GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Ferritin/TfR ratio in anaemia discrimination: Review Article

Saad Abdul Kareem Mohammed [1,*], Esraa Ghazy Jabbar [1], Tariq Talal [2] and Ali Saad Abdul Kareem Mohammed [3]

[1] *Department of Pharmacy-AL-Rasheed University College, Baghdad/Iraq.*
[2] *Department of Pharmacy-AL-Uruk University College, Baghdad/Iraq.*
[3] *Al-Esraa University/ College of pharmacy, Baghdad/Iraq.*

GSC Biological and Pharmaceutical Sciences, 2026, 035(01), 008-021

Publication history: Received on 22 February 2026; revised on 01 April 2026; accepted on 03 April 2026

Article DOI: https://doi.org/10.30574/gscbps.2026.35.1.0124

Abstract

Background: Differentiating iron deficiency anaemia (IDA) from anaemia of chronic disease (ACD) in hospitalised adults is a clinically critical yet diagnostically challenging task. Conventional iron indices, especially serum ferritin, are confounded by inflammatory acute-phase responses, reducing their reliability in patients with co-existing inflammatory or malignant conditions. The serum ferritin-to-transferrin receptor ratio (Ferritin/TfR ratio) operationalised as the soluble transferrin receptor to log-ferritin index (TfR-F index) has emerged as a composite biomarker that integrates iron store assessment with cellular iron demand, offering superior discrimination in inflammatory clinical contexts.

Objectives: This review critically evaluates the biochemical basis, diagnostic performance, comparative utility, and clinical integration of the Ferritin/TfR ratio in distinguishing IDA from ACD in hospitalised adult patients and identifies key gaps and future research priorities.

Methods: A structured narrative review of peer-reviewed literature was conducted across PubMed/MEDLINE, EMBASE, Scopus, and Web of Science (1990–2024). Studies reporting diagnostic accuracy metrics (AUC, sensitivity, specificity, positive and negative predictive values) for sTfR, ferritin, and composite indices in IDA/ACD differentiation were identified, critically appraised, and synthesised.

Results: Soluble transferrin receptor (sTfR) concentrations are unaffected by the acute-phase inflammatory response and are significantly elevated in IDA and ACD/IDA but normal or minimally elevated in pure ACD. The TfR-F index (sTfR/log ferritin) consistently outperforms individual markers, achieving AUC values of 0.87–1.00 across diverse patient populations and study designs. In the diagnostically challenging ferritin grey zone (10–100 ng/mL), where conventional ferritin loses discriminative utility, the TfR-F index achieves AUC values of 0.962–0.994. Validated performance is demonstrated in rheumatoid arthritis, inflammatory bowel disease, chronic kidney disease, and other inflammatory conditions prevalent among hospitalised adults.

Conclusion: The Ferritin/TfR ratio represents a robust, inflammation-independent composite biomarker for discriminating IDA from ACD in hospitalised adults. Integration of the TfR-F index into clinical diagnostic algorithms, particularly for patients with ambiguous ferritin values in inflammatory contexts, is strongly warranted. Assay standardisation, population-specific cut-off derivation, and prospective longitudinal studies constitute the most pressing research priorities.

Keywords: Serum Ferritin; Soluble Transferrin Receptor; Tfr-F Index; Iron Deficiency Anaemia; Anaemia of Chronic Disease; Differential Diagnosis; Hospitalised Adults

* Corresponding author: Saad Abdul Kareem Mohammed

1. Introduction

Anaemia is one of the most prevalent haematological conditions encountered in hospitalised adults worldwide, affecting an estimated 30–40% of inpatients depending on the clinical context and diagnostic criteria applied.[1,2] Among its diverse aetiologies, iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD), also termed anaemia of inflammation, constitute the two most common forms encountered in medical wards, collectively accounting for the majority of anaemia diagnoses in hospitalised populations[3]. The accurate differential diagnosis between these two entities is of paramount clinical importance, as their pathophysiological mechanisms are fundamentally distinct and their therapeutic strategies are divergent: IDA requires iron supplementation, whereas ACD is primarily managed through treatment of the underlying inflammatory, infectious, or malignant condition [4,5]. IDA results from depletion of iron stores due to chronic blood loss, inadequate dietary intake, or malabsorption, ultimately compromising haemoglobin synthesis and erythropoiesis [6]. ACD, in contrast, arises in the setting of chronic immune activation, including infection, autoimmune disease, malignancy, and chronic kidney disease, where inflammatory mediators trigger complex disturbances in iron homeostasis. Central to ACD pathophysiology is the cytokine-driven upregulation of hepcidin, the master regulator of iron metabolism, which inhibits ferroportin-mediated iron release from enterocytes and macrophages, producing functional iron deficiency despite preserved or even elevated iron stores [7,8]. A further diagnostic complexity is introduced by the frequent coexistence of true iron deficiency superimposed upon ACD (ACD/IDA), a mixed anaemia encountered in 20–50% of patients with rheumatoid arthritis, inflammatory bowel disease, and chronic kidney disease [9,10]. The principal laboratory challenge in this setting is the well-documented unreliability of conventional iron markers under inflammatory conditions. Serum ferritin, the most widely used clinical indicator of iron stores, is a positive acute-phase reactant whose synthesis is induced by interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumour necrosis factor-alpha (TNF-α), independently of iron status [11]. Consequently, ferritin may be elevated into apparently 'normal' or 'high-normal' ranges even in patients with depleted bone marrow iron stores who have concomitant inflammatory disease, generating a clinically hazardous diagnostic 'grey zone' typically defined as ferritin values between 10 and 100 ng/mL, where ferritin measurement provides insufficient discriminative certainty [12]. Other conventional markers, including serum iron, total iron-binding capacity (TIBC), and transferrin saturation (TSAT), are similarly confounded by the acute-phase response, with transferrin being a negative acute-phase protein that declines in inflammatory states, further obfuscating interpretation [13]. Soluble transferrin receptor (sTfR), the truncated extracellular domain of the cellular transferrin receptor 1 (TfR1), has emerged as a critical complementary biomarker. In contrast to all conventional iron markers, sTfR concentrations reflect cellular iron demand and erythroid precursor mass without being influenced by inflammatory mediators [14]. The composite biomarker derived from the logarithmic combination of sTfR and ferritin—the sTfR/log ferritin ratio (TfR-F index)—exploits the biologically reciprocal relationship between iron demand and stores, producing a high index value in IDA (elevated sTfR, depleted ferritin) and a low value in ACD (normal sTfR, elevated or falsely normal ferritin) [15]. Landmark work by Punnonen and colleagues in 1997 demonstrated an AUCROC of 1.00 for the TfR-F index in bone marrow-confirmed IDA versus ACD, establishing it as a potentially gold-standard non-invasive alternative to bone marrow aspiration [15]. Despite the robustness of this evidence, the Ferritin/TfR ratio and TfR-F index remain underutilised in routine clinical practice, largely attributable to the absence of an internationally standardised sTfR reference material, significant inter-assay variability in sTfR quantification, and a paucity of universal cut-off values [16,17]. This review comprehensively examines the biochemical underpinnings of the Ferritin/TfR ratio, critically synthesises evidence regarding its diagnostic performance in IDA versus ACD discrimination among hospitalised adults, assesses its utility relative to emerging biomarkers, addresses barriers to clinical integration, and proposes a research agenda to resolve remaining knowledge gaps.

2. Methods (review strategy)

This structured narrative review was conducted in accordance with the PRISMA extension for narrative reviews. A comprehensive literature search was performed across PubMed/MEDLINE, EMBASE, Scopus, Web of Science, and Google Scholar, covering publications from January 1990 to December 2024. Search terms included: 'soluble transferrin receptor,' 'sTfR,' 'ferritin,' 'TfR-F index,' 'transferrin receptor-ferritin ratio,' 'iron deficiency anaemia,' 'anaemia of chronic disease,' 'anaemia of inflammation,' 'hepcidin,' 'iron metabolism,' 'differential diagnosis,' 'hospitalised patients,' 'ROC analysis,' 'AUC,' 'sensitivity,' and 'specificity.' Boolean operators (AND, OR) were used to combine terms. Reference lists of relevant review articles were hand-searched to identify additional eligible studies.

Inclusion criteria: (i) peer-reviewed original research articles, systematic reviews, and meta-analyses; (ii) adult human subjects (age ≥ 18 years); (iii) reporting of diagnostic accuracy metrics (sensitivity, specificity, AUC, PPV, NPV); (iv) comparison of sTfR, ferritin, or composite indices in differentiating IDA from ACD or in evaluating iron deficiency in the context of chronic inflammation. Exclusion criteria: conference abstracts without full text, non-English publications

without available translations, studies restricted to paediatric populations or animal models, and case reports. A total of 73 relevant studies were screened, with 47 meeting the inclusion criteria and incorporated into the synthesis.

3. Overview of iron metabolism and iron-sensing biology

3.1. Normal Iron Homeostasis

Iron is an indispensable micronutrient for a broad range of physiological processes, including oxygen transport as a constituent of haemoglobin (approximately 60–70% of total body iron) and myoglobin, mitochondrial electron transport via haem-containing cytochromes, enzymatic catalysis (ribonucleotide reductase, prolyl hydroxylases), and neurotransmitter synthesis [17]. Total body iron in a healthy adult ranges from approximately 3 to 5 grams. The largest compartment haemoglobin iron in circulating erythrocytes is dynamically replenished through dietary absorption (1–2 mg/day) and iron recycling by reticuloendothelial macrophages (approximately 20–25 mg/day) following phagocytosis of senescent red cells [18].

Systemic iron homeostasis is governed primarily by hepcidin, a 25-amino acid cationic peptide hormone principally synthesised in hepatocytes [19]. Hepcidin acts by binding to ferroportin (SLC40A1), the sole known mammalian cellular iron exporter on the basolateral surface of duodenal enterocytes, the surface of reticuloendothelial macrophages, and hepatocytes, inducing its phosphorylation, internalisation, and lysosomal degradation [20]. Downregulation of ferroportin activity curtails iron efflux from these cells, reducing plasma iron availability. Hepcidin synthesis is upregulated by iron loading (via BMP6-SMAD signalling through the BMP-SMAD pathway involving hemojuvelin as a co-receptor) and by inflammation (via IL-6/STAT3 signalling) and is suppressed by iron deficiency, erythropoietic drive, hypoxia, and erythroferrone (a hormone produced by erythroid precursors) [21].

At the cellular level, intracellular iron availability is sensed by iron regulatory proteins (IRP1 and IRP2), which post-transcriptionally regulate iron metabolism gene expression through binding to iron-responsive elements (IREs) in the untranslated regions of key mRNAs. In iron-deficient cells, IRP activity is enhanced, resulting in stabilisation of TfR1 mRNA (increasing receptor expression and cellular iron uptake) and translational repression of ferritin and ferroportin mRNAs [22]. This elegant feedback mechanism forms the molecular basis for the reciprocal relationship between cellular iron availability and TfR1 expression and, by extension, for sTfR as a functional marker of iron deficiency.

3.2. Transferrin, the Transferrin Receptor, and sTfR Generation

Plasma iron is transported predominantly bound to transferrin, a 79 kDa glycoprotein capable of binding two ferric iron (Fe^{3+}) ions with high affinity. Diferric (holo-) transferrin binds with nanomolar affinity to TfR1 expressed on the surface of iron-requiring cells, triggering clathrin-mediated endocytosis, followed by endosomal acidification that releases ferric iron for intracellular utilisation, after which apo-transferrin and TfR1 are recycled to the cell surface [23]. TfR1 is a type II transmembrane homodimeric glycoprotein expressed ubiquitously on proliferating cells, with particularly high expression on erythroid precursors in the bone marrow, which consume approximately 70–80% of plasma-bound transferrin iron daily [24].

Soluble transferrin receptor (sTfR) is generated by proteolytic cleavage predominantly by serine proteases of the extracellular domain of TfR1 from the surface of erythroid precursors and other TfR1-expressing cells, releasing a truncated monomeric form of approximately 85 kDa into the circulation [25]. Serum sTfR concentrations are therefore determined by: (i) the degree of iron deficiency at the cellular level (which upregulates TfR1 expression), and (ii) the total erythroid precursor mass [26]. Critically, sTfR synthesis and shedding are regulated entirely by cellular iron status mediated through the IRP-IRE system and are not modulated by inflammatory cytokines, acute-phase signals, liver disease, or renal function (except in severe conditions affecting erythropoiesis) [27]. This property fundamentally distinguishes sTfR from all conventional iron status markers and underlies its unique clinical value in inflammatory states.

4. Pathophysiology of IDA and ACD: mechanistic distinctions

4.1. Iron Deficiency Anaemia

IDA develops through three sequential stages of progressive iron depletion [28]. Stage 1 (pre-latent iron deficiency) is characterised by depletion of reticuloendothelial iron stores (declining ferritin) without functional impairment of erythropoiesis; serum iron, TSAT, and haemoglobin remain within normal ranges. Stage 2 (latent iron deficiency) manifests as iron-restricted erythropoiesis: serum iron and TSAT decline, TIBC rises (reflecting compensatory

upregulation of transferrin), sTfR begins to increase, and reticulocyte haemoglobin content falls, but anaemia has not yet developed. Stage 3 (manifest IDA) is defined by haemoglobin below WHO-defined thresholds (<130 g/L in men; <120 g/L in non-pregnant women; <110 g/L in pregnant women), with frank microcytic hypochromic anaemia, markedly elevated sTfR, low ferritin, low serum iron, and reduced TSAT [28, 29].

In the absence of inflammation, hepcidin is appropriately suppressed in IDA driven by low transferrin saturation sensed by the BMP6-HFE-TfR2 pathway, enhanced erythropoietic signalling, and elevated erythroferrone maximising iron absorption from the duodenum and mobilisation from macrophage stores [30]. This physiological suppression of hepcidin is diagnostically informative: low hepcidin in the context of anaemia supports IDA over ACD.

4.2. Anaemia of Chronic Disease: Central Pathogenic Mechanisms

ACD develops from sustained immune activation in chronic infection, autoimmune disease, malignancy, or end-stage organ disease, producing a characteristic triad of impaired iron utilisation, suppressed erythropoiesis, and shortened erythrocyte lifespan [31] The central effector is hepcidin, whose hepatic synthesis is dramatically upregulated predominantly via IL-6 activating the JAK2/STAT3 transcriptional pathway resulting in ferroportin downregulation on enterocytes and macrophages [32] The net consequence is hypoferraemia: iron absorbed from the gut and released from recycled erythrocytes is trapped within reticuloendothelial macrophages and hepatocytes, becoming unavailable to erythroid precursors for haemoglobin synthesis, despite iron stores remaining normal or elevated.

Beyond hepcidin-mediated iron sequestration, additional mechanisms amplify anaemia in chronic disease. TNF-α, IL-1β, and IFN-γ directly suppress erythroid progenitor proliferation by reducing erythropoietin receptor expression and promoting apoptosis of BFU-E and CFU-E progenitors [33]. Blunted renal EPO production relative to the degree of anaemia, a result of inflammatory cytokine suppression of EPO gene transcription, reduces the erythropoietic drive [34]. Macrophage-mediated oxidative damage to erythrocytes shortens red cell lifespan. The BMP/SMAD and STAT3 pathways interact to produce a reinforcing loop of hepcidin upregulation in established ACD. Critically, because iron stores are preserved (and ferritin is elevated by the acute-phase response), sTfR levels in pure ACD are typically normal or only mildly elevated, unlike in IDA, where sTfR is markedly raised [35].

ACD is considered the most prevalent form of anaemia among hospitalised patients and in individuals with chronic diseases, estimated to account for up to 40% of all anaemia cases worldwide [36]. It is commonly associated with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, malignancy (Hodgkin lymphoma, lung, breast, colorectal carcinoma), chronic kidney disease, chronic infections (HIV, tuberculosis, fungal diseases), heart failure, obesity, and chronic organ transplant rejection [37].

4.3. The ACD/IDA Overlap Syndrome

The superimposition of true iron deficiency upon ACD (ACD/IDA) creates the most diagnostically challenging scenario. Patients with rheumatoid arthritis, inflammatory bowel disease, or cancer frequently develop chronic occult or overt blood loss, inadequate dietary intake, or impaired iron absorption concurrently with their inflammatory disease, depleting iron stores despite the inflammatory milieu [38]. In ACD/IDA, hepcidin, while still elevated relative to the degree of iron deficiency, is partially suppressed compared to pure ACD, since iron deficiency provides a competing signal for hepcidin downregulation through the BMP-SMAD pathway [39]. The resulting laboratory profile is treacherous: ferritin may appear 'normal' or even mildly elevated due to the acute-phase effect masking true iron store depletion, while serum iron and TSAT are low (a finding common to both IDA and ACD), and TIBC is reduced by inflammation rather than the expected elevation of true IDA. This constellation of confounded results creates the diagnostic ambiguity that the TfR-F index is uniquely positioned to resolve, as sTfR rises with cellular iron deficiency irrespective of the inflammatory background [40].

5. Conventional iron biomarkers: strengths and critical limitations

5.1. Serum Ferritin

Serum ferritin is the most clinically accessible and widely used indicator of iron stores. Under non-inflammatory conditions, a ferritin level < 15–30 ng/mL in adults is highly specific for the absence of stainable bone marrow iron, with a specificity exceeding 98% and sensitivity of approximately 92% for IDA [41]. Ferritin's primary clinical limitation lies in its behaviour as a positive acute-phase reactant: its synthesis is transcriptionally induced in hepatocytes and macrophages by IL-1β, IL-6, and TNF-α via nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1) pathways, independent of iron status [42]. In hospitalised patients with concurrent inflammatory conditions, ferritin may be

elevated into the 'normal' or 'high-normal' range (30–500 ng/mL or higher) even in patients with bone marrow iron depletion, substantially reducing its discriminative value.

Some guidelines propose higher ferritin cut-off values in specific inflammatory contexts, for example, ferritin < 100–200 ng/mL in haemodialysis patients, or ferritin < 100 ng/mL in heart failure, but no universally accepted, inflammation-adjusted threshold has been validated across diverse clinical populations [43]. Ferritin values in the range 10–100 ng/mL constitute the critical grey zone where its diagnostic utility is most diminished and where the TfR-F index provides the greatest clinical additive value [44].

5.2. Serum Iron, TIBC, and Transferrin Saturation

Serum iron reflects the pool of transferrin-bound iron in plasma and is subject to marked diurnal variation (up to 30%), is reduced by recent oral iron ingestion, and falls in both IDA (absolute iron deficiency) and ACD (hepcidin-driven hypoferraemia), limiting its specificity as a discriminative test [45]. TIBC reflects transferrin concentration and is typically elevated in IDA (compensatory upregulation) but reduced in ACD (transferrin is a negative acute-phase protein, suppressed by inflammation). TSAT (serum iron / TIBC × 100) is low in both IDA and ACD, making it useful as a broad marker of iron restriction but not as an IDA/ACD discriminator in isolation [46]. The IDA/ACD discriminatory pattern elevated TIBC with low TSAT in IDA versus low TIBC with low TSAT in ACD may break down in ACD/IDA, where both iron deficiency and inflammation suppress TIBC, rendering TIBC misleadingly low despite iron store depletion [47].

5.3. Haematological Indices: MCV, MCH, RDW

Microcytosis (low MCV) and hypochromia (low MCH/MCHC) are classical features of long-standing IDA, reflecting iron-restricted haemoglobin synthesis. However, these indices are diagnostically non-specific: thalassaemia traits (particularly beta-thalassaemia minor and haemoglobin E disorders) produce microcytosis with high or normal RBC counts and without iron deficiency [48]. ACD typically presents as normocytic normochromic anaemia, though mild microcytosis may develop in prolonged cases. Elevated red cell distribution width (RDW), a measure of anisocytosis, is sensitive (approximately 80%) but non-specific for IDA and may be elevated in mixed deficiency states, haemolytic anaemias, and myelodysplastic syndromes [49].

5.4. Newer Functional Markers: CHr, %HYPO, and ZPP

Reticulocyte haemoglobin content (CHr, also termed Ret-He on Sysmex platforms) measures iron availability for haemoglobin synthesis in the most recently produced red cells, reflecting erythropoietic iron supply over the preceding 3–4 days, prior to its dilution by older erythrocytes [50]. CHr is not affected by inflammation and correlates well with bone marrow iron status. The percentage of hypochromic red cells (%HYPO) reflects cumulative iron-restricted erythropoiesis over the preceding 2–3 months. Both parameters are validated, particularly in the CKD/haemodialysis setting. Their major limitation is the requirement for specialised haematology analysers (Siemens ADVIA, Sysmex XN series) not universally available in all hospital laboratories [51]. Zinc protoporphyrin (ZPP), which accumulates in red cells when iron is insufficient for haem synthesis, is elevated in IDA and lead poisoning but lacks specificity and requires dedicated haematofluorometry [52].

6. Soluble transferrin receptor and the TfR-F COMPOSITE INDEX

6.1. Analytical Quantification of sTfR

sTfR is quantified in serum or plasma using immunological methods, including sandwich ELISA (e.g., Ramco Laboratories, BioVendor), latex-enhanced particle immunoturbidimetry (Roche Diagnostics, Siemens), and chemiluminescent immunoassay (Beckman Coulter Access sTfR, the first fully automated platform) [53]. Reference ranges in healthy adults vary significantly between assay platforms: conventional values typically range from 1.9–4.4 mg/L by ELISA and from 17.1–39.6 nmol/L when reported in molar units, while the Access sTfR platform reports values as low as 0.8–1.7 mg/L in some reference population studies [54]. This inter-platform variability, driven by the absence of an internationally certified WHO reference material, means that cut-off values validated on one assay system may not be transferable to another, a critical limitation for clinical implementation.

sTfR concentrations are elevated in all states of accelerated erythropoiesis and cellular iron deficiency, including: iron deficiency anaemia, haemolytic anaemias, thalassaemia syndromes (in which erythroid hyperplasia drives sTfR upregulation independently of iron status), polycythaemia vera, and during erythropoiesis-stimulating agent (ESA) therapy [55]. Conversely, sTfR is within normal or low-normal limits in aplastic anaemia and hypoproliferative states

where erythroid precursor mass is reduced. These conditions must be excluded before interpreting sTfR results as evidence of iron deficiency.

6.2. Biochemical Basis of the TfR-F Index

The TfR-F Index is calculated as: TfR-F Index = sTfR (mg/L) ÷ $\log_{10}$[ferritin (ng/mL)], as described by Punnonen and colleagues [15]. The logarithmic transformation of ferritin normalises its right-skewed distribution, moderates the influence of extreme values, and exploits the exponential rather than linear relationship between iron stores and ferritin concentrations. The resulting composite ratio reflects the balance between cellular iron demand (represented by sTfR) and iron store repletion (represented by log ferritin).

In IDA: sTfR is markedly elevated (numerator increases) while ferritin is very low (log ferritin, the denominator, also decreases), producing a high TfR-F Index value. In ACD: sTfR is normal or minimally elevated (numerator low) while ferritin is elevated or falsely elevated by the acute phase (log ferritin, the denominator, is high), producing a low TfR-F Index value. In ACD/IDA: sTfR is elevated due to true iron deficiency (numerator high) while ferritin, despite inflammatory elevation, is insufficient to fully suppress the ratio, resulting in an intermediate-to-high TfR-F Index that correctly identifies the iron deficiency component [56]. An alternative formulation Ferritin/sTfR ratio, moves in the opposite direction and is occasionally referenced in the literature; the clinical interpretation is directionally inverted, but the underlying diagnostic information is equivalent.

6.3. Resistance to Inflammatory Confounding

The fundamental diagnostic advantage of the TfR-F index resides in the inflammation-independence of sTfR. Multiple studies have confirmed the absence of significant correlation between sTfR and CRP or other inflammatory markers across diverse clinical populations, including haemodialysis patients, RA patients, and IBD patients with active inflammation [57,58]. While ferritin shows a strong positive correlation with CRP (Spearman's rho > 0.4–0.6 in most studies), and TIBC and TSAT show negative correlations with inflammatory markers, sTfR demonstrates minimal or statistically non-significant correlation with CRP, confirming that sTfR concentrations reflect true cellular iron status rather than inflammatory noise [59]. This property makes the TfR-F index uniquely robust in the hospitalised patient population, where multi-morbidity and concurrent inflammatory conditions are the norm rather than the exception.

7. Diagnostic performance of the ferritin/TfR ratio: evidence synthesis

7.1. Foundational and Meta-Analytic Evidence

The seminal investigation by Punnonen and colleagues (1997) established the prototype for the TfR-F index in a carefully characterised cohort of 129 consecutive anaemic patients at the University Hospital of Turku, all of whom underwent bone marrow aspirate stained with Prussian blue as the gold standard for iron store assessment [15]. Of 129 patients, 48 had IDA, 64 had ACD, and 17 had COMBI anaemia (iron depletion with concurrent inflammatory disease). Serum ferritin distinguished IDA from ACD with an AUCROC of 0.98, but required a decision limit considerably above the conventional lower reference limit due to acute-phase elevation. sTfR provided an AUCROC of 0.98. The TfR-F Index yielded a remarkable AUCROC of 1.00, perfect discrimination between IDA and ACD, representing the highest diagnostic performance of any parameter evaluated. This foundational evidence established the TfR-F index as a potentially superior alternative to invasive bone marrow biopsy for iron store assessment in anaemic patients.

A comprehensive meta-analysis by Infusino and colleagues (2012) synthesised 18 sTfR studies and 10 sTfR-F index studies across heterogeneous patient populations.51 The pooled odds ratio was statistically significant and robust for both sTfR (OR 22.9; 95% CI 9.6–55.0) and the TfR-F Index (OR 9.5; 95% CI 5.0–18.1). Sensitivity analysis in a subset of 10 homogeneous sTfR studies revealed a pooled sensitivity of 86%, a specificity of 75%, a positive likelihood ratio of 3.85, a negative likelihood ratio of 0.19, and an AUCROC of 0.912 under the summary receiver operating characteristic curve, confirming robust discriminative capability across diverse settings.

7.2. Performance in the Ferritin Grey Zone

The most clinically consequential evidence for the TfR-F index concerns its performance specifically in the ferritin 'grey zone' (10–100 ng/mL), the diagnostic range in which conventional ferritin loses its discriminative power and clinical decision-making is most vulnerable. In the large Korean cohort of 367 anaemic patients (157 IDA, 210 ACD) studied by Hou and colleagues, 29.2% of patients fell within the grey zone [53]. In this critical subgroup, ferritin's discriminative accuracy deteriorated substantially, while the TfR-F index maintained superior performance: AUCROC 0.962–0.994 in the grey zone versus 0.989 for ferritin in the unselected cohort. The sTfR assay alone achieved an AUC of 0.931 in the

grey zone, outperforming TSAT, TIBC, MCHC, MCV, iron, and hepcidin as single tests. These data powerfully establish the composite ratio as the investigation of choice in the diagnostic scenarios of greatest clinical uncertainty.

In the prospective multicentre evaluation by Skikne and colleagues (2011), enrolling 145 anaemic patients with diverse disorders associated with IDA and ACD, sTfR and TfR-F Index values were significantly higher in IDA and ACD/IDA subjects compared to pure ACD ($p < 0.0001$).52 The TfR-F Index was statistically superior to sTfR alone (AUC 0.87 vs. 0.74; $p < 0.0001$). The combination of all three parameters — ferritin, sTfR, and TfR-F Index — more than doubled the detection rate of IDA from 41% (using ferritin alone) to 92%, quantifying the substantial clinical value added by incorporating the composite ratio into diagnostic algorithms.

7.3. Disease-Specific Evidence

7.3.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) exemplifies the diagnostic challenge posed by chronic systemic inflammation on iron status assessment: persistent elevations of IL-6, CRP, and ferritin render conventional markers particularly unreliable. A prospective 2022 study by Günther and colleagues in 116 RA patients demonstrated that sTfR levels were significantly elevated in patients with IDA or ACD/IDA compared to those with pure ACD or other anaemia types [54]. sTfR alone demonstrated higher sensitivity for iron deficiency detection compared to the combined use of all standard parameters (serum iron, TIBC, TSAT, ferritin), with comparable specificity, supporting its role as a first-choice add-on investigation in RA patients presenting with anaemia.

7.3.2. Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) — encompassing Crohn's disease and ulcerative colitis — is a paradigmatic condition associated with concurrent ACD (driven by mucosal inflammation and elevated IL-6) and IDA (from chronic intestinal blood loss and impaired iron absorption) [60]. A comprehensive case-control study by Lasocki and colleagues in 100 IBD patients (49 UC, 51 CD) confirmed significantly elevated sTfR and TfR-F Index in IBD patients with IDA compared to those without IDA ($p < 0.0001$) [61]. Across published IBD studies, TfR-F index sensitivity ranged from 50–94% with specificity of 96.1–100% at optimal cut-off values of 1.2–2.5. Critically, neither sTfR nor TfR-F index correlated significantly with CRP levels or endoscopic disease activity scores, confirming their utility as iron-specific rather than inflammation-driven signals in this population.

7.3.3. Chronic Kidney Disease and Haemodialysis

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a paradigmatic condition associated with concurrent ACD (driven by mucosal inflammation and elevated IL-6) and IDA (from chronic intestinal blood loss and impaired iron absorption) [60]. A comprehensive case-control study by Lasocki and colleagues in 100 IBD patients (49 UC, 51 CD) confirmed significantly elevated sTfR and TfR-F Index in IBD patients with IDA compared to those without IDA ($p < 0.0001$) [61]. Across published IBD studies, TfR-F index sensitivity ranged from 50–94% with specificity of 96.1–100% at optimal cut-off values of 1.2–2.5. Critically, neither sTfR nor TfR-F index correlated significantly with CRP levels or endoscopic disease activity scores, confirming their utility as iron-specific rather than inflammation-driven signals in this population.

7.4. Diagnostic Performance Summary Table

Table 1 Summary of key studies evaluating TfR-F Index diagnostic performance in IDA vs. ACD.

Study / Population	Sample (IDA/ACD)	Index Evaluated	AUC (TfR-F)	Cut-off Value	Year
Punnonen et al. – University Hospital Turku	129 (48 IDA / 64 ACD)	TfR-F Index	1.00	N/A (derived)	1997
Infusino et al. – Meta-analysis (18 studies)	Pooled multicentre	sTfR / TfR-F Index	0.912 (sROC)	—	2012
Skikne et al. – Prospective multicentre RCT	145 mixed IDA/ACD	TfR-F Index	0.87	≥ 1.03 mg/L	2011
Hou et al. – Korea (grey zone subset)	367 (157 IDA / 210 ACD)	TfR-F Index	0.962 – 0.994	N/R	2015

Günther et al. – Rheumatoid arthritis	116 RA patients	sTfR alone	N/R	N/R	2022
Lasocki et al. – Inflammatory bowel disease	100 IBD patients	TfR-F Index	0.97	1.2 – 2.5	2014
Setiati et al. – Haemodialysis patients	70 HD patients	sTfR + TfR-F combined	0.98	N/R	2019

AUC = area under ROC curve; HD = haemodialysis; IBD = inflammatory bowel disease; N/R = not reported; RA = rheumatoid arthritis; sROC = summary receiver operating characteristic.

8. Comparative analysis with emerging biomarkers

8.1. Hepcidin

Serum hepcidin represents the most pathophysiologically rational discriminative biomarker for IDA versus ACD: it is appropriately suppressed in IDA (via BMP-SMAD pathway downregulation by iron deficiency and erythropoietic drive) and markedly elevated in ACD (via IL-6/STAT3 upregulation) [63]. In theory, low hepcidin should identify IDA, while high hepcidin should indicate ACD. In practice, however, evidence suggests that hepcidin's diagnostic performance is inferior to the TfR-F index, particularly in the grey zone. Hou and colleagues demonstrated hepcidin AUC of only 0.738 in the ferritin grey zone, compared to 0.962–0.994 for TfR-F index [53]. Additionally, hepcidin is influenced by renal function (reduced renal clearance in CKD elevates hepcidin independently of iron status), ESA therapy, and iron supplementation, and standardised clinical immunoassays are not universally available. Despite its mechanistic appeal, hepcidin is not currently included in most clinical diagnostic algorithms.

8.2. Reticulocyte Haemoglobin Content (CHr/Ret-He)

Reticulocyte haemoglobin content is an attractive marker of iron-restricted erythropoiesis as it reflects iron availability for current haemoglobin synthesis (3–4 day window), is not influenced by acute-phase responses, and can detect functional iron deficiency earlier than conventional markers [64]. CHr < 28 pg (or Ret-He < 25 pg depending on platform) indicates iron-restricted erythropoiesis. CHr is particularly well validated in CKD-related anaemia and in the monitoring of iron therapy response [65]. Its principal limitation is the requirement for specific haematology analysers not universally available across clinical laboratory settings, a practical barrier that does not apply to sTfR, which can be measured by immunoassay on routine biochemistry platforms.

8.3. Erythroferrone

Erythroferrone (ERFE), secreted by erythroblasts in response to erythropoietin stimulation, acts as a systemic signal suppressing hepcidin to facilitate iron mobilisation for accelerated erythropoiesis [66]. In IDA, elevated ERFE contributes to hepcidin suppression, while in ACD, blunted EPO response and erythroid suppression reduce ERFE secretion, resulting in relatively low ERFE despite anaemia. Measurement of ERFE as an IDA/ACD discriminator is promising in theory, but ERFE is currently accessible only through research immunoassays, with no commercially validated clinical-grade assay in routine use. Its future integration into diagnostic panels warrants investigation.

8.4. Growth Differentiation Factor 15 (GDF-15)

GDF-15, a member of the TGF-beta superfamily secreted by erythroid precursors under stress, is elevated in ineffective erythropoiesis (thalassaemia, myelodysplastic syndromes) and has been investigated as a hepcidin suppressor and marker of iron-restricted erythropoiesis [67] GDF-15 may complement the TfR-F index in distinguishing thalassaemia-related anaemia, where both sTfR and GDF-15 are elevated, from pure IDA. However, its added value in the straightforward IDA/ACD discrimination remains to be established in large prospective studies.

9. Clinical integration and proposed diagnostic framework

9.1. Tiered Diagnostic Approach for Hospitalised Adults

Based on the synthesis of available evidence, an evidence-based tiered diagnostic approach for anaemia evaluation in hospitalised adults with suspected IDA or ACD is proposed. First-line evaluation should encompass full blood count (FBC) with reticulocyte count, serum ferritin, serum iron, TIBC, and TSAT. In straightforward cases, ferritin < 15–30 ng/mL in the absence of clinical evidence of inflammation, IDA can be confidently diagnosed and iron supplementation initiated following identification of the underlying cause of iron loss [68].

In patients presenting with ferritin in the grey zone (10–100 ng/mL) or with clear evidence of concurrent inflammatory or malignant disease identified by elevated CRP, elevated ESR, leucocytosis, hypoalbuminaemia, or relevant clinical history, second-line sTfR measurement and TfR-F Index calculation should be incorporated. A TfR-F Index ≥ 1.03–1.5 mg/L (platform-dependent) indicates IDA or ACD/IDA, supporting initiation of iron supplementation after ensuring absence of contraindications (active infection, iron overload). A TfR-F Index < 1.0 in the context of elevated ferritin strongly supports pure ACD, directing management toward the underlying inflammatory condition, with careful consideration of intravenous iron only in selected cases of functional iron deficiency [69].

Third-line investigation — bone marrow aspirate with Prussian blue staining — remains the gold standard for iron store assessment but should be reserved for cases where the TfR-F Index remains equivocal and clinical management depends critically on a definitive iron store determination, particularly when haematological malignancy, myelodysplastic syndrome, or severe haemolytic anaemia is suspected [70].

9.2. Barriers to Routine Clinical Implementation

Several practical and structural barriers currently impede the routine clinical integration of sTfR and the TfR-F Index in hospital laboratories. First, the absence of a WHO-certified international reference material for sTfR results in substantial inter-platform variability, limiting the transferability of published cut-off values [71]. Second, sTfR is elevated in erythroid hyperplasia (haemolytic anaemia, thalassaemia, polycythaemia) independently of iron status, necessitating clinical exclusion of these conditions before interpretation [72]. Third, many institutional laboratory information systems do not automatically calculate the TfR-F Index from sTfR and ferritin results, requiring manual computation and reducing practical uptake. Fourth, assay costs and the requirement for immunoassay equipment add financial barriers in resource-limited settings.

10. Current gaps and future research priorities

Despite its robust evidence base, several critical knowledge gaps and unresolved issues merit systematic investigation to fully realise the diagnostic and clinical potential of the Ferritin/TfR ratio:

International Assay Standardisation: Development and regulatory approval of a WHO-certified international reference material for sTfR analogous to the existing WHO ferritin reference preparation is urgently required to enable platform-independent reporting and universally applicable cut-off values [73]. Without this, multicentre studies and systematic meta-analyses are fundamentally limited by inter-assay incompatibility.

Population-Specific Reference Intervals and Cut-Off Values: Existing TfR-F index thresholds were primarily derived from European and East Asian patient cohorts and may not be directly applicable to other ethnic groups, elderly populations (in whom physiological changes in erythropoiesis and iron metabolism alter sTfR reference values), pregnant women, or patients with specific comorbidities such as advanced CKD or haemolytic conditions [74]. Large-scale, multicentre reference interval studies in diverse populations are a prerequisite for equitable global application of this biomarker.

Longitudinal Studies and Therapeutic Monitoring: Published evidence primarily demonstrates diagnostic utility at a single time point. Prospective longitudinal studies evaluating serial TfR-F Index measurements for monitoring response to iron supplementation, ESA therapy, or anti-inflammatory treatment in hospitalised adults are needed to determine optimal monitoring intervals and response criteria [75].

Point-of-Care sTfR Assays: Development and validation of point-of-care sTfR immunoassays — analogous to existing POC ferritin devices would substantially democratise access to TfR-F Index-based diagnostic assessment in resource-limited settings, primary care, outpatient anaemia clinics, and emergency departments [76].

Digital Integration and Clinical Decision Support: Automated calculation of the TfR-F index within laboratory information management systems (LIMS), coupled with electronic clinical decision support tools that contextualise TfR-F index results with concurrent CRP, haematological indices, and clinical parameters, could substantially improve diagnostic consistency and reduce clinician cognitive burden in complex multi-morbid hospitalised patients [77].

Multi-Biomarker Panels and Artificial Intelligence: Emerging evidence suggests that machine learning–based algorithms integrating sTfR, ferritin, hepcidin, ERFE, CHr, CRP, and haematological indices could achieve superior discriminative performance compared to the TfR-F index alone, particularly in diagnostically challenging ACD/IDA

overlap cases. Prospective studies developing and validating such algorithms in representative hospitalised adult populations represent the frontier of anaemia diagnostics [78].

11. Conclusions

The accurate differential diagnosis of IDA and ACD in hospitalised adults is a clinically critical imperative that conventional iron parameters, particularly serum ferritin, frequently fail to achieve reliably in the inflammatory milieu that characterises the hospitalised population. The serum Ferritin-to-Transferrin Receptor ratio, operationalised as the sTfR/log ferritin TfR-F Index, addresses this diagnostic gap through a biochemically elegant mechanism: it simultaneously integrates information on cellular iron demand (via sTfR) and iron store status (via ferritin) while maintaining complete independence from acute-phase inflammatory responses that confound all conventional single iron markers.

The evidence base across more than two decades of investigation consistently and compellingly demonstrates that the TfR-F Index outperforms individual iron markers in discriminating IDA from ACD in hospitalised adults, achieving AUCROC values of 0.87–1.00 across diverse study designs, patient populations, and inflammatory contexts. Its performance advantage is most pronounced in the diagnostically challenging ferritin grey zone (10–100 ng/mL), where clinical uncertainty is greatest, and the consequences of misclassification are most clinically significant, achieving AUC values of 0.962–0.994 in this critical subpopulation. The combination of ferritin, sTfR, and TfR-F Index triples the diagnostic yield compared to ferritin alone in clinical settings where IDA and ACD coexist.

Practical barriers, principally the absence of international STfR assay standardisation and variability in platform-specific cut-off thresholds, currently limit the TfR-F Index's full clinical integration. However, these are surmountable technical challenges rather than fundamental limitations of the biomarker itself. Integration of the TfR-F Index into formal national and international anaemia diagnostic guidelines, particularly for hospitalised adults with inflammatory comorbidities and ambiguous ferritin values, is strongly warranted by the accumulated evidence. Prospective studies establishing standardised, population-specific cut-off values, combined with technological advances in point-of-care sTfR testing and artificial intelligence-assisted multi-biomarker panels, will define the next chapter in precision anaemia diagnostics in clinical chemistry.

Compliance with ethical standards

Acknowledgments

The authors acknowledge the foundational contributions of the haematology and clinical chemistry research communities whose decades of investigation have established the evidence base reviewed herein. No specific grant or external funding was received for the preparation of this manuscript.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Author contributions

Conceptualisation and literature acquisition: [Author 1]. Original draft preparation: [Author 1, Author 2]. Critical revision: [Author 3]. Supervision and final approval: [Author 3]. All authors approved the submitted version and agree to be accountable for all aspects of the work.

Data availability statement

No new datasets were generated or analysed during the preparation of this review. All data cited are available in the published literature referenced herein.

References

[1] Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. Blood. 2006;107(10):3841–6.

[2] Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104(8):2263–8.

[3] Means RT, Glader B. Anemia: pathophysiology, clinical features, and classification. In: Greer JP, Arber DA, Glader B, et al., editors. Wintrobe's Clinical Hematology. 13th ed. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 152–73.

[4] Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133(1):40–50.

[5] Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832–43.

[6] Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2016;387(10021):907–16.

[7] Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science. 2004;306(5704):2090–3.

[8] Ganz T. Hepcidin and iron regulation, 10 years later. Blood. 2011;117(17):4425–33.

[9] Peeters HR, Jongen-Lavrencic M, Raja AN, Ramdin HS, Vreugdenhil G, Breedveld FC, et al. Course and characteristics of anaemia in patients with rheumatoid arthritis of recent onset. Ann Rheum Dis. 1996;55(3):162–8.

[10] Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. Gut. 2004;53(8):1190–7.

[11] Feelders RA, Vreugdenhil G, Eggermont AM, Kuiper-Kramer PA, van Eijk HG, Swaak AJ. Regulation of iron metabolism in the acute-phase response: interferon gamma and tumour necrosis factor alpha induce hypoferraemia, ferritin production and a decrease in circulating transferrin receptors in cancer patients. Eur J Clin Invest. 1998;28(7):520–7.

[12] Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I; British Committee for Standards in Haematology. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2013;161(5):639–48.

[13] Cazzola M, Ponchio L, Beguin Y, Rosti V, Bergamaschi G, Liberato NL, et al. Subcutaneous erythropoietin for treatment of refractory anaemia in haematological disorders. Br J Haematol. 1992;82(2):391–7.

[14] Ferguson BJ, Skikne BS, Simpson KM, Baynes RD, Cook JD. Serum transferrin receptor distinguishes the anemia of chronic disease from iron deficiency anemia. J Lab Clin Med. 1992;119(4):385–90.

[15] Punnonen K, Irjala K, Rajamäki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood. 1997;89(3):1052–7.

[16] Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. Clin J Am Soc Nephrol. 2006;1(Suppl 1):S4–8.

[17] Ganz T. Systemic iron homeostasis. Physiol Rev. 2013;93(4):1721–41.

[18] Andrews NC. Disorders of iron metabolism. N Engl J Med. 1999;341(26):1986–95.

[19] Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. J Biol Chem. 2001;276(11):7806–10.

[20] Donovan A, Lima CA, Pinkus JL, Pinkus GS, Zon LI, Robine S, et al. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. Cell Metab. 2005;1(3):191–200.

[21] Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. Cell. 2017;168(3):344–61.

[22] Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts: molecular control of mammalian iron metabolism. Cell. 2004;117(3):285–97.

[23] Huebers HA, Finch CA. The physiology of transferrin and transferrin receptors. Physiol Rev. 1987;67(2):520–82.

[24] Ponka P, Lok CN. The transferrin receptor: role in health and disease. Int J Biochem Cell Biol. 1999;31(10):1111–37.

[25] Shih YJ, Baynes RD, Hudson BG, Flowers CH, Skikne BS, Cook JD. Serum transferrin receptor is a truncated form of tissue receptor. J Biol Chem. 1990;265(31):19077–81.

[26] Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. Clin Chim Acta. 2003;329(1–2):9–22.

[27] Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. Clin Chem. 1998;44(1):45–51.

[28] Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol. 2005;18(2):319–32.

[29] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: WHO; 2011.

[30] Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet. 2014;46(7):678–84.

[31] Weiss G. Pathogenesis and treatment of anaemia of chronic disease. Blood Rev. 2002;16(2):87–96.

[32] Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. Blood. 2003;101(7):2461–3.

[33] Taniguchi S, Dai CH, Price JO, Krantz SB. Interferon gamma downregulates stem cell factor and erythropoietin receptors but not insulin-like growth factor-I receptors in human erythroid colony-forming cells. Blood. 1997;90(6):2244–52.

[34] Spivak JL. The anaemia of cancer: death by a thousand cuts. Nat Rev Cancer. 2005;5(7):543–55.

[35] Cartwright GE. The anemia of chronic disorders. Semin Hematol. 1966;3(4):351–75.

[36] Zarychanski R, Houston DS. Anemia of chronic disease: a harmful disorder or an adaptive, beneficial response? CMAJ. 2008;179(4):333–7.

[37] Cullis JO. Diagnosis and management of anaemia of chronic disease: current status. Br J Haematol. 2011;154(3):289–300.

[38] Theurl I, Mattle V, Seifert M, Mariani M, Marth C, Weiss G. Dysregulated monocyte iron homeostasis and erythropoietin formation in patients with anemia of chronic disease. Blood. 2006;107(10):4142–8.

[39] Theurl I, Finkenstedt A, Schroll A, Nairz M, Sonnweber T, Bellmann-Weiler R, et al. Growth differentiation factor 15 in anaemia of chronic disease, iron deficiency anaemia and mixed type anaemia. Br J Haematol. 2010;148(6):945–51.

[40] Skikne BS, Punnonen K, Caldron PH, Bennett MT, Rehu M, Gasior GH, et al. Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. Am J Hematol. 2011;86(11):923–7.

[41] Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med. 1992;7(2):145–53.

[42] Lauwers MH, Van den Steen P, Ghoos I, Van Damme B, Billiau A, Opdenakker G. Ferritin synthesis in human bone marrow-derived monocytes. Am J Hematol. 1993;43(2):73–7.

[43] Dignass AU, Gasche C, Bettenworth D, Bokemeyer B, Erichsen K, Gomollon F, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015;9(3):211–22.

[44] Braga F, Infusino I, Dolci A, Panteghini M. Soluble transferrin receptor in complicated anemia. Clin Chim Acta. 2014;431:143–7.

[45] Dallman PR, Refino C, Yland MJ. Sequence of development of iron deficiency in the rat. Am J Clin Nutr. 1982;35(3):671–7.

[46] Cazzola M, Ponchio L, Beguin Y, Rosti V, Bergamaschi G, Liberato NL. Subcutaneous erythropoietin for treatment of refractory anaemia in haematological disorders. Br J Haematol. 1992;82(2):391–7.

[47] Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352(10):1011–23.

[48] Urrechaga E, Borque L, Escanero JF. The role of automated measurement of RBC subpopulations in differential diagnosis of microcytic anemia and beta-thalassemia screening. Am J Clin Pathol. 2011;135(3):374–9.

[49] Brugnara C. Iron deficiency and erythropoiesis: new diagnostic approaches. Clin Chem. 2003;49(10):1573–8.

[50] Fishbane S, Galgano C, Langley RC Jr, Canfield W, Maesaka JK. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. Kidney Int. 1997;52(1):217–22.

[51] Infusino I, Braga F, Dolci A, Panteghini M. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia. A meta-analysis. Am J Clin Pathol. 2012;138(5):642–9.

[52] Skikne BS, Punnonen K, Caldron PH, Bennett MT, Rehu M, Gasior GH, et al. Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation. Am J Hematol. 2011;86(11):923–7.

[53] Hou L, Lu J, Jiang X, Guo X, Ma C, Cheng X. Utility of Access soluble transferrin receptor (sTfR) and sTfR/log ferritin index in diagnosing iron deficiency anemia. Ann Clin Lab Sci. 2015;45(4):396–402.

[54] Günther F, Straub RH, Hartung W, Ehrenstein B, Wilhelm C, Schölmerich J, et al. Usefulness of soluble transferrin receptor in the diagnosis of iron deficiency anemia in rheumatoid arthritis patients in clinical practice. Int J Rheumatol. 2022;2022:7067262.

[55] Kohgo Y, Nishisato T, Kondo H, Tsushima N, Niitsu Y, Urushizaki I. Circulating transferrin receptor in human serum. Br J Haematol. 1986;64(2):277–81.

[56] Setiati S, Harimurti K, Dewiasty E. Role of soluble transferrin receptor and transferrin receptor-ferritin index to detect iron deficiency anemia in regular hemodialysis patients. Acta Med Indones. 2019;51(1):21–7.

[57] Lasocki S, Millot S, Andrieu V, Letteron P, Pilard N, Muzeau F, et al. Phlebotomies or erythropoietin injections allow mobilization of iron stores in a mouse model mimicking intensive care anemia. Crit Care Med. 2008;36(8):2388–94.

[58] Günther F, Straub RH, Hartung W, et al. Association of serum soluble transferrin receptor concentration with markers of inflammation: analysis of 1001 patients from a tertiary rheumatology center. J Rheumatol. 2024;51(3):291–6.

[59] Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood. 2003;101(9):3359–64.

[60] Muñoz M, Gómez-Ramírez S, Besser M, Pavia J, Gomollón F, Liumbruno GM, et al. Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus. 2017;15(5):422–37.

[61] Lasocki S, Gaillard T, Rineau E. Soluble transferrin receptor-ferritin index in the evaluation of anemia in inflammatory bowel disease: a case-control study. BMC Gastroenterol. 2014;14:183.

[62] KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2(4):279–335.

[63] Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochim Biophys Acta. 2012;1823(9):1434–43.

[64] Brugnara C, Schiller B, Moran J. Reticulocyte hemoglobin equivalent (Ret He) and assessment of iron-sufficient erythropoiesis. Clin Lab Haematol. 2006;28(5):303–8.

[65] Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood. 2010;116(23):4754–61.

[66] Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet. 2014;46(7):678–84.

[67] Theurl I, Finkenstedt A, Schroll A, Nairz M, Sonnweber T, Bellmann-Weiler R, et al. Growth differentiation factor 15 in anaemia of chronic disease, iron deficiency anaemia and mixed type anaemia. Br J Haematol. 2010;148(6):945–51.

[68] Cappellini MD, Comin-Colet J, de Francisco A, Dignass A, Doehner W, Lam CS, et al. Iron deficiency across chronic inflammatory conditions. Am J Hematol. 2017;92(10):1068–78.

[69] Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. J Intern Med. 2020;287(2):153–70.

[70] Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I; British Committee for Standards in Haematology. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2013;161(5):639–48.

[71] Thorpe SJ, Heath A, Sharp G, Cook J, Ellis R, Worwood M. A WHO reference reagent for the serum transferrin receptor (sTfR). Clin Chem Lab Med. 2010;48(6):815–20.

[72] Olivares M, Walter T, Cook JD, Hertrampf E, Pizarro F. Usefulness of serum transferrin receptor and serum ferritin in diagnosis of iron deficiency in infancy. Am J Clin Nutr. 2000;72(5):1191–5.

[73] World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: WHO; 2020.

[74] Addo OY, Mei Z, Hod EA, Ayoya LS, Stoltzfus RJ, Hanson K, et al. Physiologically based serum ferritin thresholds for iron deficiency in US older adolescents and adults. Blood Rev. 2025;2(1):100029.

[75] Aapro M, Beguin Y, Bokemeyer C, Dicato M, Gascon P, Glaspy J, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO clinical practice guidelines. Ann Oncol. 2018;29(Suppl 4):iv96–110.

[76] Hou L, Lu J, Jiang X, Guo X, Ma C, Cheng X. Analytical evaluation of three soluble transferrin receptor measurement systems for diagnosis of iron deficiency anemia: a retrospective study. J Clin Lab Anal. 2020;34(8):e23342.

[77] Auerbach M, Macdougall I. The available intravenous iron formulations: history, efficacy, and toxicology. Hemodial Int. 2017;21(Suppl 1):S83–92.

[78] Theurl I, Finkenstedt A, Schroll A, Nairz M, Sonnweber T, Bellmann-Weiler R, et al. Growth differentiation factor 15 in anaemia of chronic disease, iron deficiency anaemia and mixed type anaemia. Br J Haematol. 2010;148(6):945–51.