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Diagnosis of Iron Deficiency in Inflammatory Bowel Disease by Transferrin Receptor-Ferritin Index

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Abstract: Iron deficiency is common in patients with inflammatory bowel disease (IBD), but can be difficult to diagnose in the presence of inflammation because ferritin is an acute phase reactant. The transferrin receptor-ferritin index (TfR-F) has a high sensitivity and specificity for iron deficiency diagnosis in chronic diseases. The diagnostic efficacy of TfR-F is little known in patients with IBD. The aim of the study was to assess the added value of TfR-F to iron deficiency diagnosis in a prospective cohort of patients with IBD.

Consecutive IBD patients were prospectively enrolled. Patients were excluded in case of blood transfusion, iron supplementation, or lack of consent. IBD activity was assessed on markers of inflammation (C-reactive protein, endoscopy, fecal calprotectin). Hemoglobin, ferritin, vitamin B9 and B12, Lactate dehydrogenase, haptoglobin, and soluble transferrin receptor (sTfR) were assayed. TfR-F was calculated as the ratio sTfR/log ferritin. Iron deficiency was defined by ferritin <30 ng/mL or TfR-F >2 in the presence of inflammation.

One-hundred fifty patients with median age 38 years (16–78) and Crohn disease (n = 105), ulcerative colitis (n = 43), or unclassified colitis (n = 2) were included. Active disease was identified in 45.3%. Anemia was diagnosed in 28%. Thirty-six patients (24%) had ferritin <30 ng/mL. Thirty-two patients (21.3%) had ferritin levels from 30 to 100 ng/mL and inflammation: 2 had vitamin B12 deficiency excluding TfR-F analysis, 13 of 30 (43.3%) had TfR-F >2. Overall, iron deficiency was diagnosed in 32.7% of the patients.

TfR-F in addition to ferritin <30 ng/mL criterion increased by 36% diagnosis rates of iron deficiency. TfR-F appeared as a useful biomarker that could help physicians to diagnose true iron deficiency in patients with active IBD.

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Abbreviations: F = ferritin, IBD = inflammatory bowel disease, LDH = lactate dehydrogenase, sTfR = soluble transferrin receptor, TfR-F = transferrin receptor-ferritin index.

INTRODUCTION

Iron deficiency is frequent in inflammatory bowel diseases (IBD) and can negatively impact quality of life of patients even without anemia.¹ Iron deficiency may be responsible for various symptoms, including impaired physical performance, decreased cognitive function, fatigue, headache, dizziness, shortness of breath, restless legs syndrome, hair loss, stomatitis, glossitis, and reduce libido.² Moreover, it can increase thromboembolic risk.² In fact, iron deficiency is the main cause of anemia in IBD patients³ as a consequence of intestinal bleeding and/or malabsorption related to inflammation and less frequently, to intestinal failure or low dietary intake. In a systematic review,⁴ the prevalence of iron deficiency ranged from 36% to 90% (depending on the definition of iron deficiency and on the type of cohort included). According to Gisbert et al,⁵ the mean prevalence of iron deficiency in IBD calculated from the available studies in the literature is 45% (95% confidence interval [CI] 40–50%).

Measurement of serum ferritin provides the most useful indirect estimate of body iron stores and ferritin level <30 ng/mL is a diagnostic criterion of iron deficiency.⁶ Nevertheless, the diagnosis of iron deficiency is difficult in the presence of inflammation, as ferritin is an acute phase reactant that increases its concentration in that context. Guidelines in IBD⁷ consider ferritin level between 30 and 100 ng/mL associated with inflammation as diagnostic criteria for iron deficiency. However, if increased ferritin cutoff improves its sensitivity, it is at the cost of loss in specificity. Confirmation of a true iron deficiency associated to inflammation is of clinical importance to prevent useless treatment.^{6,8,9} In addition, iron therapy for patients with anemia of inflammation (anemia of chronic disease) is controversial since iron is an essential nutriment for proliferation of microorganisms that could increase infectious risk.^{10,11}

Several parameters have been studied for their utility to indicate true iron deficiency in association with inflammation. One of these laboratory parameters is the concentration of soluble transferrin receptor (sTfR) in serum, which is an indicator of the needs of iron for erythropoiesis.⁶ However, transferrin receptor expression on cells is also affected by inflammation, which negatively affects the sensitivity of sTfR levels to indicate true iron deficiency in inflammatory diseases. A calculated ratio of sTfR/log ferritin (TfR-F) was developed as an accurate indicator of true iron deficiency in patients with inflammation.^{12,13} The diagnostic efficacy of TfR-F is little known in patients with IBD. To date, only one study has been published concerning the accuracy of the TfR-F index in

patients with IBD,¹⁴ which suggested a high sensitivity and specificity for iron deficiency diagnosis. The aim of our study was to assess the added value of TfR-F index to iron deficiency diagnosis in patients with IBD.

MATERIAL AND METHODS

Study Participants and Study Design

The investigational review board “Comité d'évaluation des études cliniques du service de gastroentérologie et d'oncologie digestive” of Cochin hospital approved the study protocol; all patients provided written informed consent and approved the sampling and biological analysis in compliance with the ethical principles of the revised Declaration of Helsinki (2008) and with French regulations. Consecutive IBD patients seen in our hospital from February 2013 to March 2014 were prospectively enrolled. Patients with blood transfusion in the 4 previous weeks or iron supplementation in the 3 previous months were excluded from the study. Presence of liver disease was an exclusion criterion. The recruitment procedure included a detailed history of the IBD and physical examination. Localization and phenotype of the disease were categorized according to the Montreal classification.¹⁵ IBD activity was assessed on symptoms (Harvey Bradshaw index for Crohn's disease and partial Mayo score for ulcerative colitis) and markers of inflammation (C-reactive protein [CRP], mucosal assessment by endoscopy and/or fecal calprotectin). All patients had serum dosages of hemoglobin, high-sensitivity CRP, ferritin, vitamin B9 and B12, LDH, haptoglobin, transferrin, and sTfR.

Laboratory Tests

A peripheral blood sample (3 mL) was collected in ethylenediaminetetraacetic acid-anticoagulant (Becton-Dickinson Vacutainer®, Plymouth, UK) and assessed for hemoglobin and blood cell count using a Sysmex XN-9000™ hematology analyzer (Sysmex Europe GmbH, Norderstedt Germany). Vitamin B12 and red cell folate were assessed in a clot activator tube (4 mL) (Becton-Dickinson Vacutainer®) and measured by immunoassay (Elecsys®, Roche Diagnostics, Mannheim, Germany). Two Lithium Heparin plasma samples (4 mL) (Vacuette®, Greiner Bio-One GmbH, Austria) were collected at inclusion. One was assessed the same day for CRP (Tina-quant® C-Reactive Protein Gen.3, Roche Diagnostics, Mannheim, Germany) ($N < 2.5$ mg/L), ferritin (Elecsys®, Roche Diagnostics, Mannheim, Germany), LDH (Cobas® 8000 module c502, Roche Diagnostics, Mannheim, Germany), and haptoglobin (Tina-quant® Haptoglobin, Roche Diagnostics). The second sample was stored at -40°C after centrifugation and assessed at the end of the recruitment period for sTfR (Tina-quant® sTfR, Roche Diagnostics). The method principle of sTfR is immunoturbidimetry using Roche kits on the Cobas 8000 clinical analyzer. Latex-bound anti-sTfR antibodies react with the antigen in the sample to form an antigen/antibody complex. Following agglutination, turbidity of the medium is measured by spectrophotometry. TfR-F index was calculated as $(\text{sTfR} \div \log \text{ferritin})$ in which log refers to “base-10 log.” A low TfR-F index < 1 indicates anemia of inflammation without iron deficiency, whereas a TfR-F index of > 2 reflects true iron deficiency.⁶ Patients with vitamin B12 deficiency, myelodysplasia, or hemolysis were excluded from TfR-F index analysis.¹⁶

Definitions and Methodology

Anemia was defined according to the WHO definition as a decline in blood hemoglobin to a concentration of < 12 g/dL

(120 g/L) in women and < 13 g/dL (130 g/L) in men. Active inflammatory disease was defined by the presence of symptoms (Harvey Bradshaw index > 4 for Crohn's disease and partial Mayo score > 3 for ulcerative colitis) and high-sensitivity CRP > 2.5 ¹⁷ and/or active mucosal lesions assessed by endoscopy and/or increased fecal calprotectin > 200 $\mu\text{g/g}$.¹⁸ According to Weiss et al,⁶ iron deficiency was defined by ferritin < 30 ng/mL or TfR-F index > 2 in the presence of inflammation; TfR-F index < 1 excluded iron deficiency. In case of TfR-F index between 1 and 2, iron deficiency could not be ruled out. Iron deficiency rates diagnosed by ferritin alone or by ferritin added to sTfR-F index were compared to assess the added value of TfR-F index to iron deficiency diagnosis in this cohort of IBD patients.

RESULTS

One hundred and fifty patients aged 38 years (16–78) were included in the study. The study population consisted of 69 men

TABLE 1. Characteristics of the Studied Population

Characteristic	Result
Demographic information	
Patients included	150
Female	81
Age, years	38 (16–78)
Type of IBD and activity of the disease	
CD	105
UC	43
Unclassified colitis	2
Active disease	68
Montreal classification:	
UC	
E1: ulcerative proctitis	6
E2: left-sided UC	17
E3: pancolitis	20
CD	
Age at diagnosis	
A1: below 16 years	16
A2: 17 to 40 years	87
A3 over 40 years	2
Disease location*	
L1: terminal ileum	18
L2: colon	30
L3: ileocolon	50
L4: upper gastrointestinal tract	10
Behavior	
B1: nonstricturing nonpenetrating	37
B2: stricturing	32
B3: penetrating	36
p: perianal	21
IBD treatments [†] :	
5-ASA	42
Steroids	25
Azathioprine	39
Methotrexate	8
Anti-TNF	70

5-ASA = 5-aminosalicylic acid, CD = Crohn disease, IBD = inflammatory bowel disease, TNF = tumor necrosis factor, UC = ulcerative colitis.

* L4 is a modifier that was added to L1–L3 when concomitant upper gastrointestinal disease was present.¹⁵

[†] Treatments could be associated in a same patient.

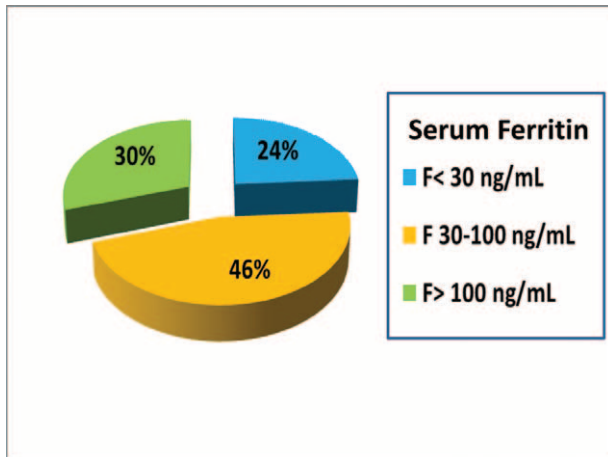


FIGURE 1. Results of serum ferritin (F) dosages in 150 patients with inflammatory bowel disease.

and 81 women. Patients had Crohn disease (n = 105), ulcerative colitis (n = 43), or unclassified colitis (n = 2). Patients' characteristics are reported in Table 1.

Sixty-eight patients (45.3%) had active disease. Forty-two patients (28%) had anemia, including 28 Crohn diseases and 14 ulcerative colitis. Nine patients (6%) had vitamin B12 deficiency and 9 vitamin B9 deficiency (6%). No one had hemolysis or myelodysplasia. Mean ferritin level was 80 (9–359)ng/mL. Thirty-six patients (24%) had ferritin <30ng/mL, 69 (46%) had ferritin between 30–100ng/mL, and 45 (30%) had ferritin >100ng/mL (Figure 1).

Thirty-two patients (21.3%) had ferritin between 30 and 100 ng/mL and inflammation (CRP >2.5 mg/L or active mucosal lesions). Two of them had vitamin B12 deficiency excluding TfR-F index analysis. Results of TfR-F index in these patients are presented in Figure 2: 13 of 30 patients (43.3%) had TfR-F index >2, 16 patients (53.3%) had TfR-F index between 1 and 2, and 1 patient (3.3%) had TfR-F index <1. Forty-five patients had ferritin >100 ng/mL, 4 of them had vitamin B12 deficiency, and 7 patients (17.1%) had TfR-ferritin >2. Ferritin levels according to TfR-F values are presented in Tables 2 and 3, respectively.

Overall, iron deficiency was diagnosed in 49 of 150 patients (32.7%), of which 36 on the basis of ferritin <30 ng/mL criterion and 13 with TfR-F index >2 in the presence of inflammation (Figure 3). Twenty-one patients (42.8 %) of 48 diagnosed with iron deficiency did not have anemia.

DISCUSSION

We herein report the first prospective study that highlight the added value of TfR-F index to iron deficiency diagnosis in IBD patients. The robustness of this study is enhanced by the use of validated biochemical measurement techniques with the thresholds currently recommended in a large sample of IBD patients. In our study, the prevalence of iron deficiency was 32.7%. TfR-F index in addition to serum ferritin <30ng/mL criterion increased by 36% diagnosis rates of iron deficiency. Iron deficiency was not associated to anemia in 42.8% of the patients.

Iron deficiency is common among patients with IBD and is responsible for multiple symptoms that can alter their quality of life, even without anemia.^{1,2} Iron deficiency rates in our study are consistent with rates reported in patients with IBD⁴ ranging from 36% to 90% depending on the population studied and

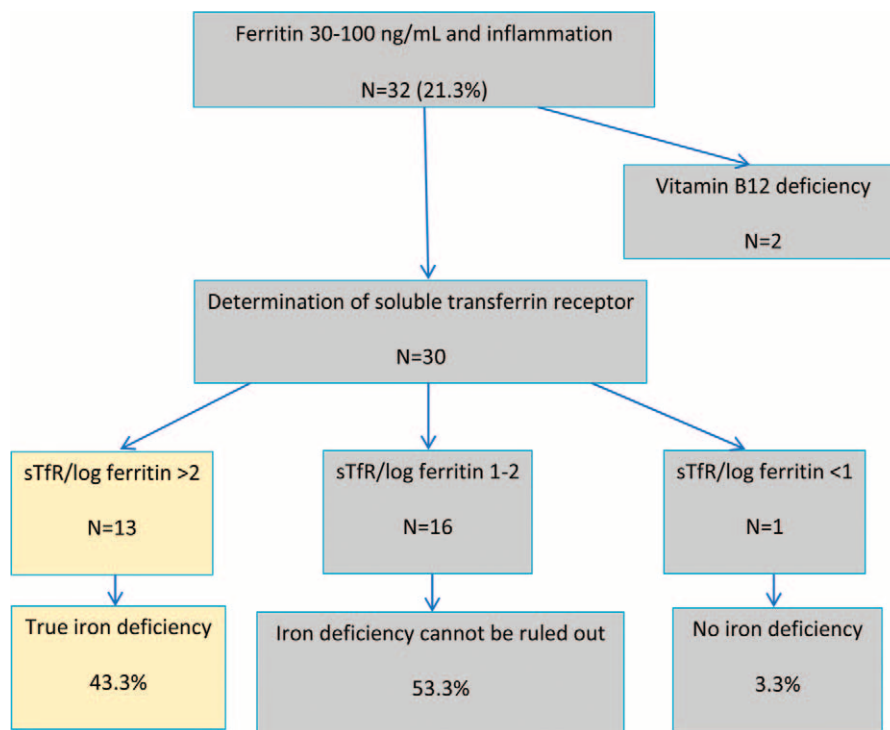


FIGURE 2. Iron deficiency diagnosis in patients with ferritin 30 to 100 ng/mL and inflammation. sTfR = soluble transferrin receptor.

TABLE 2. TfR-F Values According to Ferritin Levels

	Ferritin <30 ng/mL (N = 36)	Ferritin = 30–100 ng/mL (N = 69)	Ferritin >100 ng/mL (N = 45)
TfR-F >2*	31/33 (94%)	21/67 (31.3%)	7/41 (17.1%)
TfR-F = 1–2*	2/33 (6%)	44/67 (65.7%)	29/41 (70.7%)
TfR-F <1*	0	2/67 (3%)	5/41 (12.2%)

TfR-F = transferrin receptor-ferritin index.
*TfR-F not analyzed in 9 patients with vitamin B12 deficiency.

TABLE 3. Ferritin Levels According to TfR-F Values*

	TfR-F >2 (N = 59)	TfR-F = 1–2 (N = 75)	TfR-F <1 (N = 7)
Ferritin <30 ng/mL	29/59 (49.1%)	2/75 (2.7%)	0/7 (0%)
Ferritin = 30–100 ng/mL	23/59 (40%)	47/75 (62.7%)	2/7 (28.6%)
Ferritin >100 ng/mL	7/59 (11.9%)	26/75 (34.7%)	5/7 (71.4%)

TfR-F = transferrin receptor-ferritin index.
*TfR-F not analyzed in 9 patients with vitamin B12 deficiency.

diagnostic methods. According to Gisbert et al,⁵ the mean prevalence of iron deficiency in IBD calculated from the available studies in the literature is 45% (95% CI 40%–50%). Thus, it is important to diagnose iron deficiency in patients with IBD.

Bone marrow aspiration establishing the absence of stainable iron remains the gold standard for a diagnosis of iron deficiency. However, this examination is invasive, expensive, and requires technical expertise, so that it cannot be performed routinely in clinical practice. Ferritin is a widely used peripheral iron biomarker. It is considered to correlate with iron stores in the absence of inflammation. Indeed, ferritin is a positive

acute phase response protein whereby concentrations increase during inflammation and thereby no longer reflect the size of the iron store. The generally accepted cutoff to detect iron deficiency in IBD is 30 ng/mL and serum ferritin <30 ng/mL is a diagnostic criterion of iron deficiency.^{6,7,19} In the presence of inflammation, increased thresholds have been proposed to increase sensitivity, but at the cost of loss of specificity. According to recent guidelines in IBD,⁷ serum ferritin concentration between 30 and 100 ng/mL indicates depleted iron stores. However, these cutoffs are not validated, despite studies attempting to correlate serum ferritin measures to bone marrow hemosiderin in chronic diseases.^{19–23} We could confirm a true

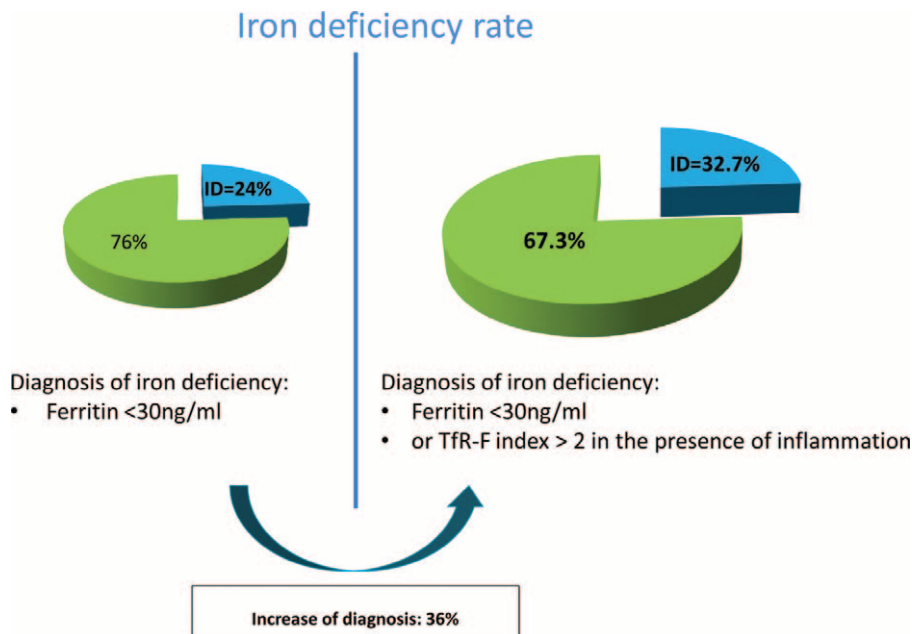


FIGURE 3. Added value of transferrin receptor-ferritin index to diagnosis of iron deficiency (ID) in the overall population.

iron deficiency in only 43.3% of our patients with active disease and ferritin between 30 and 100 ng/mL. Furthermore, 17.1% of the patients with ferritin >100 ng/mL had TfR-F index >2. These results lead us to question the relevance of the threshold of 100.

Several parameters have been studied for their utility to indicate true iron deficiency in association with inflammation. The sTfR in serum is an indicator of the needs of iron for erythropoiesis.⁶ Previous studies promoted sTfR in populations with inflammation,^{24,25} but other studies reported that inflammation may interfere with sTfR.^{26,27} The TfR-F index has been shown to provide superior discrimination to either sTfR or ferritin alone particularly in chronic disease.^{6,13,27–29} Rimón et al²⁹ performed a prospective controlled study in 49 elderly patients with chronic disease. Bone marrow aspirate confirmed iron deficiency in all patients. Only 8 patients could be diagnosed by ferritin test. In contrast, the TfR-F index disclosed iron deficiency in 43 of 49 patients, thus increasing the sensitivity from 16% to 88%. Similar results are shown in a population of 30 anemic patients with rheumatoid arthritis in whom iron deficiency diagnosis was confirmed by iron staining in the bone marrow.²⁸ According to the authors, a single value of TfR-F index helps to elucidate differential diagnosis between true iron deficiency anemia and anemia of chronic disease with functional iron deficiency.²⁷ To date, only one published study evaluated the accuracy of the TfR-F index in IBD patients.¹⁴ Patients with iron deficiency anemia had significantly higher TfR-F index compared with those without iron deficiency. TfR-F index values were not correlated with CRP levels or disease activity. TfR-F index >1.4 had a high discriminating power (sensitivity 91%, specificity 92 %) in the diagnosis of iron deficiency anemia. In our study, we chose a higher cutoff for TfR-F index, >2 as previously recommended⁶ for iron deficiency diagnosis in inflammatory chronic disease. This might explain the rate of our inflammatory patients for whom iron deficiency could not be confirmed or ruled out. In a meta-analysis by Infusino et al,³⁰ the odds ratio was significant for TfR-F index (9.5, 95% CI 5.0–18.1). However, this meta-analysis was limited by the small number of available studies with few participants and often suboptimal quality. Particularly, only one study²⁹ analyzed for TfR-F index efficacy used bone marrow as reference for iron deficiency.

Finally, response to intravenous iron cannot be used as diagnostic criterion, unlike therapeutic trial of oral iron.³¹ Indeed, IBD patients may suffer from functional iron deficiency due to iron retention in macrophages driven by proinflammatory cytokines and hepcidin.² During an acute phase response, hepcidin, which is induced in the liver by interleukin (IL)-6, reduces iron absorption from the duodenum as well as iron recycling from macrophages.⁶ Moreover, chronic inflammation could decrease erythropoiesis either directly by interferon-gamma or because of reduction in the synthesis and the biological activity of erythropoietin induced by IL-1, IL-6, tumor necrosis factor-alpha, and hepcidin.^{3,6} Hence, anemia of chronic disease, even without true iron deficiency, can improve with intravenous iron that corrects functional iron deficiency, but at the cost of increased iron storage and its associated risks.^{10,11,32}

Our results have several clinical implications. Measurement of ferritin, which is highly sensitive and specific when <30 ng/mL, should be the first step to iron deficiency diagnosis in IBD. Due to limited availability and cost constraints, sTfR assay for the TfR-F index analysis should be performed in a second step and reserved only to patients with inflammation and normal ferritin.

In conclusion, this prospective study in 150 patients with IBD shows that TfR-F index in addition to serum ferritin <30 ng/mL criterion, increases by 36% diagnosis rates of iron deficiency. TfR-F index helps to diagnose true iron deficiency in patients with active IBD and prevents from overtreating by intravenous iron patients with normal iron storage.

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