



Alimentary Tract

Soluble transferrin receptor and soluble transferrin receptor/log ferritin index in diagnosis of iron deficiency anemia in pediatric inflammatory bowel disease[☆]

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ABSTRACT

Background: There is no single reliable marker of iron homeostasis in inflammatory bowel disease.**Aims:** To determine diagnostic usefulness of soluble transferrin receptor and soluble transferrin receptor/log ferritin index in iron deficiency anemia in children with inflammatory bowel disease.**Methods:** We assessed soluble transferrin receptor in serum and calculated soluble transferrin receptor/log ferritin index in 75 children with inflammatory bowel disease. Diagnostic ability to identify iron deficiency anemia was examined by receiver operating characteristic analysis.**Results:** Study group comprised 27 cases of iron deficiency anemia, 6 anemia of chronic disease with iron deficiency, 5 anemia of chronic disease. Soluble transferrin receptor was significantly increased in children with iron deficiency anemia (median: 1.63 µg/ml) compared to non-anemic children (median: 1.02 µg/ml). Soluble transferrin receptor/log ferritin index was significantly higher in iron deficiency anemia (median: 1.76) than in anemia of chronic disease (median: 0.55), anemia of chronic disease with iron deficiency (median: 0.68) or patients without anemia (median: 0.72). Soluble transferrin receptor and its index were not correlated with disease activity or inflammatory markers. Diagnostic power for soluble transferrin receptor/log ferritin index (0.864) was superior to soluble transferrin receptor (0.768) in iron deficiency anemia recognition.**Conclusion:** Soluble transferrin receptor/log ferritin index has better diagnostic utility than soluble transferrin receptor for iron deficiency anemia detection in pediatric inflammatory bowel disease.© 2018 The Authors. Published by Elsevier Ltd on behalf of Editrice Gastroenterologica Italiana S.r.l. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Anemia is the most common complication and extra-intestinal manifestation of inflammatory bowel disease (IBD) [1]. The main type of anemia in patients with IBD is iron deficiency anemia (IDA) followed by anemia of chronic disease (ACD) and anemia of chronic disease with iron deficiency (ACD + ID) [2]. Iron deficiency anemia may result from gastrointestinal bleeding, malnutrition or malabsorption of iron [1,3]. Anemia of chronic disease is a consequence of upregulation of hepcidin expression, decrease erythropoietin production and inhibition of erythropoiesis caused by inflammatory mechanisms underlying IBD pathogenesis [1]. The recognition of the cause of anemia in IBD patients allows implementation of

efficient therapeutic option. However, there is no single, reliable marker of iron homeostasis since all traditional hematological and biochemical iron status parameters are influenced by inflammatory process underlying IBD [4].

Several new parameters have been under investigation in the diagnosis of anemia in patients with chronic inflammatory diseases including soluble transferrin receptor (sTfR). The transferrin receptor is a transmembrane glycoprotein which is localized on the surface of virtually all cells except mature red blood cells and plays a major role in iron delivery to cells. The transferrin receptor is a molecule of 190,000 Da, composed of two disulphide-linked monomers each containing 760 amino acids. Each subunit of the receptor contains 671 amino acid C-terminal extracellular domain, 28 amino acid transmembrane domain and 61 amino acid N-terminal cytoplasmic domain [5,6]. Proteolytic cleavage of extracellular domain of transferrin receptor between arginine-100 and leucine-101 mediated by a metalloproteinase results in the formation of a truncated monomer of soluble transferrin receptor (sTfR)

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that circulates in the blood [7]. The concentration of the sTfR in the plasma is proportional to the number of transferrin receptors expressed on cells' membrane and therefore it reflects the cellular iron requirement [5,6].

In contrary to traditional parameters of iron homeostasis sTfR appears to be unaffected by concomitant inflammation or hepatic injury [5,8]. Erythropoietin activity of bone marrow and intracellular requirements of iron are key regulators of sTfR level. Thus, in iron deficiency and conditions associated with stimulated erythropoiesis i.e. congenital dyserythropoietic anemia, hemolytic anemia, hereditary spherocytosis, sickle cell anemia, thalassemia, megaloblastic anemia or polycythemia, sTfR concentration is increased. However, it seems to be reduced in aplastic anemia conditions with hypo-proliferative erythropoiesis, chronic renal failure or after chemotherapy [5,8].

The sTfR/log ferritin ratio is a measure based on a relationship between two variables of iron metabolism. Therefore, it may increase the diagnostic efficacy of each one of them in the diagnosis of iron deficiency [7]. While sTfR is an indicator of iron supply available for erythropoiesis and a marker of functional iron pool, serum ferritin concentration provides information of iron storage [8]. Although there is no clearly defined agreement on sTfR/log ferritin thresholds, it is known that high values of these markers are connected with iron depletion while high values are seen in anemia of chronic disease [3].

To date, only few studies have been conducted to assess sTfR and sTfR/log ferritin in IBD patients [8–11]. To the best of our knowledge there appears to exist no study regarding both sTfR and sTfR/log ferritin in children and adolescents with IBD. The aim of the study, then, was to determine sTfR and sTfR/log ferritin levels in children with IBD and to assess the role of sTfR and sTfR/log ferritin in the evaluation of iron deficiency anemia in children with IBD.

2. Materials and methods

2.1. Subjects

We enrolled 75 consecutive IBD children hospitalized at the Department of Pediatrics and Gastroenterology (former name Department of Pediatrics), Medical University of Lublin, Poland between February 2013 and August 2015. We excluded those patients who had iron supplementation or erythropoiesis-stimulating agent treatment (ESA) in the 3 months preceding the enrolment, blood transfusion in the 4 weeks preceding the enrolment, a history of acute infection in the 4 weeks preceding the enrolment, clinical signs of acute infection at the time of recruitment.

Paris Classification was used for the disease phenotyping [12]. The patients were categorized into two groups – with active IBD and in remission of the disease – according to the clinical activity indexes i.e. Pediatric Crohn's Disease Activity Index (PCDAI) [13] and ulcerative colitis severity scale by the Truelove–Witts scale modified by Ryżko and Woynarowski [14].

In the study group there were 46 (61.3%) children with ulcerative colitis and 29 (38.7%) with Crohn's disease. In IBD children prevailed children with new-onset of disease and treatment naïve (47; 62.7%).

Among children with ulcerative colitis there were 21 (45.7%) boys and 25 (54.3%) girls. The mean age of children with ulcerative colitis was 12.6 ± 3.99 years of age. In active phase of ulcerative colitis there were 28 (60.9%) children while 18 (39.1%) were in remission of the disease. The majority of patients with ulcerative colitis presented with pancolitis (36; 78.3%).

There was a slight male preponderance in children with Crohn's disease with 19 (65.5%) boys and 10 (34.5%) girls. The mean age

of patients with Crohn's disease was 13.2 ± 3.2 years of age. There were 26 (89.7%) children with active phase and 3 (10.3%) in remission of Crohn's disease. The most common location of Crohn's disease was ileocolonic one with (9; 31%) or without (9; 31%) the involvement of the upper gastrointestinal tract. A full description of the study group has been published previously [15].

Controls were recruited from children with functional constipation and functional abdominal pain hospitalized in our center in the same study period. In the control group, there were 21 children with functional abdominal pain or functional constipation including 13 (62%) girls and 8 (38%) boys aged 4–16 years old (median: 12 years; mean: 11.2 ± 3.3 years old).

We excluded children from the control group if they had iron deficiency or anemia, any clinical or laboratory signs of inflammation, iron supplementation or ESA in the 3 months preceding the enrolment, blood transfusion in the 4 weeks preceding the enrolment.

2.2. Methodology

A peripheral blood sample was collected from all patients and controls for complete blood count, iron metabolism parameters and inflammatory markers. Complete blood count was obtained using the Sysmex XT2000i Hematology Analyzer (Sysmex). Iron metabolism parameters included iron, transferrin and saturation of transferrin (satTf) were assessed with the Analyzer ADVIA1800 (Siemens Healthcare) and ferritin assessed with the Analyzer ADVIA Centaur XP (Siemens Healthcare) according to standard laboratory practice. Serum concentration of sTfR was measured with enzyme-linked immunosorbent assay (ELISA) using sTfR ELISA kit (BioVendor Laboratorini medicina a.s. Brno).

The sTfR/log ferritin index was calculated by the following formula [16]:

$$\text{sTfR}_{\log \text{ ferritin}} = \frac{\text{sTfR} \left[\frac{\text{mg}}{\text{L}} \right]}{\log_{10} \text{ferritin} \left[\frac{\text{ng}}{\text{mL}} \right]}$$

Markers of inflammation included erythrocyte sedimentation rate (ESR) assessed with the Analyzer ROLLER20 (ALIFAX), high sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) measured with enzyme-linked immunosorbent assay using Human Interleukin-6 ELISA – BioVendor Laboratorini medicina a.s. Brno, Czech Republik and hs-CRP ELISA – LDN GmbH&Co. KG, Nordhorn.

We defined anemia as a decrease of hemoglobin and/or hematocrit below the lowest limits of normal values for children age and sex according to the World Health Organization (WHO) [17]. Anemic patients were allocated into groups depending on the background of anemia based on ferritin and satTf. The level of ferritin <30 ng/ml and satTf <20% in anemic children corresponded to iron deficiency anemia (IDA). The level of ferritin >100 ng/ml and satTf <20% in anemic children with active IBD defined anemia of chronic diseases (ACD). Serum ferritin between 30 and 100 ng/ml with satTf <20% in anemic patients with active IBD indicated ACD with true iron deficiency [1,2].

2.3. Statistical analysis

For statistical analysis *Statistica v. 12.0* software (StatSoft, Poland) was used. The data are presented as mean and standard deviation or median and range. We used appropriate non-parametric tests for analysis considering skewed distribution of variables and inhomogeneity of variance as indicated by W Shapiro–Wilk test and F-Fisher test, respectively. To test differences between two groups Mann–Whitney *U*-rank test was applied, to test differences between more than two means for more than two groups The H Kruskal–Wallis test was used. For categorical vari-

Table 1
Comparison of sTfR and sTfR/log ferritin between IBD children and the control group.

		Ulcerative colitis	Crohn's disease	Control group	
sTfR [$\mu\text{g/ml}$]	Mean \pm SD	1.55 \pm 1.04	1.31 \pm 0.50	0.86 \pm 0.19	†, ‡
	Median (range)	1.18 (0.63–5.27)	1.29 (0.49–2.83)	0.79 (0.62–1.35)	
sTfR/log ferritin	Mean \pm SD	2.22 \pm 2.86	1.23 \pm 1.71	0.54 \pm 0.15	†, ‡
	Median (range)	1.09 (0.37–11.05)	0.82 (0.24–9.39)	0.52 (0.32–0.80)	

† $p < 0.05$ when comparing ulcerative colitis and controls.‡ $p < 0.05$ when comparing Crohn's disease and controls.**Table 2**
Correlations between sTfR, aTfR/log ferritin and traditional iron metabolism markers.

	sTfR	sTfR/log ferritin
Hb	$p < 0.001$	$p < 0.0001$
	$R = -0.52$	$R = -0.44$
Ht	$p < 0.001$	$p = 0.001$
	$R = -0.45$	$R = -0.37$
MCV	$p < 0.001$	$p = 0.005$
	$R = -0.44$	$R = -0.33$
MCH	$p < 0.001$	$p = 0.001$
	$R = -0.52$	$R = -0.41$
MCHC	$p < 0.001$	$p = 0.01$
	$R = -0.47$	$R = -0.37$
RDW-CV	$p < 0.001$	$p = 0.006$
	$R = 0.40$	$R = 0.33$
Iron	$p < 0.001$	$p = 0.01$
	$R = -0.43$	$R = -0.30$
Tf	$p = 0.35$	$p = 0.001$
	$R = 0.11$	$R = 0.38$
satTf	$p < 0.001$	$p < 0.001$
	$R = -0.50$	$R = -0.50$
Ferritin	$p < 0.001$	$p < 0.001$
	$R = -0.47$	$R = -0.86$

ables chi-square test was used. Correlations between parameters were expressed by the Spearman's rank correlation coefficient. The ability of diagnostic parameters to identify IDA was examined by receiver operating characteristic (ROC) analysis and area under the receiver operating curve (AUROC). Sensitivity (SENS), specificity (SPEC), accuracy (ACC), positive predictive value (PPV) and negative predictive value (NPV) were calculated for each cut-off. The p -value less than 0.05 was considered statistically significant.

2.4. Ethics approval and consent to participate

Written informed consent for participation in this study was obtained from the subjects' parents and also from a patient in case of a child aged ≥ 16 years. The study was approved by the Bioethical Committee of Medical University of Lublin (KE-0254/22/2013). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

3. Results

3.1. sTfR and sTfR/log ferritin attributes in IBD children and controls

Table 1 presents comparison of sTfR and sTfR/log ferritin between IBD children and the control group. Although both parameters were significantly increased in children with IBD compared to controls, there were no differences between patients with Crohn's disease compared to those with ulcerative colitis.

In IBD children, significant correlations between both sTfR and sTfR/log ferritin and traditional markers of iron homeostasis i.e. hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, serum iron, satTf, ferritin were found as shown in Table 2.

However, both sTfR and sTfR/log ferritin levels were independent of IBD clinical activity and inflammatory markers. There were no significant correlations between sTfR concentration and IBD activity indexes i.e. PCDAI ($p = 0.76$) and modified Truelove and Witts severity index ($p = 0.19$). Moreover, we did not find any correlation between sTfR/log ferritin and PCDAI ($p = 0.05$) or modified Truelove and Witts severity index ($p = 0.31$).

In IBD children there were no significant correlations between sTfR and markers of inflammation including hsCRP ($p = 0.73$) and IL-6 ($p = 0.32$). However, we found a weak, positive correlation between sTfR and ESR ($p = 0.006$; $R = 0.33$). In the study group the sTfR/log ferritin ratio did not correlate with any laboratory marker of inflammation i.e. hsCRP ($p = 0.28$), IL-6 ($p = 0.05$) and ESR ($p = 0.20$).

We did not state any significant differences in sTfR concentration between children with active phase and in remission of IBD ($Z = 1.05$; $p = 0.29$). Moreover, there were also no significant differences in sTfR/log ferritin between children with active phase and in remission of IBD ($Z = 0.34$; $p = 0.74$).

There were no significant associations between sTfR or sTfR/log ferritin with Crohn's disease localization ($H = 8.23$; $p = 0.14$ and $H = 3.29$; $p = 0.66$ respectively) or ulcerative colitis extent ($H = 2.21$; $p = 0.53$ and $H = 1.76$; $p = 0.62$ respectively).

3.2. sTfR and sTfR/log ferritin in IBD children with different types of anemia

In the study group 38 (51%) children had anemia, including 27 (36%) with iron deficiency anemia, 6 (8%) with anemia of chronic disease with iron deficiency and 5 (7%) with anemia of chronic disease.

The concentration of sTfR was significantly higher in IBD children with anemia (median: 1.37 $\mu\text{g/ml}$; range 0.72–5.27 $\mu\text{g/ml}$) than in IBD children without anemia (median: 1.02 $\mu\text{g/ml}$; range: 0.49–1.89 $\mu\text{g/ml}$) ($p = 0.0003$). Moreover, sTfR/log ferritin was significantly increased in IBD children with anemia (median: 1.19; range: 0.43–11.05) compared to non-anemic patients (median: 0.72; range: 0.24–2.07) ($p = 0.0003$).

Fig. 1 presents comparison of sTfR in IBD children with different types of anemia compared to non-anemic IBD patients. Fig. 2 presents comparison of sTfR/log ferritin in IBD children with several types of anemia compared to non-anemic IBD patients.

3.3. sTfR and sTfR/log ferritin usefulness in IDA

To determine diagnostic utility of sTfR and sTfR/log ferritin in the recognition of IDA in IBD children we performed ROC analysis. The cut-off values derived from that analysis were as follows: for sTfR 1.78 $\mu\text{g/ml}$ and for sTfR/log ferritin 1.145. The sTfR/log ferritin (AUROC 0.864; 95% CI 0.776–0.952) was found to be superior to sTfR (AUROC 0.768; 95% CI 0.644–0.891) in the diagnosis of IDA. Results are plotted as ROC curve in Fig. 3. In Table 3 there are presented sensitivity, specificity, positive and negative predictive values and accuracy of sTfR and sTfR/log ferritin for the recognition of IDA among IBD children.

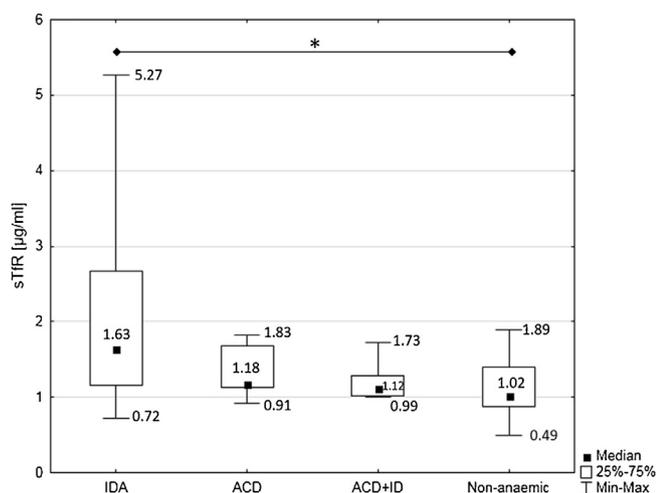


Fig. 1. Distribution of sTfR values by anemia classification in IBD children H = 15.19 p = 0.001 (* – when statistically significant differences).

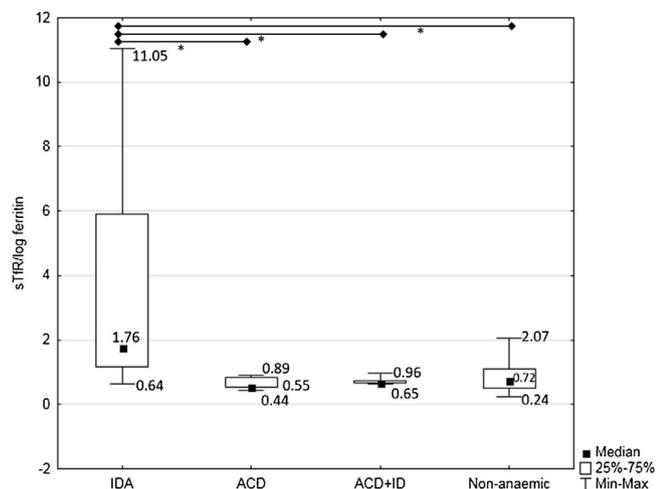


Fig. 2. Distribution of sTfR/log ferritin values by anemia classification in IBD children H = 25.66 p < 0.0001 (* – when statistically significant differences).

4. Discussion

In our study we pointed out the fact that sTfR and sTfR/log ferritin were significantly higher in IBD children compared to the control group. The detailed analysis revealed that among IBD children sTfR was significantly increased in children with iron deficiency anemia compared to children without anemia. However, sTfR/log ferritin was significantly higher in IBD children with iron deficiency anemia compared to IBD patients with other types of anemia (ACD and ACD with iron deficiency) and to those without anemia. Both sTfR and sTfR/log ferritin were independent on IBD activity and inflammatory markers despite of a minor association between sTfR and ESR. Ultimately, we proved that sTfR/log ferritin has a better diagnostic efficacy to identify iron deficiency anemia among IBD children than sTfR.

To date there have been several studies exploring the efficacy of sTfR in the recognition of iron deficiency anemia in IBD patients. However, to the best of our knowledge there has been no study concerning the accuracy of both sTfR and sTfR/log ferritin in the diagnosis of anemia in children and adolescents with IBD.

Our results are consistent with the previous studies. In adults with IBD and iron deficiency anemia sTfR levels were significantly higher (median: 2.6 mg/dL; range: 1.2–6.8 mg/dL) than in

those without IDA i.e. those with other types of anemia and without anemia (median: 1.2 mg/dL; range: 0.7–3.1 mg/dL). Moreover, sTfR/log ferritin was also significantly elevated in adults with IBD and IDA (median: 2.9; range: 1.0–11.8) compared to those without IDA (median: 0.7; range: 0.4–2.8). It was also demonstrated that both sTfR and sTfR/log ferritin were significantly increased in IBD patients with iron deficiency anemia compared to those with anemia of chronic disease [8].

In the study among 63 children with IBD Revel-Vilk et al. found that serum sTfR was significantly higher in patients with iron deficiency anemia (8.2 ± 3.1 mg/L) than in patients with anemia of chronic disease (5.3 ± 2.3 mg/L) and controls (3.8 ± 8 mg/L) [9]. Similarly to the results of Revel-Vilk in our study there were no significant differences in the serum concentration of sTfR among IBD children with anemia of chronic disease, IBD patients without anemia and controls [9].

Contrary to our results, in a group of 15 children with IBD Kaya et al. did not find any differences in sTfR between anemic (4.1 ± 1.6 mg/L) and non-anemic children (4.1 ± 1.4 mg/L). In this study there is a lack of clear data regarding types of anemia in IBD children. However, baseline characteristic of patients including low medium value of red blood cells and elevated serum ferritin suggested that in IBD group anemia may be referred to anemia of chronic disease. That fact could be a possible explanation of lack of differences in serum sTfR in their study group. Moreover, Kaya et al. proved that children with pure IDA without any concomitant chronic disease had higher sTfR (6.1 ± 0.7 mg/L) than IBD children (4.1 ± 1.4 mg/L) and that in the IBD group sTfR was significantly higher than in control group (2.8 ± 0.8 mg/L) [11].

It has been shown that sTfR is not affected by a concomitant inflammation [8,16]. In our study sTfR did not correlate with hsCRP, IL-6 or disease activity, however a modest correlation between sTfR and ESR was found. It has been presented that under *in vitro* experimental conditions the pro-inflammatory cytokines tumour necrosis factor- α and interleukin-1 β diminished surface transferrin receptors expression [18]. Thus, it could affect the sensitivity of sTfR to detect iron deficiency in inflammatory diseases [10]. Moreover, the fact that transferrin-receptor expression is negatively affected by inflammatory cytokines could explain the lack of difference in sTfR levels between patients with anemia of chronic diseases and controls [18,19].

We did not find any significant associations between sTfR/log ferritin or any inflammatory marker or IBD clinical activity, which is one of the most important advantages of that index. Oustamanolakis et al. showed also that sTfR/log ferritin were not associated with CRP, IBD duration and activity [8].

Ultimately, we found that sTfR/log ferritin is superior to sTfR in the recognition of iron deficiency anemia in children with IBD. Our results are in the accordance with previous findings which suggested that sTfR/log ferritin has a better discriminating power than sTfR in the recognition of iron deficiency anemia in patients with chronic conditions [8,16,20–22]. It could be explained by the fact that a calculation sTfR/log ferritin covers the entire spectrum of body iron status providing information of iron storage and functional iron pool [23]. However, in meta-analysis assessing diagnostic utility of sTfR and sTfR/log ferritin Infusino et al. proved that sTfR/log ferritin does not improve diagnostic accuracy of sTfR. It should be highlighted that in that meta-analysis only three studies reported binary data needed to calculate sensitivity and specificity of sTfR/log ferritin, thus it could be a limitation of the comparison of sTfR with sTfR/log ferritin [7].

There is a little agreement regarding specific cut-off values for sTfR and sTfR/log ferritin for the recognition of iron deficiency anemia. This may result from the lack of standardization of sTfR assays from different manufacturers and poor correspondence between

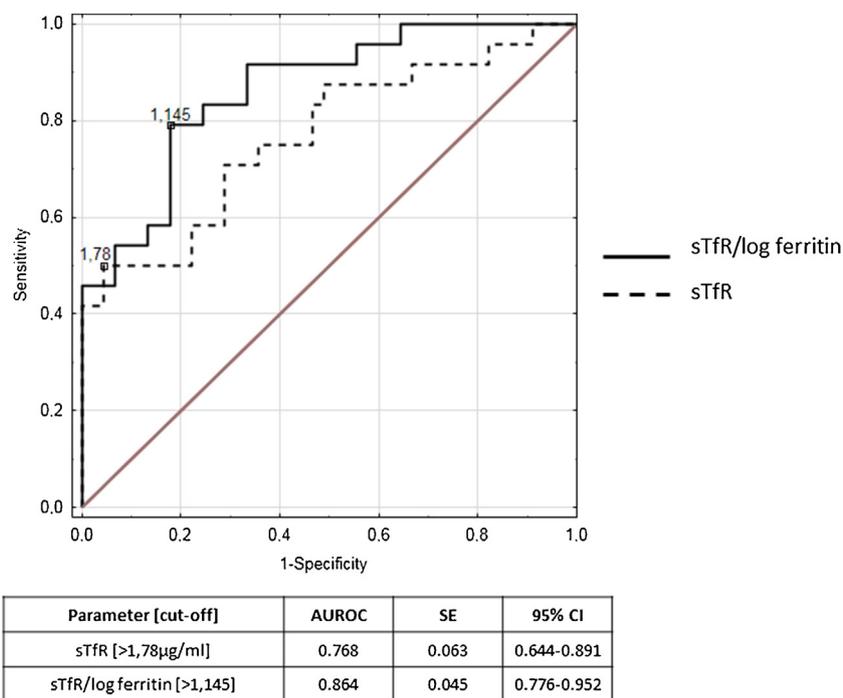


Fig. 3. ROC curves for sTfR and sTfR/log ferritin in the diagnosis of IDA in IBD children.

Table 3

Sensitivity (SENS), specificity (SPEC), positive (PPV) and negative (NPV) predictive values and accuracy (ACC) of sTfR and sTfR/log ferritin for the recognition of IDA among IBD children.

Parameter [cut-off]	SENS	SPEC	PPV	NPV	ACC
sTfR [$>1,78\mu\text{g/ml}$]	0.50	0.96	0.86	0.78	0.77
sTfR/log ferritin [>1.145]	0.79	0.82	0.70	0.88	0.81

analytical methods, which hinder comparison sTfR data between studies [24–27].

Moreover it should also be emphasized that iron deficiency anemia is a late manifestation of iron deficiency. Iron deficiency without anemia is a common medical issue in IBD however it remains underdiagnosed and undertreated. Recently, the researches have focused on the concept of innovative approach based on early intervention, treating to target and tight monitoring in the management of iron deficiency in IBD [28]. Peyrin-Biroulet et al. underlined that nowadays diagnosis of iron deficiency in IBD is based on combination of two markers i.e. ferritin and saturation of transferrin with an assessment of patient's inflammatory status [28]. In terms of future work, it would be important to determine the potential use of sTfR and sTfR/log ferritin as sole markers of iron deficiency in children with IBD.

The generalizability of our results is subject to certain limitations including small sample size and relative homogeneity of IBD patients in terms of disease duration and activity.

In conclusion, our results demonstrate that both sTfR and sTfR/log ferritin are efficient, independent on inflammation and IBD clinical activity, tools for the diagnosis of iron deficiency anemia. The sTfR/log ferritin index has a better diagnostic utility than sTfR for detection iron deficiency anemia in children with IBD. Therefore, sTfR/log ferritin could provide added value in the routine diagnostic anemia work-up in children with IBD particularly in those with active phase of the disease. However, further studies are needed to determine reliable cut-off values of sTfR and sTfR/log ferritin indicative of iron deficiency anemia in IBD children.

Conflict of interest

None declared.

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