DECIPHERING IRON DEFICIENCY ANEMIA AND ANEMIA OF CHRONIC DISEASE : A LABORATORY APPROACH BEYOND FERRITIN

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ABSTRAK
Anemia defisiensi besi (ADB) dan anemia penyakit kronis (APK) merupakan jenis anemia yang paling sering ditemukan, namun perbedaan keduanya sering sulit ditegakkan karena pengaruh proses inflamasi. Ferritin tetap menjadi penanda standar cadangan besi, tetapi spesifisitasnya menurun karena perannya sebagai reaktan fase akut. Permasalahan penelitian ini adalah perlunya interpretasi pemeriksaan besi yang lebih akurat dalam kondisi inflamasi. Metode penulisan berbentuk tinjauan pustaka yang menganalisis literatur terkini mengenai peran indeks besi konvensional dan biomarker baru untuk membedakan ADB dari APK, dengan penekanan pada interpretasi dalam kondisi inflamasi. Data diperoleh dari publikasi tahun 2015-2025 yang membahas ferritin, *C-reactive protein* (CRP), *soluble transferrin receptor* (sTfR), laju endap darah (LED), hepcidin, dan *reticulocyte hemoglobin content* (CHr) dalam konteks inflamasi yang disintesis secara kualitatif untuk menilai nilai diagnostik, keunggulan, dan keterbatasannya. Ferritin tetap penting untuk menilai status besi, namun perlu penyesuaian terhadap inflamasi di mana dengan nilai ambang <100 ng/mL serta CRP >5 mg/L meningkatkan sensitivitas deteksi ADB. sTfR dan rasio sTfR/log ferritin memberikan spesifisitas lebih tinggi untuk defisiensi besi absolut, sedangkan hepcidin membedakan defisiensi fungsional pada APK dari defisiensi absolut pada ADB. CHr mencerminkan pasokan besi eritropoietik secara hampir *real-time* dan dipengaruhi inflamasi secara minimal. Kombinasi biomarker fungsional dan inflamasi meningkatkan akurasi diagnosis. Tidak ada uji tunggal yang bersifat definitif; pendekatan *multi-marker* dengan integrasi ferritin, biomarker baru, dan penanda inflamasi direkomendasikan untuk meningkatkan ketepatan diagnosis anemia pada kondisi inflamasi.

Kata kunci **:** anemia defisiensi besi, anemia penyakit kronis, diagnostik laboratorium, ferritin, inflamasi

ABSTRACT
Iron deficiency anemia (IDA) and anemia of chronic disease (ACD) represent the two predominant types of anemia, but distinguishing between them is often difficult due to the influence of inflammation. Ferritin remains the standard marker of iron stores, but its specificity is reduced due to its role as an acute-phase reactant. The problem addressed in this study is the need for more accurate interpretation of iron parameters under inflammatory conditions. This paper is a narrative review analyzing recent literature on the role of conventional iron indices and novel biomarkers in differentiating IDA from ACD, with emphasis on interpretation in inflammatory conditions. Data were obtained from publications between 2015 and 2025 discussing ferritin, C-reactive protein (CRP), soluble transferrin receptor (sTfR), erythrocyte sedimentation rate (ESR), hepcidin, and reticulocyte hemoglobin content (CHr), synthesized qualitatively to assess their diagnostic value, advantages, and limitations. Ferritin is still essential for assessing iron status but requires adjustment for inflammation, where a ferritin threshold of <100 ng/mL combined with CRP >5 mg/L increases the sensitivity for detecting IDA. sTfR and the sTfR/log ferritin index provide higher specificity for absolute iron deficiency, whereas hepcidin differentiates functional deficiency in ACD from absolute deficiency in IDA. CHr reflects erythropoietic iron supply in near real time and is minimally influenced by inflammation. No single test is definitive; a multi-marker approach integrating ferritin, novel biomarkers, and inflammatory indicators is recommended to improve diagnostic precision in anemia associated with inflammation.

Keywords ***:*** *anemia of chronic disease, ferritin, inflammation, iron deficiency anemia, laboratory diagnostics*

INTRODUCTION

Adequate iron availability is fundamental for maintaining vital biological functions, including oxygen transport, cell growth, immune regulation, and mitochondrial energy metabolism (Yang et al., 2023). Disruptions in iron metabolism may lead to anemia, most commonly iron deficiency anemia (IDA) and anemia of chronic disease (ACD), which collectively represent the predominant types of anemia cases globally. Both forms are highly prevalent among chronically ill and hospitalized populations, yet they arise from distinct pathophysiological mechanisms and require different diagnostic and therapeutic approaches (Rohr et al., 2023; Svenson et al., 2021). IDA is caused by true iron deficiency, which usually results from prolonged blood loss, insufficient food intake, or compromised gastrointestinal absorption (Koleini et al., 2021). In contrast, ACD – or anemia of inflammation – develops when iron stores are adequate but become inaccessible due to immune-mediated dysregulation. Elevated interleukin-6 (IL-6) promotes hepatic release of hepcidin, which reduces intestinal iron absorption and traps iron inside macrophages and hepatocytes (Nemeth & Ganz, 2021). The cytokine-hepcidin pathway leads to functional iron deficiency, decreased erythropoietin responsiveness, and impaired red blood cell production, collectively contributing to anemia in chronic inflammatory states, including infections, malignancies, and autoimmune disorders (Bondarchuk et al., 2021; Nemeth & Ganz, 2023).

Although IDA and ACD often present with similar hematologic profiles – such as microcytic or normocytic anemia and low serum iron – their management strategies differ markedly (Svenson et al., 2021). Iron supplementation is essential for IDA but may be ineffective or even harmful in ACD if administered without addressing the underlying inflammatory process. Therefore, accurate differentiation between these two conditions is clinically crucial to avoid mistreatment and optimize patient outcomes (Bondarchuk et al., 2021; Svenson et al., 2021). Historically, serum ferritin has served as the primary biomarker of iron storage (Galetti et al., 2021). However, ferritin levels can rise during systemic inflammation, as it acts as an acute-phase reactant regardless of the body's true iron status (DePalma et al., 2021). In such cases, despite an underlying iron deficiency, serum ferritin may seem normal or even increased, which could result in an incorrect diagnosis and ineffective treatment (Svenson et al., 2021). Consequently, reliance on ferritin alone may be insufficient when evaluating anemia in patients with chronic inflammation.

To address this diagnostic limitation, several alternative or complementary biomarkers have been explored. The soluble transferrin receptor (sTfR) serves as an indicator of cellular iron requirements and is minimally affected by inflammation, whereas the sTfR/log ferritin index provides improved differentiation between IDA and ACD (Rohr et al., 2023; Santhosh et al., 2024). Hepcidin measurement provides insight into the pathophysiologic mechanism of iron sequestration, helping distinguish functional from absolute deficiency (Nemeth & Ganz, 2023; Svenson et al., 2021). Reticulocyte hemoglobin content (CHr) offers near real-time information on iron availability for erythropoiesis (Kılıç et al., 2022; Rusch et al., 2023). Indicators of inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), also provide valuable context for interpreting iron parameters in the setting of systemic disease (Cacoub et al., 2022; Farrag et al., 2024). Collectively, these indicators provide better diagnostic accuracy in distinguishing between IDA and ACD when interpreted combined with conventional measurements (Svenson et al., 2021).

Previous reviews have examined aspects of iron metabolism and the utility of emerging biomarkers in distinguishing IDA from ACD. However, most focused on isolated parameters or specific clinical settings, leaving a need for an integrated evaluation framework that combines conventional and novel indicators within the inflammatory context. This review therefore aims to provide a comprehensive and clinically practical overview of iron study

interpretation in the context of inflammation. By analyzing the diagnostic value, limitations, and optimal application of key biomarkers – such as ferritin, CRP, hepcidin, sTfR, and CHr – this paper seeks to support more accurate differentiation of IDA and ACD and enhance evidence-based laboratory interpretation in anemic patients.

METHODS

This review employed a narrative literature review design focusing on the interpretation of iron studies in inflammatory settings. Relevant literature was searched through electronic databases, including Google Scholar, ScienceDirect, Scopus, and PubMed, using combinations of the following keywords and phrases: *iron deficiency anemia*, *anemia of chronic disease*, *anemia of inflammation*, *ferritin*, *hepcidin*, *soluble transferrin receptor*, *reticulocyte hemoglobin content*, *C-reactive protein*, and *functional iron deficiency*. Search strings included conceptual phrases such as *"interpretation of iron studies in inflammatory settings"* and *"iron biomarkers beyond ferritin"* to capture integrative diagnostic discussions. Articles published between 2015 and 2025 were considered, prioritizing full-text papers in English that emphasized diagnostic evaluation of iron markers in inflammatory contexts. Data from the selected literature were reviewed and summarized narratively to highlight diagnostic principles, biomarker interpretation, and recent advances beyond ferritin. No quantitative or statistical analysis was performed, and no ethical clearance was required, as this study did not involve human or animal subjects.

RESULTS

As a critical micronutrient, iron underpins diverse physiological functions such as oxygen delivery, nucleic acid synthesis, energy production through cellular respiration, and regulation of immune responses (Galy et al., 2024). Total body iron stores are estimated at about 3-4 grams, with about two-thirds utilized in hemoglobin synthesis within red blood cells. The remaining iron is retained as ferritin or hemosiderin, primarily in the bone marrow, liver, and spleen. In the duodenum, enterocytes facilitate dietary iron uptake through the divalent metal transporter 1 (DMT1) and release it into circulation via ferroportin, a process tightly regulated by the hepatic hormone hepcidin (Vogt et al., 2021).

A decrease in hemoglobin concentration below reference intervals specific to age and sex is known as anemia, and it impairs the delivery of oxygen to tissues (Leung et al., 2024). IDA develops when iron demand outpaces supply, usually due to chronic blood loss, insufficient nutritional intake, or malabsorption, leading to depleted iron stores and microcytic, hypochromic erythrocytes (Cappellini et al., 2022; DePalma et al., 2021). Typical laboratory features include low ferritin, low transferrin saturation (TSAT), elevated total iron-binding capacity (TIBC), and increased sTfR (DePalma et al., 2021; Leung et al., 2024). ACD, in contrast, results from increased hepcidin synthesis – often induced by IL-6 – that decreases ferroportin expression and traps iron in macrophages and hepatocytes (Han & Wang, 2021; Marginean et al., 2023). As a result, serum iron levels decrease, whereas ferritin concentrations may stay within the normal range or become elevated, consistent with its behavior as an acute-phase reactant (DePalma et al., 2021).

Ferritin serves as the primary intracellular reservoir for iron, with the capacity to store as many as 4,500 iron atoms within its structure. Serum ferritin is a widely utilized laboratory indicator of iron status, as under normal physiological conditions it accurately reflects the body's iron storage levels (Arosio et al., 2024; Plays et al., 2021). In the absence of inflammation, ferritin levels below 15-30 ng/mL signify exhausted iron reserves and are consistent with a diagnosis of IDA (Jäger et al., 2024). Ferritin also functions as an acute-

phase reactant. Its production is stimulated by pro-inflammatory cytokines, particularly IL-6, in the setting of inflammation (Plays et al., 2021), infection (Zhao et al., 2024), tissue injury (Panther et al., 2022), or malignancy (Shesh & Connor, 2023). The specificity of ferritin for identifying true iron insufficiency in patients with inflammatory states is greatly diminished by this acute phase reactant impact (Arosio et al., 2024; Plays et al., 2021).

Studies have shown that ferritin levels between 30 and 100 ng/mL cannot exclude IDA when inflammatory markers such as CRP or ESR are elevated (Bondarchuk et al., 2021). CRP and ESR are key inflammatory biomarkers that contextualize iron studies (Farrag et al., 2024). Elevated CRP, mediated by IL-6, indicates active inflammation and often parallels ferritin elevation (Rizo-Téllez et al., 2023; Santos-Silva et al., 2021). Some studies suggest adjusting ferritin criteria in the presence of increased CRP in order to improve diagnostic accuracy (Pita-Rodríguez et al., 2022). For instance, a ferritin level below 100 ng/mL may nevertheless be consistent with IDA in inflammatory conditions where CRP is greater than 5 mg/L (Sama et al., 2023). In contrast, the standard ferritin threshold in non-inflammatory situations is <15–30 ng/mL (Truong et al., 2024). ESR increases more gradually than CRP and is influenced by fibrinogen levels and other plasma proteins, reflecting chronic rather than acute inflammation (Alharthi et al., 2024). However, ESR's usefulness as a stand-alone marker in the assessment of iron deficiency is limited due to its slower kinetics and dependence on age, sex, and other factors (Kahar, 2022).

Novel biomarkers such as hepcidin, sTfR, and CHr improve diagnostic precision in distinguishing IDA from ACD (Almashjary, 2024; Ghias et al., 2022; MH et al., 2021). The sTfR reflects erythroid iron demand and is minimally influenced by inflammatory processes, making it a dependable marker of iron availability for erythropoiesis. Its levels are generally elevated in IDA but remain normal or only slightly increased in ACD (Günther et al., 2024; Rohr et al., 2023; Tarancon-Diez et al., 2022). The sTfR/log ferritin index further refines interpretation, where values exceeding 1.5-2.0 are suggestive of IDA, while lower ratios indicate ACD (Ghoraba et al., 2025; Safarova et al., 2021). Hepcidin serves as the key regulator of body iron balance, being suppressed in IDA and elevated in ACD, although its clinical application is limited by assay standardization issues (Fathi et al., 2022; Gao et al., 2023). In contrast, CHr, which reflects the functional iron supply for erythropoiesis, is significantly decreased in IDA and only mildly decreased in ACD (Agarwal et al., 2021; Kılıç et al., 2022). Additional indicators have also been investigated. Zinc protoporphyrin (ZPP) accumulates in erythrocytes when iron is unavailable for hemoglobin synthesis and may be elevated in IDA, though it lacks specificity in inflammatory conditions (Leventi et al., 2021).

DISCUSSION

This literature synthesis highlights the complexity of evaluating iron status in the presence of inflammation. Conventional markers, particularly ferritin, provide valuable information but lose specificity when acute-phase responses are activated. Integrating inflammation markers such as CRP or ESR allows contextual interpretation and prevents misclassification between ACD and IDA. Accordingly, several reviews recommend using modified ferritin thresholds or complementary indicators – such as CHr or sTfR – to improve diagnostic accuracy in chronic disease settings (Aedh et al., 2023; Rohr et al., 2023). Emerging biomarkers – including sTfR, hepcidin, and CHr – address diagnostic gaps left by traditional parameters. sTfR and the sTfR/log ferritin index reflect true iron demand independent of inflammatory influence; a study by Rohr et al. supports using this index as a useful tool in distinguishing functional iron deficiency in inflammatory conditions (Rohr et al., 2023). As the key regulator of iron homeostasis, hepcidin links iron metabolism with immune signaling, and its elevated levels in inflammatory states are well described in both mechanistic and clinical contexts

(Nemeth & Ganz, 2023). CHr offers a functional perspective on iron availability, measurable via automated analyzers and less influenced by acute inflammatory changes (Agarwal et al., 2021; Kılıç et al., 2022).

Combining CRP, ferritin, and additional iron markers enhances diagnostic reliability, enabling differentiation between ACD (elevated CRP, normal or high ferritin, and low serum iron) and concurrent IDA (elevated CRP but low ferritin) (Wieczorek et al., 2022). When the CRP is <5 mg/L, ferritin <15–30 ng/mL supports IDA. In the presence of inflammation (CRP >5-10 mg/L), the interpretation criteria for ferritin require adjustment; values below 100 ng/mL can still suggest iron deficiency, especially when accompanied by reductions in other iron indices (Sama et al., 2023; Truong et al., 2024). An increased sTfR level or a high sTfR/log ferritin index (greater than 2.0) provides additional evidence supporting the presence of IDA (Ghoraba et al., 2025; Günther et al., 2024; Safarova et al., 2021). IDA is supported by low CHr (<28 pg), particularly when it is associated with sTfR or hepcidin (Agarwal et al., 2021; Kılıç et al., 2022). A multi-marker evaluation incorporating ferritin, CRP, sTfR, CHr, and hepcidin offers the highest diagnostic accuracy.

Compared with earlier studies that relied primarily on ferritin and TSAT, recent evidence supports a composite diagnostic framework. For example, a study by Kriel et al. highlights how misinterpretation of iron studies is common when inflammation is unaccounted for and argues strongly for combining traditional and novel biomarkers (Kriel et al., 2025). Moreover, the review by Marques et al. emphasizes how inflammation induces hepcidin expression, which subsequently reduces ferroportin-mediated iron export, limiting the diagnostic sensitivity of standard iron tests (Marques et al., 2022). This multi-marker approach not only increases diagnostic precision but also guides therapy – ensuring that patients with functional iron restriction due to ACD are not inappropriately given iron and that true iron deficiency in inflammatory states is not overlooked.

The findings also emphasize methodological challenges. Lack of standardized assays, particularly for hepcidin and sTfR, limits inter-study comparability and result interpretation – a concern raised in recent reviews (Fathi et al., 2022; Kriel et al., 2025; Nemeth & Ganz, 2023). Mixed anemia – common in chronic disease, elderly populations, or malignancy – remains a diagnostic gray zone, as overlapping features of IDA and ACD often blur biomarker interpretation. Additionally, a study by Czempik et al. showed that in septic patients, correlations between standard and novel biomarkers are weak, further cautioning against overreliance on single markers (Czempik & Wiórek, 2023). Despite their advantages, biomarkers such as hepcidin and sTfR are limited by assay variability, lack of reference standards, and limited access in clinical laboratories (Fathi et al., 2022).

Additionally, comorbidities such as chronic kidney or liver disease may affect marker reliability. Future research should focus on assay standardization, establishment of population-specific reference intervals, and development of cost-effective, integrated diagnostic algorithms. The incorporation of machine learning for multi-parametric interpretation could further refine the assessment of iron metabolism in inflammatory states, especially in resource-limited settings. Overall, interpreting iron studies beyond ferritin represents a paradigm shift toward a more comprehensive, physiology-based diagnostic approach. By combining conventional and emerging markers, clinicians can achieve more accurate differentiation between IDA and ACD, improving patient management and treatment outcomes.

CONCLUSION

Determining iron availability during inflammatory states remains a major challenge for accurate diagnosis. Ferritin continues to serve as the most commonly used marker of iron

stores; however, its ability to discriminate between IDA and ACD is constrained by its role as an acute-phase reactant. Inflammatory conditions can mask true iron deficiency, potentially leading to misdiagnosis and inappropriate management. A more comprehensive assessment of iron metabolism and erythropoietic activity can be achieved through the integration of additional laboratory markers, such as CRP, sTfR, hepcidin, and CHr, to overcome these limitations. Compared to traditional measures alone, these biomarkers provide better diagnostic accuracy when interpreted within the inflammatory context. Based on this narrative review, interpreting iron studies beyond ferritin using a multi-marker, inflammation-aware approach represents an important development in clinical pathology. As assay accessibility and standardization improve, these approaches could help guide more precise anemia diagnosis and therapy for individuals with complicated medical conditions.

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