 8, pp. 904–920, 2023, doi: 10.1093/nutrit/nuac106.

[26] P. Peng *et al.*, "Association between serum ferritin and bone mineral density in US adults," *J. Orthop. Surg. Res.*, vol. 1, pp. 1–6, 2022, doi: 10.1186/s13018-022-03357-1.

[27] S. P. Demirdjian, M. A. Kerr, M. S. Mulhern, P. D. Thompson, M. Ledwidge, and M. T. McCann, "Association between Adiposity and Iron Status in Women of Reproductive Age: Data from the UK National Diet and Nutrition Survey (NDNS) 2008–2019," *J. Nutr.*, vol. 154, no. 10, pp. 3048–3059, 2024, doi: 10.1016/j.tjnut.2024.08.026.

[28] S. Mutiah, M. N. Aidi, A. Saefuddin, and F. Ernawati, "Application of the Cokriging Method to Estimate Iron Deficiency Prevalence Based on Ferritin and C- Reactive Protein," *Media Penelit. dan Pengemb. Kesehat.*, vol. 35, no. 3, pp. 1025–1035, 2025, doi: https://doi.org/10.34011/jmp2k.v35i3.3167 1025.

[29] G. Omuse, A. Chege, D. E. Kawalya, E. Kagotho, and D. Maina, "Ferritin and its association with anaemia in a healthy adult population in Kenya," *PLoS One*, vol. 17, no. 10 October, 2022, doi: 10.1371/journal.pone.0275098.

[30] K. Martens and T. G. DeLoughery, "Sex, lies, and iron deficiency: a call to change ferritin reference ranges," *Hematol. (United States)*, vol. 2023, no. 1, pp. 617–621, 2023, doi: 10.1182/hematology.2023000494.

[31] S. Pavord, J. Daru, N. Prasannan, S. Robinson, S. Stanworth, and J. Girling, "UK guidelines on the management of iron deficiency in pregnancy," *Br. J. Haematol.*, vol. 188, no. 6, pp. 819–830, 2020, doi: 10.1111/bjh.16221.

[32] J. A. Rusch, D. J. van der Westhuizen, R. S. Gill, and V. J. Louw, "Diagnosing iron deficiency: Controversies and novel metrics," *Best Pract. Res. Clin. Anaesthesiol.*, vol. 37, no. 4, pp. 451–467, 2023, doi: 10.1016/j.bpa.2023.11.001.

[33] L. Lanser, D. Fuchs, K. Kurz, and G. Weiss, "Physiology and inflammation driven pathophysiology of iron homeostasis—mechanistic insights into anemia of inflammation and its treatment," *Nutrients*, vol. 13, no. 11, 2021, doi: 10.3390/nu13113732.

[34] R. Mehta, A. C. Platt, X. Sun, M. Desai, D. Clements, and E. L. Turner, "Efficacy of iron-supplement bars to reduce anemia in urban Indian women: A cluster-randomized controlled trial," *Am. J. Clin. Nutr.*, vol. 105, no. 3, pp. 746–757, 2017, doi: 10.3945/ajcn.115.127555.

[35] J. Chandra *et al.*, "Diagnosis, Treatment and Prevention of Nutritional Anemia in Children: Recommendations of the Joint Committee of Pediatric Hematology-Oncology Chapter and Pediatric and Adolescent Nutrition Society of the Indian Academy of Pediatrics," *Indian Pediatr.*, vol. 59, no. 10, pp. 782–801, 2022, doi: 10.1007/s13312-022-2622-2.

https://doi.org/10.34011/jmp2k.v36i1.4137