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The American Journal of Public Health

ISSN 3064-6677

Review Article

Clinical Integration Focus Integrating Reticulocyte Hemoglobin Into Contemporary Hematological Diagnostic Pathways: A Systematic Review.

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Abstract

Iron-deficiency anemia (IDA) constitutes a worldwide health issue, and its extensive prevalence along with its multifaceted consequences for diverse populations, especially within developing nations, highlights the pressing need for effective diagnostic and management approaches. Although conventional diagnostic approaches, including ferritin and transferrin saturation, remain essential, their shortcomings in sensitivity and specificity create difficulties for the early identification and successful management of IDA. This review offers a thorough analysis of IDA, with emphasis on the progression of diagnostic techniques that has led to the use of reticulocyte hemoglobin content (CHr) as a key biomarker. At the heart of this review lies the in-depth assessment of CHr as a biomarker. Its arrival has been crucial owing to its enhanced sensitivity and specificity in detecting iron deficiency and in tracking the effectiveness of therapy. The review examines the comparative benefits of CHr relative to conventional methods, encompassing its capacity to identify IDA at an earlier stage and its applicability across diverse demographic groups, such as children and pregnant women. Directions for future research are put forward, comprising the incorporation of CHr into routine clinical practice, cost-effectiveness analysis, and technological developments aimed at improved measurement and accessibility. In conclusion, CHr possesses considerable potential to transform IDA management, opening the path toward more precise and personalized medical interventions, and thereby enhancing patient outcomes across diverse populations.

Keywords: IDA; CHr; Hematological Diagnostic Pathways.

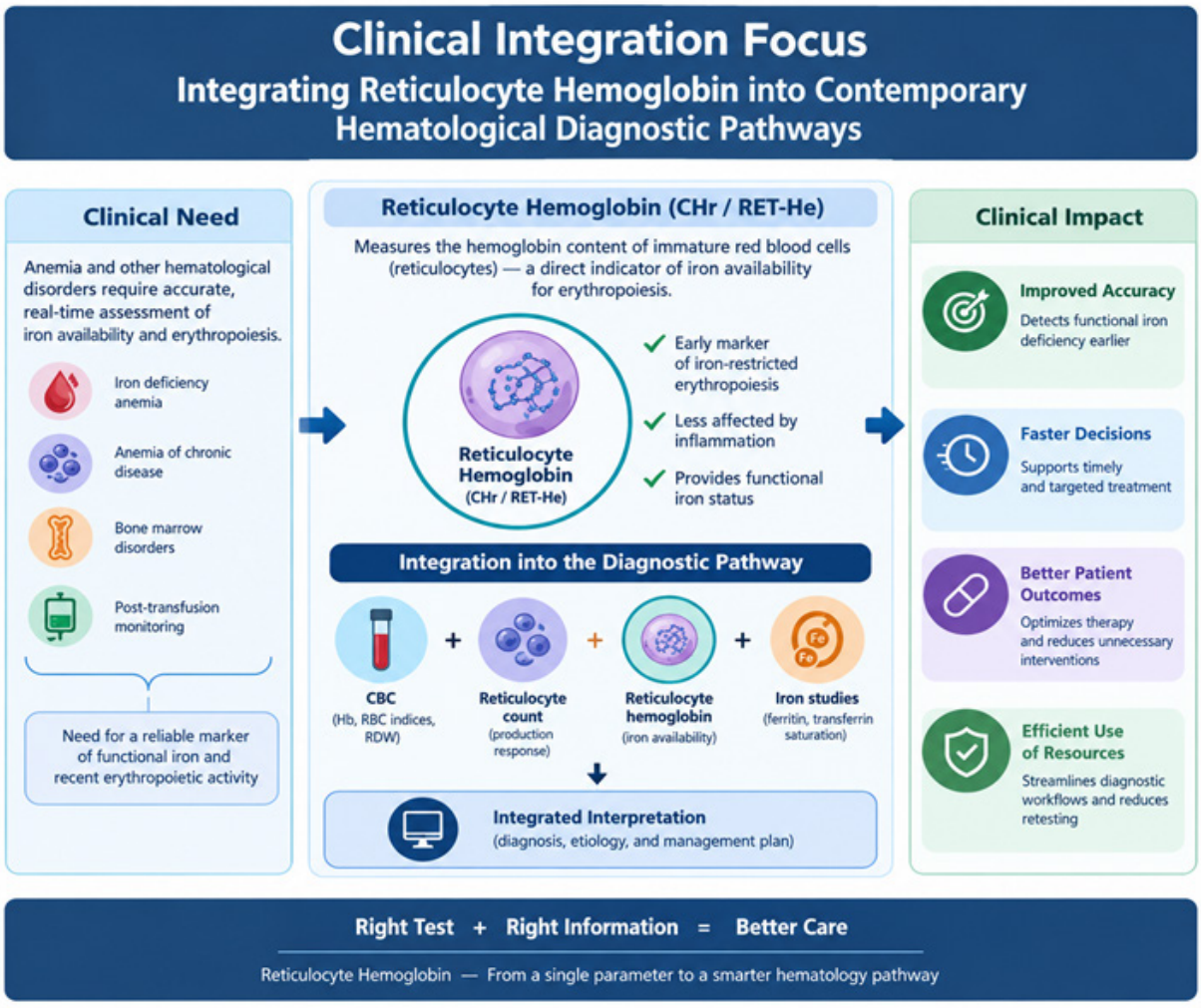
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Received: 11-September-2026, Manuscript No. TAJOPH - 6191**; Editor Assigned:** 21-September-2026 **; Reviewed:** 03-October-2026, QC No. TAJOPH - 6191 **; Published:** 17-October-2026.**DOI:** 10.52338/tajoph.2026.6191.

Citation: Hussein Naji Abdullah Alshammari. Clinical Integration Focus Integrating Reticulocyte Hemoglobin Into Contemporary Hematological Diagnostic Pathways: A Systematic Review. The American Journal of Public Health. 2026 October; 19(1). doi: 10.52338/tajoph.2026.6191.

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GRAPHICAL ABSTRACT



IRON-DEFICIENCY ANEMIA

Iron-deficiency anemia (IDA) constitutes a widespread public health concern that impacts billions of individuals globally, resulting in numerous health complications and economic repercussions [1], the objective of this review paper is to offer a thorough background regarding IDA, its worldwide impact, and the diverse strategies utilized to tackle this critical issue. IDA is defined by a reduction in red blood cell count or a decline in the blood's hemoglobin, stemming from an insufficient iron supply.[2] Iron serves as a vital micronutrient in multiple physiological processes, such as oxygen transport, energy production, and immune function [3]. IDA represents the most prevalent type of anemia, comprising roughly 50% of all anemia cases [4]. It is a multifactorial condition, with causes spanning from inadequate diet, malabsorption, and blood loss to genetic factors and infections [5].

IDA impacts over 1.6 billion individuals worldwide, and its prevalence is greatest in developing nations, where approximately 50% of preschool-aged children and pregnant women are affected.[4] Though it occurs less frequently in developed nations, IDA continues to represent a substantial public health issue, especially among women of childbearing age and individuals from low-income backgrounds.[5] Vulnerable groups, such as children, women of reproductive age, and pregnant women, are affected by IDA at disproportionate rates [6]. Among children, IDA may result in impaired cognitive development, weakened immune function, and heightened vulnerability to infections [7]. Moreover, IDA places children at elevated risk of mortality, since anemia contributes to roughly 20% of all maternal deaths [8].

Research indicates that women of reproductive age affected by IDA may face diminished work capacity, reduced physical performance, and a lower overall quality of life [9]. Pregnant women suffering from IDA confront an even higher risk of complications, including low birth weight, premature delivery, and maternal mortality. 10]. Moreover, IDA has been linked to adverse consequences for maternal mental health, such as postpartum depression [11]. IDA carries considerable economic consequences owing to its effects on human productivity, healthcare expenditures, and overall quality of life. According to estimates from the World Health Organization, the annual loss of productivity attributable to IDA amounts to roughly US $22.4 billion [12]. In addition,

healthcare systems across the globe encounter major financial burdens from the costs tied to diagnosing, treating, and managing IDA [13].

Among the diverse efforts to alleviate IDA, a range of interventions has been developed, encompassing iron supplementation, food fortification, and dietary diversification [14] Advocacy for iron supplementation has been particularly pronounced, especially within populations at elevated risk, such as pregnant women and young children. Nevertheless, this intervention is not without possible disadvantages, as documented adverse effects extend from gastrointestinal issues to an increased vulnerability to infectious diseases [15]. The fortification of staple foods, including wheat flour and rice, with iron has been broadly recognized as an effective means of lowering the prevalence of IDA across numerous countries. [16] However, the effectiveness of this approach depends on the bio accessible iron compounds utilized and is affected by other dietary components that influence iron absorption [17]. Encouraging a varied diet, promoting the consumption of iron-rich foods, and incorporating dietary components that enhance iron absorption offers an alternative pathway in the fight against IDA [18].

This approach has proven successful in particular settings, particularly when combined with additional interventions.[19] Nevertheless, the effectiveness of dietary diversification is often constrained by barriers including food insecurity, deeply rooted cultural dietary practices, and limited availability of diverse food resources [10].

Addressing and surmounting obstacles to the deployment of IDA remediation strategies is essential, as these challenges encompass insufficient financial resources, inadequate health infrastructures, and weak surveillance and assessment mechanisms [11]. Moreover, tackling the underlying determinants of iron deficiency such as economic hardship, food insecurity, and constrained access to health care, is necessary to achieve sustained progress in reducing the global IDA burden [12-15]. A multispectral approach can strengthen the effectiveness of IDA countermeasures, and this approach depends on collaboration among diverse stakeholders, including governmental bodies, civil society organizations, and the private sector. Joint endeavors, including extensive fortification programs and community-based nutritional initiatives, have contributed substantially to attaining this objective [16]. Furthermore, integrating IDA prevention and management strategies into existing health care structures, such as maternal and child health services, could enable more efficient use of resources and enhance both the reach and the effectiveness of these interventions [17-20].

In expanding comprehension of the molecular and genetic underpinnings of IDA has driven the emergence of groundbreaking therapeutic approaches. Investigations into hepcidin, a principal regulator of iron homeostasis within the body, have led to the development of hepcidin antagonists. Such agents may potentially act as efficacious therapies for IDA, enhancing the health of individuals afflicted by this condition [21-25]. Precision nutrition interventions customized to an individual's genetic profile have acquired significance owing to the emphasis placed on assimilation and metabolism [26-27].

IDA, Diagnostic Approaches

The standard methods conventionally used to diagnose IDA depend on the careful assessment of hematologic indices, serum iron measurements, and iron deposition in the bone marrow.[14] Hematologic indices, including hemoglobin concentration, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH), are routinely measured to identify the presence of anemia and to classify its phenotype as microcytic, normocytic, or macrocytic.[28-30] However, depending on these parameters alone may not be enough to determine the cause of anemia, nor do they consistently reflect an individual's iron reserve status [31-32].

Indicators of iron status in serum, particularly ferritin, transferrin saturation (TSAT), and the soluble transferrin receptor (STfR), function as more refined measures of iron homeostasis [33]. Since serum ferritin is intimately associated with the iron content of bone marrow, it is regarded as the foremost indicator for evaluating the body's iron stores and is conventionally considered the reference standard [34]. Nevertheless, the interpretive usefulness of ferritin can be distorted by unrelated conditions, including inflammatory states, infectious diseases, and hepatic pathologies, which may confound the evaluation of iron status [35]. TSAT offers an indication of the balance between iron supply and demand, whereas STfR concentrations reveal the functional iron deficit occurring within erythropoiesis [36]. Nonetheless, the diagnostic accuracy of these indices is not absolute, as their sensitivity and specificity may be diminished by diverse factors, including inflammatory processes and renal function [37-38].

The definitive evaluation of IDA by directly assessing bone marrow iron content via aspiration and subsequent histological staining is regarded as the gold standard diagnostic approach [39]. Nevertheless, the invasive nature of this procedure entails several limitations, such as the need for specialized equipment and trained personnel, the possibility of patient discomfort, and the associated risk of procedural complications.↻ In addition, the assessment of bone marrow iron content is not immune to inter-observer variability, and its diagnostic conclusiveness for IDA may be ambiguous [36,40]. The intrinsic shortcomings of these standard diagnostic approaches for IDA have substantial consequences for clinical practice as well as public health

policy. Erroneous diagnoses, or postponements in reaching an accurate diagnosis, may give rise to inadequate patient management, rising healthcare costs, and missed pivotal opportunities to apply effective therapeutic interventions [20, 32]. Furthermore, reliance on invasive diagnostic methods such as bone marrow aspiration can intensify health-care inequities, especially in settings where resources are limited.

The current research trajectory into iron metabolism and the pathophysiology underlying IDA has set the stage for developing novel diagnostic methodologies. Identifying hepcidin as a pivotal regulator in iron homeostasis has incited interest in its application as a biomarker for IDA [41]. Correlations between hepcidin levels and iron status offer insights into anemia's etiology, whether due to iron scarcity or inflammatory processes [42]. However, establishing hepcidin as a diagnostic tool necessitates the development of standardized measurement protocols and the corroboration of its clinical pertinence through rigorous research [43].

IDA may be identified by means of several approaches, among them invasive procedures. Nonetheless, noninvasive imaging modalities, for instance magnetic resonance imaging and quantitative susceptibility mapping, are likewise applicable for the detection of IDA. Such imaging modalities have demonstrated promise in determining iron distribution and concentration throughout tissues without the need for any invasive procedures [44-45]. In spite of this potential, these technologies have not yet been universally implemented in standard IDA diagnostics, owing to concerns regarding cost, accessibility, and the necessity of thorough validation [46]. Nonetheless, the use of these imaging techniques in routine IDA diagnosis continues to be constrained by cost, availability, and the requirement for additional validation field [47].

The advent of omits technologies spanning genomics, proteomics, and metabolomics – heralds a transformative epoch in diagnosing IDA, facilitating a nuanced delineation of the molecular architectures orchestrating the disorder.[48] These investigative modalities offer the potential to unveil novel biomarkers and molecular signifiers emblematic of IDA, thus propelling diagnostic procedures toward greater precision and personalization [49]. Exemplifying this, proteomic analysis has surfaced a cadre of proteins germane to iron metabolism and erythropoiesis, whose altered expression in IDA patients underscores their diagnostic significance [50].

Complementarily, metabolomic assessments have discerned variations in the metabolic spectra of individuals with IDA, paving the way for these alterations to be harnessed as diagnostic and prognostic indices. Notwithstanding the promising course of these emerging diagnostic methods, a range of obstacles remains to be addressed prior to their widespread adoption in clinical and public health settings. Such barriers encompass the excessive expenses linked to omics and advanced imaging technologies, the requirements for standardizing protocols and reference standards, as well as the ethical and privacy issues pertinent to the use of genomic data [51]. Furthermore, the effective incorporation of these novel diagnostic instruments into conventional medical practice demands a collaborative endeavor involving a broad group of stakeholders, including the research community, clinicians, and policymakers, to guarantee that these developments are equitable, economical, and suitable across diverse health-care contexts [52].

HEMOGLOBIN CONTENT AS A PROMISING BIOMARKER

Reticulocytes, the immature precursors of mature erythrocytes, are released from the bone marrow and have a higher hemoglobin concentration than their mature counterparts [53]. The reticulocyte hemoglobin content (CHr) measure quantifies the amount of hemoglobin contained within reticulocytes, thus furnishing an indicator of iron availability at the level of erythropoiesis and of iron adequacy for hemoglobin synthesis during erythropoiesis.[38] Because reticulocytes persist only briefly in the bloodstream, approximately 1–2 days, CHr provides a more current and dynamic evaluation of iron status than do conventional hematologic parameters and serum iron indices [54-55].

Within today's scientific context, efforts to discover new biomarkers that could improve the diagnosis and treatment of IDA have grown more intense. Among these candidates, the (CHr, Ret-He, or MCHr) has emerged as a notable biomarker, especially capable of differentiating IDA from anemia of inflammation [56-60]. This part of the review will examine the benefits of CHr, referred to throughout this review as CHr, as a tool for diagnosis and prognosis, along with its clinical uses, and the possible obstacles and future directions in this area. Numerous investigations have confirmed the clinical utility of CHr in the diagnosis and management of IDA. It demonstrates considerable sensitivity and specificity in detecting iron deficiency across varied demographic groups, including children, adults, and pregnant women [59, 61-62]. In contrast to serum ferritin, the levels of which can be distorted by inflammation, infection, and hepatic disease, CHr is less vulnerable to these confounding factors, thereby potentially providing a more accurate indicator of iron status in patients with coexisting inflammatory or infectious conditions.

Moreover, the prognostic utility of CHr within IDA management has been recognized. It functions as a reliable means of monitoring the hematologic response to iron supplementation and as a basis for modifying iron dosages across the entire course of treatment [58,63-66]. CHr has likewise been proposed as an early indicator of iron-restricted erythropoiesis (IRE) in patients receiving erythropoiesis-

stimulating agents (ESAs) for anemia linked to chronic kidney disease, cancer, or other chronic conditions [67].

The range of clinical utility associated with CHr extends beyond the diagnosis and treatment of IDA. CHr has come to be acknowledged as an essential parameter for evaluating functional iron deficiency among patients afflicted with heart failure, thereby aiding in the distinction between genuine ID and the anemia of inflammation [68]. Furthermore, the capacity of CHr to serve as a biomarker for the early identification of iron overload in persons with hereditary hemochromatosis and other iron-loading disorders has been suggested [69].

Future investigations ought to address these obstacles and more closely examine the clinical value of CHr as a biomarker for IDA. Extensive, multicenter studies are necessary to establish standardized reference values and thresholds for CHr that encompass diverse populations and age groups. At the same time, efforts should be directed toward improving the availability and cost-effectiveness of CHr testing, particularly in resource-limited settings where accurate and timely IDA diagnosis is urgently required.

The development of point-of-care testing (POCT) devices for CHr may alleviate many existing difficulties by enabling rapid, economical, and decentralized IDA assessments [70-73]. Advances in microfluidics, biosensing, and digital health technologies have laid the groundwork for portable POCT devices capable of measuring CHr and other hematologic parameters with minimal sample volume and equipment demands [74]. Such devices hold the potential to transform IDA diagnosis and treatment, enabling healthcare practitioners to make immediate, well-informed decisions about iron supplementation, dosage adjustment, or additional diagnostic workup [75].

ADVANTAGES OF HEMOGLOBIN CONTENT IN RETICULOCYTES

Early detection of deficiency

The CHr emerges as an index of central importance in the early identification of ID and IDA, thereby providing the rationale for timely intervention and the prevention of sequelae associated with untreated iron deficits. CHr measures the hemoglobin content of reticulocytes, furnishing a rapid and dynamic indicator of iron status that surpasses conventional hematological parameters and serum iron indices with respect to immediacy [76]. Given the brief circulatory lifespan of reticulocytes, generally 1–2 days, their hemoglobin content reflects emerging shifts in iron availability for erythropoiesis, preceding the appearance of overt anemia [77].

Empirical findings emphasize the enhanced sensitivity and specificity of CHr in identifying the onset of ID and IDA. Work by Ullrich et al. confirms that CHr surpasses established hematological indicators, including MCV and MCH, in identifying early iron deficiency in healthy infants [78]. In a similar vein, Mast et al. demonstrated that CHr displays greater sensitivity and specificity in diagnosing IDA among adults when compared with serum ferritin, TSAT, and red blood cell indices.

Detect functional iron deficiency

CHr offers a foundational advantage through its ability to identify functional ID, a condition in which iron is insufficiently assimilated for erythropoiesis despite normal or elevated total body iron stores. This condition is commonly observed within the setting of chronic diseases such as chronic kidney disease, heart failure, and various inflammatory states. Conventional indices of iron status are frequently obscured by the inflammatory response and coexisting disorders, thus rendering the diagnosis of functional iron deficiency more difficult.

Evidence indicates that CHr is reliable as an indicator of functional ID across a range of clinical scenarios. Among the chronic kidney disease patient population, CHr has been validated as a more accurate measure of IRE than serum ferritin and TSAT, particularly in the setting of inflammatory processes or concurrent administration of ESAs [7 9-81] In individuals with heart failure, CHr effectively distinguishes between genuine iron deficiency and anemia of inflammation, thereby guiding the management strategy for such patients [82]. Furthermore, CHr has been proposed as an effective instrument for monitoring responses to iron therapy among diverse groups, including pediatric cohorts, expectant mothers, and patients with chronic illnesses. Its dynamic character permits a prompt assessment of the efficacy of iron supplementation, thereby enabling clinicians to adjust treatment plans and dosages with greater speed than traditional iron status measures would allow.

Reticulocyte Hemoglobin Content

A salient merit of CHr as a biomarker for IDA is its relative insusceptibility to inflammatory processes, a trait not shared by other iron metrics such as serum ferritin and TSAT [83]. Inflammatory responses, precipitated by a spectrum of acute and chronic disorders, can perturb iron homeostasis, thereby obfuscating the assessment of traditional iron indices. Cytokines, particularly interleukin-6, are known to increase hepcidin synthesis, culminating in diminished iron absorption and mobilization from stores, leading to functional iron deficiency.

Assessment of iron availability for erythropoiesis

By offering a more direct and dynamic indicator of iron's availability for erythropoiesis, CHr may enhance the diagnosis and therapeutic management of IDA and its related

conditions. Empirical studies have demonstrated that CHr exhibits greater sensitivity and specificity as a marker of iron-limited erythropoiesis than conventional iron indices. This is particularly relevant for individuals receiving ESA treatment for anemia associated with chronic kidney disease, cancer, or other chronic health conditions [84].

Research corroborates the effectiveness of CHr in assessing iron status during concurrent inflammatory or infectious conditions. For instance, in pediatric research conducted by Mäkelä et al., CHr emerged as a more precise indicator of iron deficiency than serum ferritin and TSAT in acute infections [85]. Similarly, work by Dignass et al. showed that CHr's reliability as an iron status marker was less compromised by inflammatory states than serum ferritin in patients with anemia of chronic disease, thereby offering a more dependable measure of iron status in this demographic.

CHr provides an improved assessment of iron bioavailability for erythropoiesis relative to conventional iron indices by quantitatively measuring hemoglobin within reticulocytes, thus reflecting the status of iron reserves in erythropoietic tissues [86]. Traditional iron metrics such as serum ferritin and TSAT provide indirect evaluations of iron status, which may not reliably reflect iron's availability for erythropoietic processes, especially in cases of functional iron deficiency or concurrent inflammatory conditions.

Therapy and Monitoring Treatment Response

The CHr plays a central role in coordinating iron therapy and in monitoring therapeutic outcomes among individuals with IDA. Because it can promptly mirror shifts in the iron available for erythropoiesis, CHr permits a more expedited assessment of therapeutic efficacy than conventional iron indices, thereby supporting timely modifications to iron dosage and treatment approaches [87].

Research has confirmed the effectiveness of CHr in guiding iron therapy and evaluating therapeutic responses among diverse demographic groups, such as children, adults, and pregnant women. For example, Neef et al. documented that iron therapy guided by CHr produced a more rapid and sustained therapeutic response in pediatric patients with IDA than methods depending on serum ferritin and TSAT. Almashjary et al. have recognized CHr as a better marker than hemoglobin for detecting the swift improvement following iron therapy within one week among adult subjects with ID and IDA. Likewise, an analytical review by Govindappagari and Burwick has shown that iron therapy centered on CHr enhances the efficacy of iron supplementation in pregnant women with IDA, while simultaneously reducing the need for intravenous iron interventions [88].

In addition, CHr has demonstrated value in tracking the response to iron therapy among patients who receive ESAs for the management of anemia in the setting of chronic conditions such as chronic kidney disease or cancer [77-81, 89] By providing a more prompt and dynamic indicator of iron availability for erythropoiesis, CHr helps health-care professionals to adjust the dosing and administration of ESAs, thus reducing possible adverse effects and improving overall therapeutic outcomes.

CONCLUSION

IDA constitutes a prevalent health condition affecting a considerable segment of the global population. In recent times, the adoption of the CHr test has demonstrated encouraging outcomes in the diagnosis and management of this condition. CHr serves as a sensitive and specific indicator of iron deficiency, and its clinical effectiveness underscores its capacity to raise care standards and enhance patient outcomes. Notwithstanding its promise, several obstacles remain regarding the use of CHr within existing diagnostic and treatment protocols. Additional research is required to address these obstacles and to formulate explicit guidelines for incorporating CHr into routine clinical practice. Through deepening our comprehension of CHr and its applications, we can reduce the global burden of IDA and improve the well-being of affected populations. The integration of CHr into existing frameworks holds the promise of enhancing the identification and management of iron deficiency along with its related disorders. This will allow health-care providers to make better-informed decisions regarding patient care and treatment options, thereby producing improved health outcomes for patients. On the whole, CHr possesses considerable potential to transform the manner in which we diagnose and manage IDA, and additional research in this domain is essential for enhancing patient care and health outcomes.

Conflict of Interest

The authors declare no conflict of interest

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