Iron deficiency in heart failure: Diagnostic markers, prognostic accuracy and evolving definitions

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Iron deficiency (ID) is one of the most prevalent and clinically significant comorbidities in heart failure (HF), affecting approximately 30–70% of patients with chronic HF and up to 80% of those with acute decompensation. Importantly, ID confers adverse outcomes independent of anemia, including impaired exercise capacity, reduced quality of life, increased hospitalization and excess mortality. Despite two decades of clinical trials and guideline recommendations, substantial uncertainty persists regarding the optimal definition of ID in HF and the diagnostic and prognostic accuracy of individual biomarkers. Current definitions rely predominantly on serum ferritin and transferrin saturation (TSAT). However, emerging evidence challenges ferritin-based criteria, highlighting the inflammatory distortion of ferritin and suggesting that TSAT and serum iron may more accurately reflect biologically relevant hypoferremia. Novel markers such as soluble transferrin receptor, composite ferritin–TSAT models and inflammation-adjusted ferritin indices offer refined risk stratification and pathophysiologic insight. This state-of-the-art review critically appraises established and emerging markers of ID in HF, focusing on diagnostic performance, prognostic discrimination, pathophysiologic relevance and therapeutic implications. We discuss the evolving transition from ferritin-driven definitions toward TSAT-based hypoferremia models and propose an integrated biomarker strategy aligned with mechanistic understanding and clinical outcomes.

Keywords

Biomarkers, ferritins, heart failure, iron deficiencies, transferrin, transferrin receptors

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Heart failure (HF), first recognized as a distinct clinical syndrome in the early 20th century, has evolved from a largely descriptive diagnosis into a major global public health challenge and a leading cause of morbidity, mortality and healthcare expenditure worldwide, with the advent of modern cardiovascular physiology and imaging. Despite advances in neurohormonal modulation, device therapy and disease-modifying pharmacology, residual risk remains substantial. Consequently, growing attention has shifted toward non-hemodynamic comorbidities that independently drive functional impairment and adverse clinical outcomes.

Iron deficiency (ID) has emerged as one of the most important non-hemodynamic determinants of prognosis in HF. Unlike anemia, which may be multifactorial, ID directly affects mitochondrial respiration, skeletal muscle energetics, myocardial contractility, erythropoiesis and systemic inflammatory pathways. The 2016 European Society of Cardiology (ESC)/ Heart Failure Association (HFA) guidelines formally recognized ID as a treatable comorbidity in HF and recommended routine screening.[1] Since then, multiple randomized trials of intravenous (IV) iron have demonstrated improvement in symptoms, exercise capacity and reduction in HF hospitalizations, particularly in patients defined by transferrin saturation (TSAT) <20%.[2]

Despite these advances, defining ID in HF remains contentious. The traditional ferritin-based framework, extrapolated from chronic kidney disease (CKD) populations, may not adequately reflect tissue-level iron availability or predict therapeutic responsiveness.[2] Emerging mechanistic and prognostic data have therefore prompted reconsideration of existing diagnostic thresholds. This article synthesizes contemporary evidence to address three central questions:

- Which biomarkers most accurately diagnose ID in HF?
- Which markers independently predict adverse outcomes?
- How should definitions evolve to align with pathophysiology and treatment response?

To frame this discussion, it is first necessary to revisit the physiologic principles governing systemic iron homeostasis. A mechanistic understanding of iron absorption, transport, recycling and hormonal regulation provides the foundation for interpreting biomarker discordance and contextualizing iron dysregulation in HF.

Literature search strategy

This state-of-the-art review was based on a comprehensive search of PubMed, Embase and Scopus from database inception through January 2026. Search terms included combinations of heart failure, iron deficiency, transferrin saturation, ferritin, serum iron, soluble transferrin receptor,

Figure 1: Overview of iron metabolism in the human body

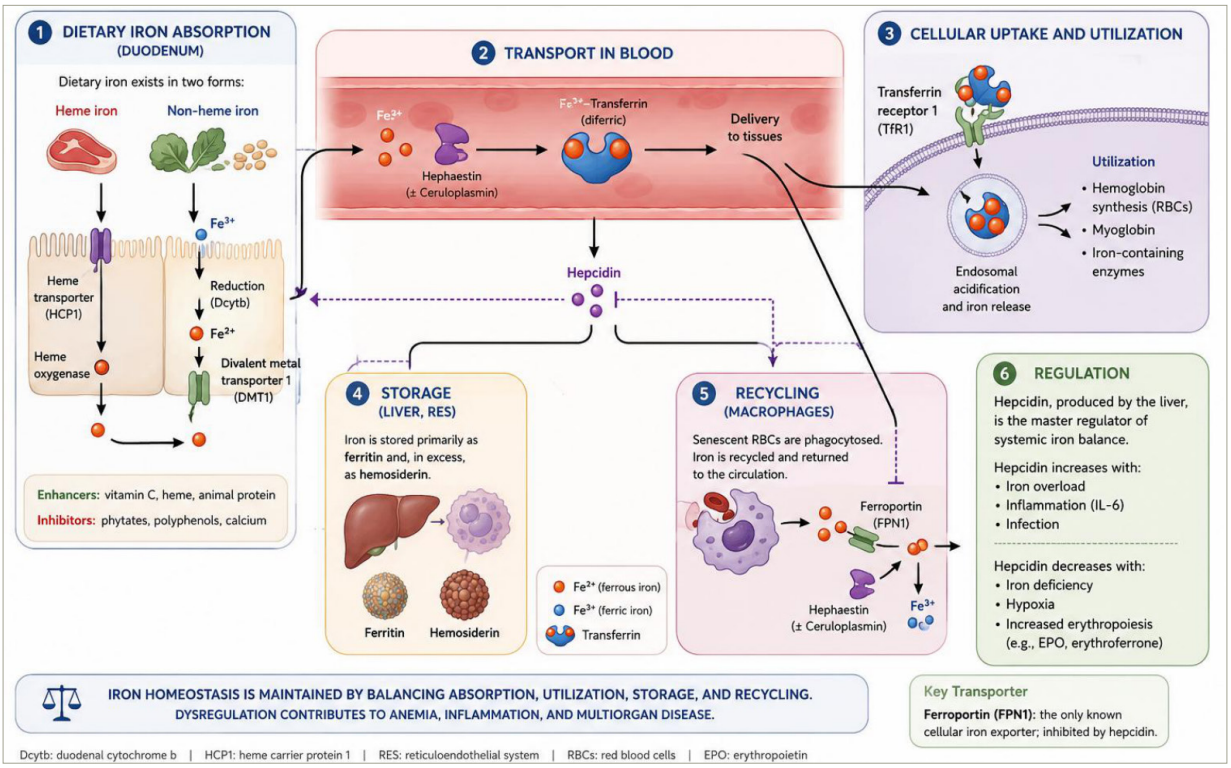


Figure was created using BioRender and ChatGPT (OpenAI)
Dcytb = duodenal cytochrome b; DMT1 = divalent metal transporter 1; EPO = erythropoietin; HCP1 = heme carrier protein 1; FPN1 = ferroportin 1; HCP1 = heme carrier protein 1; IL-6 = interleukin-6; RBC = red blood cells; RES = reticuloendothelial system; TfR1 = transferrin receptor 1.

hepcidin, reticulocyte hemoglobin content, erythroferrone and related keywords. Reference lists of relevant articles were manually searched to identify additional publications. Priority was given to randomized controlled trials, prospective cohort studies, mechanistic investigations, meta-analyses, clinical practice guidelines and consensus statements published in English. The final selection of studies was based on their relevance to the evolving understanding of iron metabolism, diagnostic biomarkers, prognostic significance and therapeutic implications in HF.

Physiology of iron metabolism

Iron is essential for oxygen transport, mitochondrial energy production and numerous enzymatic reactions. Systemic iron homeostasis is maintained through coordinated regulation of intestinal absorption, macrophage-mediated recycling and hepatic storage under the control of the hepcidin–ferroportin axis (*Figure 1*).[3–6] Dietary iron is absorbed in the duodenum and exported into the circulation via ferroportin, while the majority of daily iron requirements are met through macrophage-mediated recycling of senescent erythrocytes rather than intestinal absorption. Hepcidin, a peptide hormone synthesized by the liver, regulates ferroportin activity and thereby controls systemic iron availability. Inflammatory cytokines, particularly interleukin-6 (IL-6), increase hepcidin production, promoting iron sequestration within macrophages and reducing circulating iron availability. Conversely, increased erythropoietic demand suppresses hepcidin, facilitating iron mobilization and absorption. These opposing regulatory mechanisms explain why ferritin, a storage protein and acute-phase reactant, may become discordant from markers of circulating iron availability such as TSAT and serum iron in chronic inflammatory conditions, including HF.

At the cellular level, iron is required for heme synthesis, iron–sulfur cluster formation and mitochondrial adenosine triphosphate (ATP) production in cardiomyocytes and skeletal muscle. Consequently, tissue ID may occur despite preserved systemic iron stores, particularly in HF where myocardial and skeletal muscle iron depletion have been demonstrated. Biomarkers, such as soluble transferrin receptor (sTfR), reticulocyte hemoglobin (Ret-He), hepcidin and erythroferrone (ERFE), provide complementary information regarding cellular iron demand and systemic iron regulation, forming the physiologic basis for the diagnostic biomarkers discussed in subsequent sections.[7,8]

Epidemiology of iron deficiency in heart failure

ID is highly prevalent across the entire spectrum of HF phenotypes and clinical settings. Contemporary cohort studies consistently demonstrate that approximately 50–55% of patients with chronic HF meet criteria for ID, while the prevalence rises dramatically – to nearly 80% – among patients hospitalized with acute decompensated HF.[9] Hospital-based series have reported a wide range of prevalence estimates, from 30% to 83%, reflecting differences in patient populations, clinical acuity and diagnostic definitions.[10]

Importantly, ID frequently occurs in the absence of overt anemia, underscoring its independent pathophysiologic relevance.[11] This observation underscores a critical conceptual shift: ID in HF is not merely a hematologic disorder but a systemic metabolic disturbance with independent pathophysiologic and prognostic implications. Registry analyses and consensus documents, such as the Austrian consensus statement, report that ID is present in ~55% of chronic HF and up to 80% of acute HF, irrespective of ejection fraction.[12] Similar findings are reported in large registry-based cohorts. Furthermore, ID prevalence increases with worsening New York Heart Assoication (NYHA) functional class, suggesting that ID both reflects advancing disease severity and may actively contribute to clinical deterioration.[13]

Pathophysiology of iron deficiency in heart failure

Absolute and functional iron deficiency

ID in HF is not a uniform entity but rather represents a spectrum of biologically distinct states:

- Absolute ID
- Functional ID

Absolute ID (low ferritin) denotes true depletion of total body iron (TBI) stores, typically reflected by low ferritin concentrations, reduced bone marrow iron content and usually low hepcidin. In contrast, functional ID arises when iron stores are preserved or even increased and results from hepcidin-driven sequestration – normal or high ferritin with low TSAT – and frequently coexists with chronic inflammation.[14] In functional ID, circulating iron availability is inadequate to meet metabolic demands. Recognizing which axis predominates in a given patient determines diagnostic interpretation and therapeutic strategy: iron repletion is effective when iron is bioavailable and deliverable to tissues, but in pure hepcidin-mediated sequestration, strategies that bypass enteric absorption (IV iron) or modulate hepcidin are mechanistically preferable.

In HF, multiple converging mechanisms promote iron dysregulation. As mentioned before, chronic systemic inflammation, characterized by elevated cytokines such as IL-6, induces hepcidin expression and restricts ferroportin-mediated iron export. Intestinal congestion and mucosal edema may impair enteral absorption, while renal dysfunction and erythropoietic stress further perturb iron handling.[3,7] These interacting processes create a milieu in which iron becomes sequestered within reticuloendothelial stores, resulting in reduced TSAT despite normal or elevated ferritin levels. Given that ferritin behaves as an acute-phase reactant, inflammatory activation may obscure true depletion and complicate diagnostic interpretation.

Mechanistic pathways of iron-deficient heart failure

Emerging mechanistic data suggest that ID contributes to HF progression through at least three interrelated biological pathways:

- Systemic hypoferremia (TSAT <15–16%)
- Skeletal muscle iron depletion
- Myocardial iron depletion

First, systemic hypoferremia – often reflected by TSAT levels below 15–16% – impairs erythropoiesis and reduces oxygen delivery capacity.[11] However, the consequences extend beyond hemoglobin synthesis. Second, skeletal muscle iron depletion disrupts mitochondrial oxidative phosphorylation, leading to reduced ATP generation, early lactate accumulation and impaired exercise tolerance. This mechanism helps explain why IV iron improves functional capacity even in patients without anemia. Third, myocardial iron depletion has been implicated in adverse ventricular remodeling, impaired contractility and altered cardiomyocyte energetics.[11]

Experimental and translational studies demonstrate that myocardial iron content correlates with mitochondrial enzyme activity and systolic performance.[15] Crucially, these mechanistic disturbances are more closely aligned with circulating iron availability than with storage markers. Ferritin concentrations may remain within reference ranges despite profound intracellular or mitochondrial iron depletion, reinforcing the concept that bioavailable iron – not total stored iron – may be the clinically relevant determinant.[16] These pathways and their associated biomarkers are illustrated in *Figure 2*.

Mechanistic basis of intravenous iron therapy

The benefits of IV iron therapy in HF extend beyond correction of anemia and are primarily attributed to restoration of cellular iron availability. Iron is essential for mitochondrial oxidative phosphorylation, ATP production

Figure 2: Iron dysregulation in heart failure: mechanisms, biomarkers and clinical impact

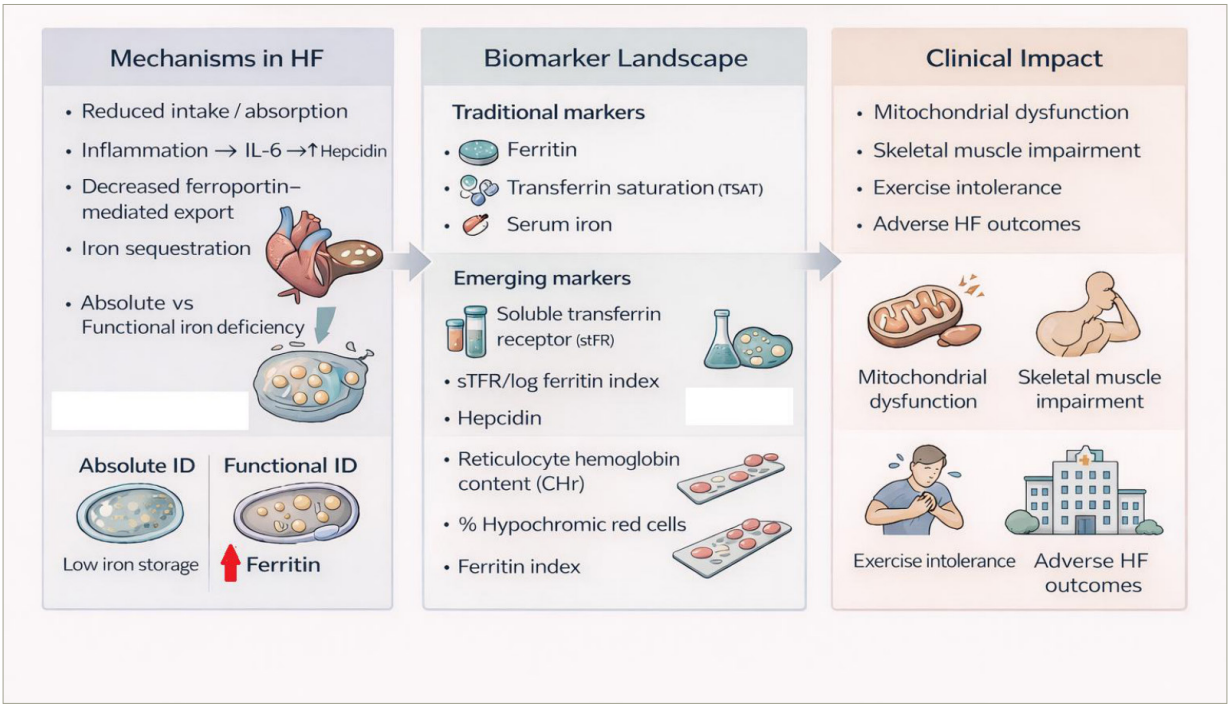


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CHr = reticulocyte haemoglobin content; HF = heart failure; ID = iron deficiency; IL-6 = interleukin-6; sTFR = soluble transferrin receptor; TSAT = transferrin saturation.

and the function of iron-containing enzymes in both cardiomyocytes and skeletal muscle.[17–19] ID impairs myocardial energetics, reduces skeletal muscle oxidative capacity and contributes to exercise intolerance even in the absence of anemia. Accordingly, improvements in symptoms and functional capacity after IV iron often precede significant changes in hemoglobin, suggesting that restoration of tissue iron availability is the principal therapeutic mechanism. Supporting this concept, De Biase et al. demonstrated that low TSAT was independently associated with congestion, impaired peak oxygen uptake (peak VO_2) and adverse clinical outcomes across the HF spectrum, whereas ferritin-based definitions showed weaker associations.[20]

These findings reinforce the concept that restoration of circulating iron bioavailability, rather than iron stores alone, underpins the clinical benefits of IV iron therapy and further support a TSAT-centered approach to identifying patients most likely to benefit from treatment.

Traditional diagnostic criteria

Current HF guidelines define ID as a serum ferritin concentration below 100 µg/L or a ferritin concentration between 100 and 299 µg/L in the presence of TSAT below 20%.[21] This definition was originally extrapolated from CKD populations and adopted to standardize eligibility criteria across early IV iron trials.[1]

However, these thresholds were not derived from bone marrow validation studies specific to HF populations. As such, their biological accuracy in reflecting true tissue ID has been questioned.[22] The reliance on ferritin, an inflammation-sensitive storage marker, may lead to misclassification – particularly in patients with chronic low-grade inflammatory activation.[11] Increasing evidence suggests that this framework may inadequately capture clinically meaningful hypoferremia and may not optimally identify patients most likely to benefit from iron repletion.

Comprehensive classification of iron deficiency biomarkers

ID in HF reflects a multilayered disturbance. Biomarkers can be grouped into five categories:

- Storage markers (ferritin, bone marrow iron)
- Transport markers (serum iron, transferrin, total iron binding capacity [TIBC], TSAT)
- Functional erythropoietic markers (sTfR, Ret-He, zinc protoporphyrin [ZPP], reticulocyte distribution width [RDW])
- Regulatory markers (hepcidin, ERFE, growth differentiation factor 15 [GDF-15])
- Inflammatory modulators (C-reactive protein [CRP], IL-6)

Regulatory and inflammatory markers provide mechanistic insight but are not yet standardized for routine clinical decision-making. GDF-15, although strongly prognostic in HF, reflects systemic stress rather than specific iron depletion. Composite indices (e.g. sTfR/log ferritin ratio, TBI models) attempt to integrate these domains into a more coherent representation of iron status. Discordance between ferritin and TSAT should therefore be viewed as a reflection of complex iron biology rather than laboratory inconsistency.

Storage markers

Serum ferritin has long been regarded as the principal marker of iron stores. In the absence of inflammation, ferritin concentrations below 100 µg/L reliably indicate depleted iron reserves. However, in HF – where chronic inflammatory activation is common –interpretation becomes considerably more complex. Ferritin functions as an acute-phase reactant and may be elevated independent of iron status, thereby masking underlying depletion. Prognostically, ferritin has demonstrated inconsistent associations with mortality and hospitalization. Several contemporary analyses show that ferritin alone does not independently predict adverse outcomes once other covariates are considered.[23] Furthermore, patients who satisfy ferritin-based criteria for ID but maintain a TSAT ≥20% appear to derive limited symptomatic benefit from IV iron therapy. These observations collectively challenge the primacy of ferritin in defining biologically relevant ID in HF. Ferritin, unlike other conventional markers, did not correlate with right heart catheterization parameters and, in hospitalized patients, has been shown to be the only marker with poor correlation with NYHA-defined performance status. It has also been demonstrated by Bakosova et al. to be the least reliable conventional ID parameter, especially for in-patients with decompensated HF (area under the curve of sensitivity and specificity analysis=0.59).[23]

In certain trials, bone marrow iron content was used as the gold standard for the diagnosis of ID.[22] Bone marrow tissue may be stained with Prussian blue, followed by microscopic examination to evaluate iron reserves. The percentage of sideroblasts reflects the functional availability of iron for erythropoiesis. Approximately 20–50% of erythroblasts contain iron under normal conditions; 10–20% of erythroblasts containing iron is considered low normal, and patients with sideroblasts <10% are considered to have functional ID.[24] Quantitative assessment of iron in bone marrow can be performed using the Gale histological grading system.[25] With reference to bone marrow iron as the gold standard, serum ferritin was noted to have a sensitivity and specificity of 70.6% and 60.0%, respectively.[22]

Transport markers

Serum iron represents the circulating pool of transferrin-bound iron at a given time point. Serum iron has been shown to have a sensitivity and specificity of 94.1% and 88.0%, respectively, when using bone marrow iron as the gold standard.[22] Although dynamic and subject to diurnal variation, low serum iron concentrations independently predict mortality in HF cohorts. Serum iron also correlates strongly with N-terminal brain natriuretic peptide (NT-proBNP) levels and inflammatory markers, suggesting that it may capture the intersection of congestion, inflammation and metabolic stress. Some investigators argue that serum iron may, in fact, represent the most direct indicator of biologically active ID.

Serum transferrin levels may also be directly assessed, which may in turn be used to derive the TIBC and TSAT. Serum transferrin levels increase in ID, but, being a negative acute phase reactant, serum levels have been noted to decrease in acute inflammatory states. TSAT reflects the proportion of circulating transferrin binding sites occupied by iron and therefore provides a direct estimate of iron immediately available for tissue uptake. Unlike ferritin, TSAT is less strongly influenced by inflammatory activation and more closely mirrors systemic hypoferremia. TSAT has been observed to have a sensitivity and specificity of 94.1% and 84.0%, respectively.[22] Multiple studies consistently demonstrate that TSAT independently predicts functional status and HF hospitalization.[26–28] It also correlates with natriuretic peptide concentrations, exercise capacity and functional status in advanced disease. Importantly, TSAT <20% has been the most consistent biomarker associated with clinical responsiveness to IV iron therapy, reinforcing its pathophysiologic and therapeutic relevance.

TIBC is a calculated parameter derived from the serum transferrin concentration, which measures the blood's capacity to bind iron with

transferrin. A study by Asif et al. demonstrated that when using ferritin as the gold standard, TIBC was noted to have a sensitivity and specificity of 64.5% and 42.8%, respectively.[29]

Functional markers

The levels of sTfR reflect cellular iron demand and erythroid precursor activity; sTfR levels increase with ID. This is also a reflection of increased shedding of the cell-surface transferrin receptor 1, a protein upregulated in response to low intracellular iron levels.[30] Unlike ferritin, sTfR provides a better reflection of erythropoiesis, is minimally influenced by inflammation and may therefore provide a clearer window into tissue-level iron requirements. Elevated sTfR concentrations have been associated with adverse outcomes even among patients without anemia, and correlations with invasive hemodynamic parameters have been reported in advanced HF.[23] Despite its mechanistic appeal, widespread clinical adoption remains limited by assay cost, lack of standardization and restricted availability. At a diagnostic cutoff of >2.8 mg/L, sTfR demonstrated a sensitivity of 92% and specificity of 84% for detecting ID, with a positive predictive value of 42% in the studied population; however, this cohort was not composed exclusively of patients with HF.[31]

Ret-He is a parameter that may be obtained from automated hematology analyzers. Ret-He reflects the hemoglobin content of circulating reticulocytes. As reticulocytes mature into erythrocytes within approximately 2 days in peripheral blood, this index provides a near-real-time indicator of iron availability for erythropoiesis. According to Tahara et al., a Ret-He threshold of 32.4 pg may be used to screen for ID.[32]

During the final step of heme synthesis, ferrochelatase inserts ferrous iron into protoporphyrin IX to form heme. When iron availability is insufficient, zinc is incorporated instead, producing ZPP. Elevated ZPP, therefore, reflects impaired iron supply for heme synthesis and rises as ID progresses, often preceding overt anemia. Although not widely used in routine practice, ZPP can serve as a marker of both absolute ID and functional ID; however, diagnostic thresholds vary across studies and assay platforms.[33]

Clinically, ZPP has been used to assess iron status in several settings. In pediatrics, it can help detect early iron depletion before anemia develops, while in pregnancy, the ZPP/hemoglobin ratio may reduce misinterpretation caused by plasma volume expansion. In blood donor screening, ZPP can identify imbalances between erythropoietic iron demand and supply. Measurement is typically performed in whole blood using a hematofluorometer, either directly or as free erythrocyte protoporphyrin after extraction.[33]

RDW is a measure of anisocytosis, reflecting the variability in the size of circulating erythrocytes. It is routinely reported as part of the complete blood count and is elevated in ID and chronic HF. Higher RDW levels have therefore been associated with poorer outcomes in both acute and chronic HF.[34] However, it is nonspecific and affected by several pathophysiologic processes, resulting in poor sensitivity and specificity for diagnosing ID in chronic HF (sensitivity=58.8% and specificity=75.0%).[22]

Regulatory markers

Hepcidin is a small (± 2.8 kDa) peptide hormone produced predominantly by hepatocytes and serves as the central regulator of systemic iron homeostasis, as highlighted previously. In ID, hepcidin levels fall, facilitating increased intestinal iron absorption and mobilization of stored iron.[35] Conversely, iron excess stimulates hepcidin production, which restricts further iron absorption and release from storage sites. Inflammatory states also increase hepcidin levels, reducing iron availability for erythropoiesis and contributing to the development of anemia of chronic disease (ACD). In the study by Grote Beverborg et al., hepcidin showed a sensitivity of 52.9% and specificity of 84.0% for detecting ID in patients with HF.[22]

ERFE is a hormone released by erythroblasts during stress-induced erythropoiesis that enhances iron availability to meet the increased demands of red blood cell production.[36] During increased erythropoiesis, erythropoietin stimulates erythroblasts in the bone marrow to release ERFE, which reduces hepatic hepcidin production and promotes the mobilization of iron for hemoglobin synthesis. In conditions of ineffective erythropoiesis, excessive ERFE production can lead to persistent hepcidin suppression and subsequent iron overload. Because of this role, ERFE is being investigated as both a biomarker of ineffective erythropoiesis and a potential therapeutic target.[37]

GDF-15 is a stress-responsive cytokine belonging to the transforming growth factor-β superfamily and is released into the circulation in response to cellular injury and metabolic stress.[38] Although minimally expressed in the normal adult myocardium, its expression increases following myocardial injury and during cardiac stress, where it contributes to pathways involved in cellular survival, metabolic regulation and tissue remodeling. Circulating GDF-15 levels are elevated in several cardiovascular conditions, including HF, and have also been observed in patients with ID. Higher levels have been associated with markers of worse clinical status in HF. These observations suggest that GDF-15 may reflect the combined burden of metabolic stress, inflammation and disease severity in patients with HF. A universal cut-off value of 1,400 pg/mL has been observed to perform well in discriminating between patients with and without HF.[39]

Inflammatory modulators

Acute inflammatory events accompanying an acute myocardial infarction (AMI) initiate an inflammatory response aimed at necrotic tissue clearance and repair promotion. However, when this response becomes excessive or prolonged, it can contribute to adverse myocardial remodeling and progression to HF.[40] During AMI, the release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-6 promotes infiltration of inflammatory cells into the myocardium. While initially protective, this process may also lead to additional cardiomyocyte injury, cell loss and the development of myocardial fibrosis.

Chronic low-grade inflammation occurs in patients with comorbidities and is closely associated with aging. These conditions create an unresolved inflammatory state involving effectors such as pro-inflammatory cytokines and components of the innate and humoral immune response, which contribute to progressive left ventricular dysfunction. This state is characterized by sustained release of inflammatory cytokines such as IL-1, TNF-α and IL-6, which promote pathways including nuclear factor kappa B activation and nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR) and pyrin domain-containing protein 3 (NLRP3) inflammasome signaling. These processes contribute to systemic inflammation, oxidative stress, endothelial dysfunction and arterial stiffness, thereby increasing cardiovascular risk and accelerating the progression of HF.[41] Additional upregulation of cytokines such as IL-1β and IL-18 further amplifies this process, promoting myocardial fibrosis, hypertrophy and diastolic dysfunction.

In patients admitted following decompensated HF, the prevalence of ID has been observed to decline in the weeks following discharge, with

Table 1: Biomarkers of iron deficiency in heart failure[1,20,22,30–33,37,39,43–47]

Biomarker	What it reflects	Advantages	Limitations	Clinical utility
Serum ferritin	Iron storage	Widely available, inexpensive	Acute-phase reactant; elevated in inflammation, infection, liver disease	Historically used for ID definition; limited reliability in HF <100 µg/L (absolute ID) or 100–299 µg/L with TSAT <20% (functional ID)[1]
TSAT	Circulating iron available for cellular uptake	Reflects bioavailable iron; strong prognostic associations in HF	Diurnal variation; affected by recent iron intake	Increasingly considered the most clinically relevant marker of ID in HF Emerging evidence supports TSAT <20% as the preferred definition of clinically relevant ID in HF[30]
Serum iron	Circulating iron bound to transferrin	Simple test; correlates with TSAT	High biological variability; influenced by inflammation	Useful adjunct marker of hypoferremia ≤13 µmol/L (≈73 µg/dL) showed optimal discrimination against bone marrow ID[20]
sTfR	Cellular iron demand and erythropoietic activity	Less influenced by inflammation; reflects tissue ID	Higher cost; limited availability	Helpful in differentiating absolute versus functional ID General hematology studies have used >2.8 mg/L, while HF studies often analyze sTfR as a continuous variable or by cohort-specific thresholds[31]
sTfR/log ferritin index	Integrated measure of transport and storage iron	Improved diagnostic accuracy over single markers	Requires sTfR measurement; limited standardization	Useful in complex anemia or inflammatory states No universally accepted HF-specific cut-off In non-HF populations, values >1.5–2.0 (assay-dependent) suggest absolute ID[46,47]
Ret-He/CHr	Iron availability for erythropoiesis	Early indicator of iron-restricted erythropoiesis; available from automated analyzers	Variable cut-offs; limited HF validation	Early detection of iron-restricted erythropoiesis Common laboratory reference values range from <28 to 30 pg (assay-dependent), reflecting iron-restricted erythropoiesis. No validated HF-specific threshold[32]
RDW	Variability in erythrocyte size (anisocytosis)	Routinely available; prognostic marker in HF	Nonspecific; influenced by multiple conditions	Marker of disease severity and adverse prognosis No diagnostic cut-off for ID. Most HF studies evaluate RDW as a continuous variable; values >14.5–15% are generally associated with adverse outcomes[22]
Hepcidin	Master regulator of systemic iron homeostasis	Reflects iron regulatory pathways	Limited assay availability; significant biological variability	Potential diagnostic and therapeutic target No universally accepted clinical cut-off[43–45]
ERFE	Suppressor of hepcidin during stress erythropoiesis	Reflects erythropoietic drive	Emerging biomarker; limited clinical validation	Potential marker of ineffective erythropoiesis No validated clinical cut-off. ERFE is measured primarily in research settings, and assays lack standardization[37]
GDF-15	Stress-response cytokine linked to inflammation and metabolic stress	Associated with HF severity and adverse outcomes	Not specific to iron metabolism	May reflect metabolic stress in HF with ID No accepted diagnostic threshold for ID in HF Most studies evaluate GDF-15 as a continuous biomarker or by study-specific quartiles[39]
ZPP	Impaired heme synthesis due to iron restriction	Detects iron-restricted erythropoiesis	Limited availability; variable reference ranges	Potential marker of absolute and functional ID Common laboratory threshold >40–70 µmol/mol heme (assay-dependent) suggests iron-restricted erythropoiesis. No validated HF-specific threshold[33]

Where available, commonly used or proposed diagnostic thresholds are shown. For several emerging biomarkers, no universally accepted HF-specific cut-offs have been established because of assay variability and limited prospective validation.
CHr = reticulocyte hemoglobin content; ERFE = erythroferrone; GDF-15 = growth differentiation factor 15; HF = heart failure; ID = iron deficiency; RDW = reticulocyte distribution width; Ret-He = reticulocyte hemoglobin equivalent; sTfR = soluble transferrin receptor; TSAT = transferrin saturation; ZPP = zinc protoporphyrin.

modest changes in iron indices correlating with shifts in inflammatory markers, suggesting that inflammation may influence iron metabolism in this population.[42] Elevated IL-6 levels have been associated with lower circulating iron and higher hepcidin concentrations, although some cohorts have shown that patients with ID may exhibit lower hepcidin levels despite higher inflammatory markers.[43–45] These findings suggest that inflammation may contribute differently to the pathophysiology of functional and absolute ID. An overview of these biomarkers is provided in *Table 1*.[1,20,22,30–33,37,39,43–47]

Composite and inflammation-adjusted indices

Given the limitations of individual markers, composite approaches have been proposed. Assessing TBI is challenging because iron is distributed across several physiologic compartments. Although ferritin is widely used as a marker of iron stores, combining it with sTfR provides a more integrated view of iron status. Hence, several composite indices combining sTfR and ferritin have been proposed.

The body iron index, described by Cook and colleagues, estimates TBI by integrating sTfR and ferritin through the logarithmic sTfR/ferritin ratio; positive values indicate adequate iron stores, whereas negative values suggest tissue iron deficit. The sTfR/ferritin ratio itself is also clinically informative. ID anemia (IDA) typically shows high sTfR with low ferritin, producing a high ratio, whereas ACD often shows normal or elevated ferritin with relatively stable sTfR levels. A related metric, the sTfR index (sTfR/log ferritin), attempts to account for the non-linear relationship between ferritin and iron availability and may aid in distinguishing IDA from ACD. Clinically, low ferritin with reduced Ret-He suggests absolute ID, whereas normal or elevated ferritin with reduced Ret-He suggests functional ID. However, their broader application is limited by the absence of universally accepted diagnostic cut-offs for ID.

The Thomas plot is based on the relationship between sTfR/log ferritin and Ret-He and is a useful tool for differentiating types of anemia, particularly ID, as well as helping to guide therapy and monitor treatment response.[46] A modified Thomas plot replaces sTfR with the transferrin/log ferritin ratio combined with Ret-He, allowing similar diagnostic interpretation while relying on the more widely available transferrin measurement.[47] This approach can help distinguish various types of ID. The Adjusted Ferritin Inflammation Index incorporates ferritin, CRP and albumin to account for inflammatory distortion.[48]

These strategies attempt to integrate storage and inflammatory signals to refine diagnostic precision.

Comparative diagnostic and prognostic performance

Direct comparisons of iron biomarkers across HF cohorts reveal consistent differences in diagnostic and prognostic performance. Ferritin, although historically central to the definition of ID, demonstrates

relatively weak and inconsistent associations with clinical outcomes. In contrast, markers reflecting circulating iron availability – particularly TSAT and serum iron – have repeatedly shown stronger prognostic value.

Multiple cohort studies demonstrate that low TSAT independently predicts mortality, HF hospitalization and reduced functional capacity, even after adjustment for anemia and other clinical covariates.[49–51] These associations appear consistent across HF phenotypes and clinical settings. In contrast, ferritin levels often show weak or absent correlations with hemodynamic parameters, natriuretic peptide concentrations and functional status.[52]

Mechanistic validation studies have provided further support for this distinction. When bone marrow iron staining was used as the reference standard, TSAT ≤19–20% demonstrated superior sensitivity and specificity for identifying true ID compared with ferritin-based definitions.[22]

Functional biomarkers such as sTfR also provide incremental information regarding cellular iron demand and erythropoietic activity. Elevated sTfR levels have been associated with reduced functional capacity and worse outcomes even in patients without systemic ID or anemia, suggesting the presence of tissue-level iron restriction that may not be captured by conventional markers.[53] Collectively, these findings indicate that biomarkers reflecting bioavailable iron and cellular demand outperform storage-based markers in identifying clinically relevant ID and predicting adverse outcomes in HF.

Iron deficiency across heart failure phenotypes

ID is highly prevalent across the spectrum of HF, affecting patients with HF with reduced ejection fraction (EF) (HFrEF), HF with mid-range EF (HFmrEF) and HF with preserved EF (HFpEF) to a comparable extent. This observation suggests that disturbances in iron metabolism are a fundamental feature of HF biology rather than a consequence of impaired left ventricular ejection fraction (LVEF) alone. In patients with HFrEF, ID is consistently associated with greater symptom burden, elevated natriuretic peptide concentrations, increased risk of hospitalization and reduced functional capacity. Accordingly, the major randomized trials evaluating IV iron therapy have predominantly enrolled patients with HFrEF.[17–19,54–56]

Although therapeutic evidence in HFmrEF and HFpEF remains limited, accumulating observational data indicate that the clinical significance of ID extends across the entire HF spectrum. In particular, HFpEF is characterized by exercise intolerance, impaired peripheral oxygen utilization, skeletal muscle dysfunction and microvascular abnormalities, all of which may amplify the physiologic consequences of impaired iron availability. Consequently, biomarkers reflecting circulating iron supply, particularly TSAT, may have greater pathophysiologic and prognostic relevance than markers of iron storage in these phenotypes.[52]

Recent evidence has further strengthened this concept. In a prospective multicenter study of 1,502 ambulatory patients with HF, De Biase et al. compared conventional guideline-defined ID with alternative definitions based on TSAT and serum iron. Patients identified by TSAT <20% demonstrated greater left atrial enlargement, more severe ultrasound evidence of congestion, poorer exercise capacity and worse clinical outcomes irrespective of LVEF, whereas ferritin-based definitions showed weaker and less consistent associations with these clinically relevant parameters.[20]

Importantly, reduced TSAT was closely associated with objective markers of systemic congestion, including pulmonary congestion assessed by lung ultrasound (B-lines), abnormal renal venous flow patterns, inferior vena cava dilatation and elevated cardiac filling pressures. Progressive worsening of congestion was accompanied by declining TSAT and serum iron concentrations, whereas ferritin levels remained relatively stable, suggesting that circulating iron availability more accurately reflects the hemodynamic and inflammatory consequences of worsening HF than stored iron alone.[20]

Beyond congestion, TSAT also demonstrated a strong relationship with functional capacity. Lower TSAT was independently associated with reduced peak VO_2, diminished peak cardiac output and impaired exercise performance even after adjustment for hemoglobin, NT-proBNP, inflammatory markers and other clinical covariates. In contrast, ferritin was not independently associated with these functional measures. Notably, these relationships were observed across both HFrEF and HFpEF, reinforcing the concept that impaired iron availability contributes to exercise intolerance independently of anemia or LVEF.[20]

Perhaps most importantly, TSAT <20% and serum iron ≤13 µmol/L independently predicted the composite endpoint of HF hospitalization or all-cause mortality after adjustment for conventional prognostic variables, including LVEF and NT-proBNP. Conversely, guideline-defined ID and ferritin-based thresholds provided less robust prognostic discrimination.[20]

Collectively, these findings suggest that biomarkers reflecting iron bioavailability, rather than iron stores alone, are more closely linked to congestion, exercise capacity and clinical outcomes across the HF spectrum. The consistency of these associations across different HF phenotypes lends further support to an evolving availability-based approach to defining ID, in which TSAT assumes a central role in identifying patients with biologically relevant ID who are most likely to benefit from therapeutic intervention.

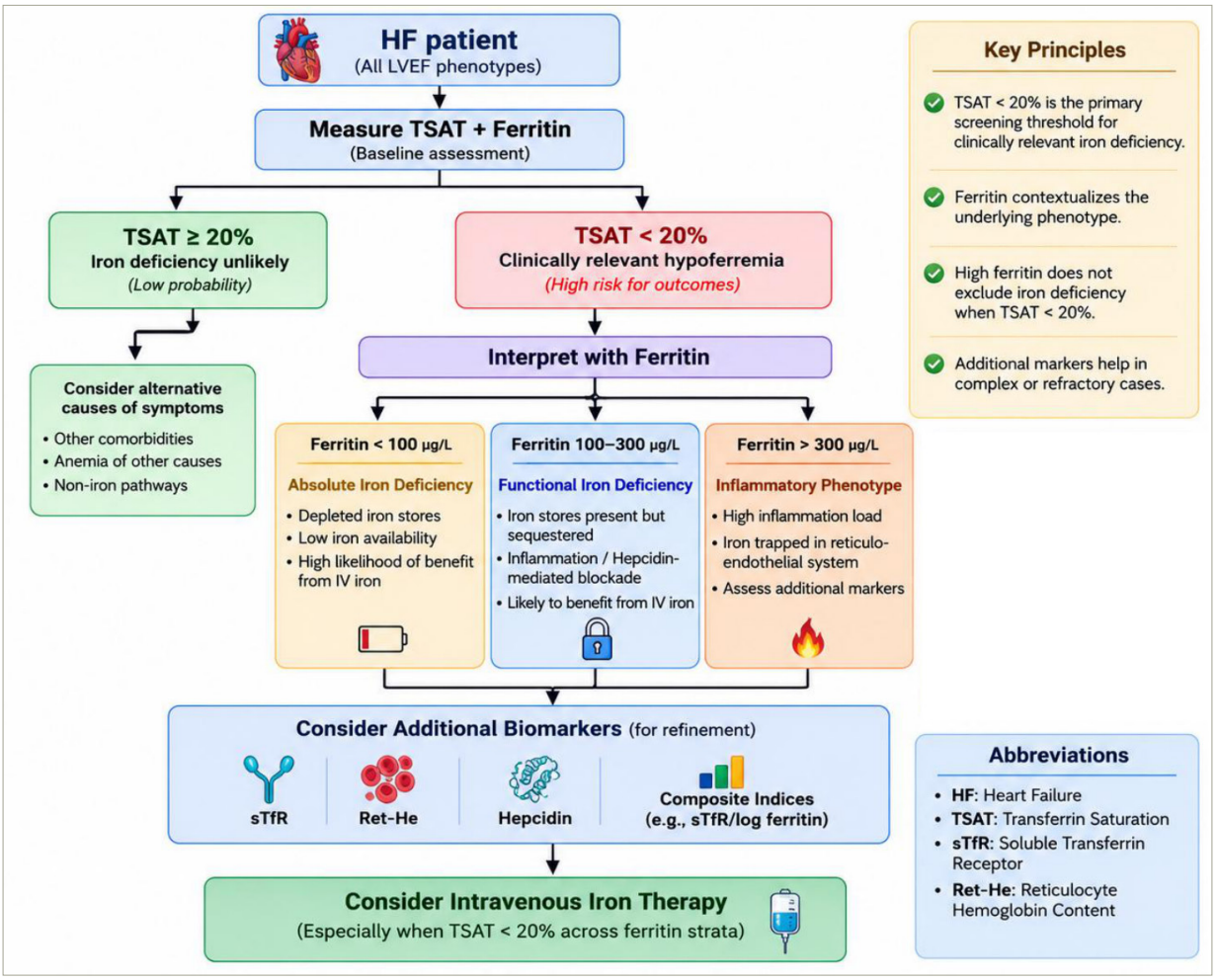
Monitoring iron status

Assessment of iron status should not be viewed as a one-time diagnostic exercise but rather as a dynamic component of longitudinal HF care. Current consensus recommendations advocate routine measurement of ferritin and TSAT at baseline and periodic reassessment thereafter, particularly in patients with persistent symptoms, recurrent hospitalization or recent IV iron therapy.[57]

However, the interpretation of serial measurements requires clinical nuance. Ferritin concentrations may fluctuate in response to intercurrent infection, congestion or systemic inflammation, potentially obscuring meaningful changes in iron stores. In contrast, TSAT and serum iron – markers more closely reflecting circulating iron availability – may provide more immediate insight into biologically relevant hypoferremia and therapeutic response.[58]

Following IV iron therapy, reassessment is typically recommended within several months to document restoration of iron availability and guide retreatment decisions. Importantly, normalization of ferritin alone should not be equated with correction of functional ID if TSAT remains low. Similarly, declining TSAT values over time may signal recurrent iron restriction even in the absence of anemia.[21]

Figure 3: Proposed diagnostic approach to iron deficiency in heart failure



Initial assessment includes measurement of TSAT and serum ferritin. A TSAT <20% identifies clinically relevant hypoferremia and serves as the primary screening threshold for biologically relevant iron deficiency. Ferritin is subsequently used to phenotype iron deficiency as absolute (<100 µg/L), functional (100–300 µg/L) or inflammation-associated (>300 µg/L), recognizing its limitations as an acute-phase reactant. In selected patients with diagnostic uncertainty, additional biomarkers, including sTfR, Ret-He, hepcidin and composite indices may provide complementary information. The algorithm integrates current evidence supporting a TSAT-centered approach to improve diagnostic precision and facilitate selection of patients who are most likely to benefit from IV iron therapy. Figure was created using BioRender and ChatGPT (OpenAI)
HF = heart failure; IV = intravenous; LVEF = left ventricular ejection fraction; Ret-He = reticulocyte hemoglobin equivalent; sTfR = soluble transferrin receptor; TSAT = transferrin saturation.

Ultimately, monitoring strategies should integrate biomarker trends with clinical context, including symptom burden, exercise tolerance and natriuretic peptide trajectories. As definitions of ID evolve, monitoring paradigms will likely shift toward greater emphasis on availability-based markers, ensuring that treatment decisions remain aligned with physiologically meaningful iron status rather than static storage thresholds.[59] Integrating these biomarkers into a structured clinical framework may facilitate the identification of clinically relevant ID in HF. A proposed diagnostic algorithm is shown in *Figure 3*.

Clinical implications

From a practical perspective, assessment of iron status should be incorporated into routine HF evaluation. Current evidence supports TSAT as the most clinically relevant screening biomarker, with TSAT <20% identifying patients most likely to benefit from IV iron therapy.

Ferritin should not be interpreted in isolation, particularly in inflammatory states where elevated concentrations may mask underlying iron depletion. In cases of discordant findings – such as preserved ferritin despite low TSAT – additional biomarkers, including sTfR, hepcidin, ERFE or composite indices, may help further characterize the underlying iron phenotype.

However, despite their biological and mechanistic appeal, none of these emerging biomarkers has yet demonstrated superiority over TSAT for identifying patients most likely to benefit from IV iron in prospective therapeutic studies. Accordingly, their current role should be considered complementary to, rather than a replacement for, TSAT in routine clinical practice.

Emerging evidence also suggests that incorporating inflammatory markers into multimarker assessment models may improve diagnostic accuracy and reduce misclassification in patients with chronic inflammatory conditions. As evidence evolves, integrated approaches combining TSAT with biomarkers of iron regulation and inflammation may enable more precise phenotyping of ID and facilitate individualized therapeutic strategies. However, until prospective interventional studies validate these approaches, TSAT remains the best-validated biomarker for current clinical decision-making.

Toward redefinition of iron deficiency in heart failure

The accumulating body of mechanistic, prognostic and therapeutic evidence increasingly challenges ferritin-centered definitions of ID in HF. A TSAT-based definition – centered on hypoferremia (TSAT <20%) – appears

more closely aligned with bone marrow depletion, symptomatic burden and responsiveness to IV iron therapy.[30]

Emerging evidence suggests that diagnostic emphasis may gradually transition from stored iron to bioavailable iron. Such a transition mirrors earlier evolution in CKD but is uniquely informed by HF-specific data. A TSAT-centered framework may therefore represent a more biologically coherent and clinically actionable definition of ID.

Future directions

Future research should prioritize prospective validation of TSAT-centered definitions across diverse HF populations and clinical settings. Standardization of emerging biomarkers such as sTfR and hepcidin, together with the development of inflammation-adjusted composite biomarker panels, may further improve diagnostic precision. Advances in proteomics, metabolomics and artificial intelligence- or machine learning-based integration of multimodal biomarker data may facilitate more accurate phenotyping of ID and individualized therapeutic decision-making.

In parallel, improvements in point-of-care assays and non-invasive myocardial iron imaging may enhance early diagnosis and provide insights into the relationship between circulating biomarkers and myocardial iron homeostasis.

Ultimately, a multidimensional classification of ID incorporating iron availability, storage, regulation, inflammation and tissue iron status may enable precision-guided therapeutic strategies in HF.

Conclusion

ID has become recognized as far more than a laboratory abnormality in HF. It represents a common and clinically meaningful disturbance in metabolic homeostasis that influences symptoms, exercise tolerance, quality of life and long-term outcomes – often independent of anemia. Over the past decade, therapeutic trials have firmly established that correcting ID can improve patient-centered outcomes. Yet, even as treatment strategies have matured, the biological definition of ID in HF continues to evolve.

Traditional ferritin-based criteria, although historically pragmatic, may not fully capture the complexity of iron regulation in the inflammatory milieu characteristic of HF. Growing evidence suggests that measures reflecting circulating iron availability – particularly TSAT and serum iron – align more closely with pathophysiology, prognostic risk and therapeutic responsiveness. This does not render ferritin obsolete but rather places it within a broader interpretive context, where storage, availability, regulation and inflammation must all be considered.

The emerging shift toward an availability-centered framework reflects a deeper understanding of iron biology in HF. Ultimately, future definitions will likely move beyond single-marker thresholds toward integrated, biologically coherent models that better identify patients with clinically relevant iron restriction. As this field advances, the goal remains simple but important: to ensure that diagnostic criteria reflect true metabolic need and guide therapy in a manner that is both precise and patient-centered. ❑

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