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When Should Endoscopic Interventions Be Performed in Children with Severe Anemia?

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What is already known on this topic?

- *Anemia is a common problem in pediatric outpatient clinics, and nutritional deficiencies especially iron, folic acid, and vitamin B12 deficiency are the major causes of anemia in infants and adolescents.*
- *Endoscopic interventions are the initial steps to rule out gastrointestinal problem in children when evaluating the etiology of anemia especially associated with gastrointestinal system-related symptoms.*
- *The presence of anemia especially hemoglobin levels below 7 g/dL may affect cardiovascular stability during endoscopy.*

What this study adds on this topic?

- *The presence of hypoalbuminemia, high erythrocyte sedimentation rate, and high C-reactive protein are associated with positive findings in endoscopic interventions.*
- *We recommend performing upper gastrointestinal endoscopy and/or colonoscopy in patients with severe anemia associated with gastrointestinal symptoms and using laboratory findings of hypoalbuminemia, high erythrocyte sedimentation rate, and C-reactive protein in order to rule out gastrointestinal pathologies.*

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ABSTRACT

Objective: Anemia is a common problem in outpatient clinics, and endoscopic interventions are one of the initial steps to rule out the gastrointestinal causes. In this study, we aimed to analyze the diagnostic yield of endoscopic interventions in children with severe anemia.

Materials and Methods: The demographic features, laboratory findings, and endoscopic and histopathological findings of 65 children with severe anemia (hemoglobin <7 g/dL) (mean age of 12.1 ± 4.4 years, 73.8% female) who underwent endoscopic interventions were recorded from the files. Patients were divided into 2 groups according to the presence of positive endoscopic findings and/or histopathological examination. Factors that may predict the presence of positive endoscopic findings and/or histopathological examination were analyzed.

Results: After a colonoscopy and/or upper gastrointestinal endoscopy, the etiology of anemia was identified in 35 patients, and the major diagnosis of *Helicobacter pylori* gastritis in 16.9% and gastrointestinal ulcer in 10.8% of the patients was made. No gastrointestinal pathology was detected in 30 patients. The diagnostic yield of endoscopic examination in patients with severe anemia was 53.8% (95% CI: 63.3-67.7). Presence of hypoalbuminemia ($P = .021$), high erythrocyte sedimentation rate ($P = .006$), and high C-reactive protein ($P = .03$) was significantly associated with positive findings in endoscopic interventions.

Conclusion: We recommend performing upper gastrointestinal endoscopy and/or colonoscopy in patients with severe anemia associated with gastrointestinal symptoms and using laboratory findings of hypoalbuminemia, high erythrocyte sedimentation rate, and C-reactive protein in order to rule out gastrointestinal pathologies.

Keywords: endoscopy, Helicobacter pylori, hypoalbuminemia, nutritional anemia

INTRODUCTION

Pediatric endoscopic procedures are considered an important tool in the evaluation, diagnosis, and treatment of many pediatric gastrointestinal diseases. Due to technological improvements in endoscope devices, diagnostic and therapeutic indications have been increased over the recent years. It is important to consider the balance between diagnostic yields and complication risks when deciding to perform an endoscopic intervention on a child.[1]

Anemia is a common problem in pediatric outpatient clinics, and nutritional deficiencies especially iron, folic acid, and vitamin B12 deficiency are the major causes of anemia in infants and adolescents. Acute and chronic gastrointestinal bleeding may also cause anemia and patients may need transfusions to maintain hemodynamic stability. Additionally, when gastrointestinal bleeding is not clinically evident, it is important to rule out obscure or chronic blood loss from the gastrointestinal tract for the differential diagnosis and treatment of anemia. Chronic malabsorptive syndromes, parasitosis, inflammatory bowel

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diseases, *Helicobacter pylori* gastritis, esophagitis, and intestinal and colonic polyps may lead to anemia in children without clinically evident blood loss by chronic microscopic bleeding or by decreasing the absorption of vitamins and minerals.[2,3] Endoscopic interventions including upper gastrointestinal endoscopy (UGE) and colonoscopy are the initial steps to rule out the gastrointestinal problem in children when evaluating the etiology of anemia especially associated with gastrointestinal system-related symptoms or failure to thrive.[1]

The presence of anemia was reported to increase the diagnostic yield of UGE in children.[4,5] Additionally, anemia is only improved after the eradication of underlying gastrointestinal problem in these patients.[3] However, the presence of severe anemia (hemoglobin (Hg) levels below 7 g/dL) may affect cardiovascular stability during endoscopy.[1] In this study, we aimed to analyze the diagnostic yield of endoscopic intervention (both UGE and colonoscopy) in children especially with severe anemia without clinically evident bleeding in order to assess who will benefit from the endoscopic intervention for the defining underlying pathology. Additionally, we aimed to find out some clinical and laboratory parameters to predict the positive endoscopic findings. Thus, our results may prevent unnecessary endoscopic intervention in this patient group.

MATERIALS AND METHODS

Study Design

This is a retrospective study. We included the patients with severe anemia who underwent UGE or colonoscopic interventions between January 2010 and December 2018 in this study. Patients presenting with major gastrointestinal bleeding or previously diagnosed chronic diseases such as inflammatory bowel disease, peptic ulcers, *H. pylori* gastritis, end-stage kidney disease, or malign hematologic diseases were excluded from the study. Additionally, patients with insufficient data on hospital files were not included in the study.

All the patients with severe anemia were initially evaluated by the pediatric hematologist for the underlying causes by clinical and laboratory parameters. Patients with suspected gastrointestinal pathology (such as patients with chronic abdominal symptoms, failure to thrive, severe or unresponsive iron deficiency anemia, chronic diarrhea) underwent endoscopic interventions by pediatric gastroenterologists in our unit.

The demographic features, and clinical and laboratory findings including Hg levels, mean corpuscular volume (MCV), serum ferritin, vitamin B12 and folic acid, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and albumin levels, and endoscopic and histopathological findings were recorded from the hospital files. Severe anemia was defined as the value of Hg levels <7 g/dL.[6] Anemia is classified into subtypes according to laboratory parameters: (i) mixed anemia, (ii) iron-deficiency anemia (IDA), (iii) megaloblastic anemia (MA), and (iv) chronic disease anemia as defined elsewhere.[7]

In order to define the factors associated with the diagnostic yield of endoscopic intervention, patients were divided into groups according to the presence of endoscopic findings and/or histopathologicalSPSS examination; group A: patients who had positive findings on endoscopic and/or histopathological examination for the etiology of anemia and group B: patients whose endoscopic and/or histopathological examinations failed to find the etiology of anemia. Factors that may predict or are associated with the diagnostic yield were defined as (i) low mean corpuscular volume (MCV): below −2 standard deviation (SD) of the normal limit according to age and gender, (ii) low ferritin levels: <15 ng/mL, (iii) low vitamin B12: <200 pg/mL, (iv) low folic acid: <3.1 µg/L, (v) leukopenia: $<4500 \times 10^3$ µL, (vi) leukocytosis: $<15\ 000 \times 10^3$ µL, (vii) thrombocytosis: $>450\ 000 \times 10^3$ µL, (viii) thrombocytopenia: $<150\ 000 \times 10^3$ µL, (ix) hypoalbuminemia: <3 g/dL, (x) high ESR >15 mm/h, and (xi) increased CRP >0.5 mg/L.[8]

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences, version 16.0 software (SPSS Inc.; Chicago,IL, USA). Continuous variables were expressed in mean ± SD, and categorical variables were expressed in number (n) and percentage (%). Comparison of the continuous variables between the groups was performed using Student's *t*-test in the normally distributed variables and Mann–Whitney *U* test in the non-normally distributed variables, whereas categorical variables were compared using the chi-squared test (or the Fisher's exact test when needed). The Shapiro–Wilk test was used for the assessment of normal distribution. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the positive endoscopic and/or histopathological findings in laboratory significant parameters as defined elsewhere.[9] The area under the receiver operating characteristic curve was used to analyze the power of number positive laboratory parameters for predicting diagnostic endoscopic and/or histopathological findings in children with severe anemia. *P* values ≤ .05 were considered statistically significant.

RESULTS

Patients and Clinical Findings

During the study period, an endoscopic intervention was performed for a total of 4570 patients (54.5% female, mean age ± SD: 9.4 ± 4.5 years) and 78 patients (1.7%) had severe anemia. Also, 13 of 78 patients were excluded from the study because of being presented with active bleeding (n = 8) and inflammatory bowel disease (IBD) relapse (n = 5). A total of 65 patients were included in the study (75.4% female, mean age ± SD = 12.1 ± 4.4 years) (Figure 1). A total of 74 procedures (53 UGE, 3 colonoscopies, and 9 both UGE and colonoscopy) were performed to 65 patients.

The most common accompanying symptoms in patients with severe anemia were chronic abdominal pain (n = 19, 29.2%), growth retardation (n = 6, 9.2%), chronic diarrhea (n = 4, 6.2%), and vomiting (n = 1, 1.5%). Mean ± SD Hg level was 6.1 ± 1.1 g/dL (range: 3.2-7 g/dL). Mixed anemia was detected in 31 (47.7%), IDA in 31 (47.7%), MA in 2 (3.1%), and chronic disease anemia in 1 patient (1.5%). The demographic features and laboratory findings of the patients are shown in Table 1.

Endoscopic Findings

After UGE and/or colonoscopy, positive findings for the etiology of anemia were found in 35 patients (group A). The diagnosis of *H. pylori* gastritis in 11 (16.9%), gastrointestinal ulcer in 7

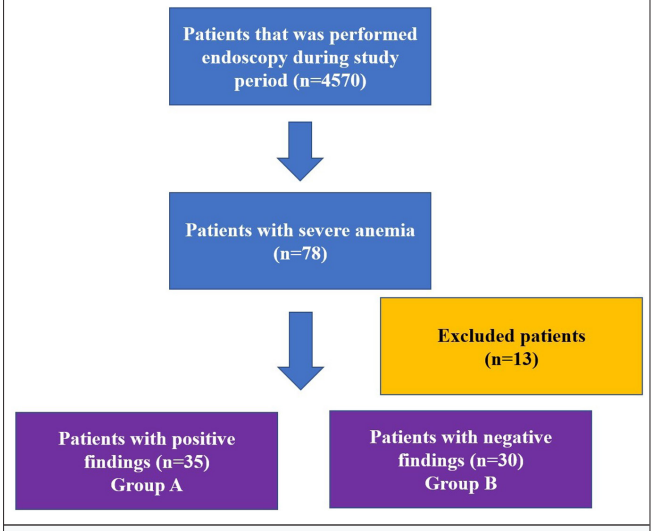


Figure 1. Flowchart of the study.

(10.8%, esophageal ulcer in 4, peptic ulcer in 2, duodenal ulcer in 1 patient), erosive gastritis in 5 (14.3%), celiac disease (CD) in 4 (6.2%), IBD in 2 (3.1%), familial Mediterranean fever-related amyloidosis, post-transplant lymphoproliferative disorder, gastric lymphoma, asymptomatic esophageal varices, allergic enteropathy, and giardiasis in each 1 (1.5%) patient was identified. During the follow-up, hemoglobin levels of 11 patients with *H. pylori* gastritis were increased after *H. pylori* eradication therapy without iron supplementation. The other patients who had gastrointestinal disorders were treated according to their diagnosis, and anemia improved after therapy in all of them. In 30 patients (46.2%), no gastrointestinal pathology was detected by UGE and/or colonoscopy (group B, n = 30). The etiology of anemia in group B patients was nutritional anemia in 24, menorrhagia in 3, Meckel diverticulitis, abdominal tuberculosis, and Immerslund–Gräsbeck anemia in each 1 patient (Figure 2). The diagnostic yield of endoscopic examination in the evaluation of patients with severe anemia was 53.8% (95% CI: 41-66.3).

Table 1. Demographic and Clinical Findings of the Patients with Severe Anemia (n = 65).

	Patients with Severe Anemia (n = 65)
Age, mean ± SD, year	12.1 ± 4.4
Gender, female, n (%)	48 (73.8)
Hemoglobin levels, g/dL, mean ± SD	6.1 ± 1.1
Range	3.2-7.0
Median	6.5
Anemia subgroup, n (%)	
Mixed anemia	31 (47.7)
IDA	31 (47.7)
MA	2 (3.1)
CDA	1 (1.5)
Accompanying symptoms, n (%)	
Chronic abdominal pain	19 (29.2)
Failure to thrive	6 (9.29)
Chronic diarrhea	4 (6.2)
Vomiting	1 (1.5)

CDA, chronic disease anemia; IDA, iron deficiency anemia; MBA, megaloblastic anemia; SD, standard deviation.

Parameters for the Positive Endoscopic Findings

When the groups were compared, patients were older in group A (12.7 ± 3.8 vs. 11.4 ± 4.9 years) but did not reach a significant difference. Presence of hypoalbuminemia (40% vs. 13.3%, OR: 4.33, 95% CI: 1.24-15.1, $P = .021$), high ESR (48.5% vs. 16.6%, OR: 4.72, 95% CI: 1.47-15.1, $P = .006$), and high CRP (48.5% vs. 28.3%, OR: 3.1, 95% CI: 1-9, $P = .03$) was significantly higher in patients of group A. Other factors such as gender, Hg levels, type of anemia, accompanying symptoms, presence of hypoferritinemia, low folate and vitamin B12 levels, leukopenia, leukocytosis, thrombocytopenia and thrombocytosis, and fecal occult blood positivity did not differ among the groups ($P > .05$ for all) (Table 2).

Sensitivity, specificity, PPV and NPV of hypoalbuminemia, and high CRP and ESR for the positive endoscopic findings are shown in Table 3. Sensitivity (71.2%) and NPV (65.5%) were highest in the presence of "at least 1 parameter positivity," and specificity (90%) and PPV (83.3%) were highest in the presence of "at least 2 parameters positivity" ($P < .05$) (Figure 3).

DISCUSSION

In this study, we evaluated the diagnostic yield of endoscopic intervention in children with severe anemia and found that (i) diagnostic yield of endoscopic intervention was 53.8% (95% CI: 63.3-67.7), (ii) presence of hypoalbuminemia, high ESR, and high CRP were associated with increased diagnostic yield, and (iii) major identifiable cause of severe anemia by endoscopic intervention in our study group was *H. pylori* gastritis.

Unexplained anemia, refractory anemia, anemia associated with gastrointestinal symptoms such as chronic abdominal pain, chronic diarrhea, and gastrointestinal bleeding are major indications for both UGE and colonoscopy in children. Sometimes, patients may also undergo endoscopic examinations in the presence of iron deficiency or low ferritin levels, and vitamin B12 and folate deficiency in the absence of low Hg levels.[3] Diagnostic utility of endoscopic interventions in children was evaluated in previous studies. Sheiko et al[10] reported diagnostic yield of endoscopy in 1000 children with gastrointestinal symptoms and found a positive endoscopic and histopathological abnormality in 34.7% and 40.7% of the patients, respectively. Positive findings were associated with age (lower in <1-year-old age) and indications of the endoscopy (increased in positive celiac serology and in the presence of stricture in upper gastrointestinal radiology). Wani et al[11] found that the diagnostic yield of UGE was 45.8% in children, highest in patients with upper gastrointestinal bleeding (71.3%), followed by variceal surveillance (54.8%) and recurrent vomiting (38%). Berger et al[12] found the diagnostic yield of UGE to be 59.2%, and the most common new diagnoses were CD (28%), *H. pylori*-positive gastritis (16.5%), and Crohn's disease (5.4%). Contrary to these studies, Zuleta et al[13] reported that the diagnostic yield of UGE was low in children and suggested performing UGE in selected indications. The diagnostic utility of colonoscopy in children with gastrointestinal symptoms was

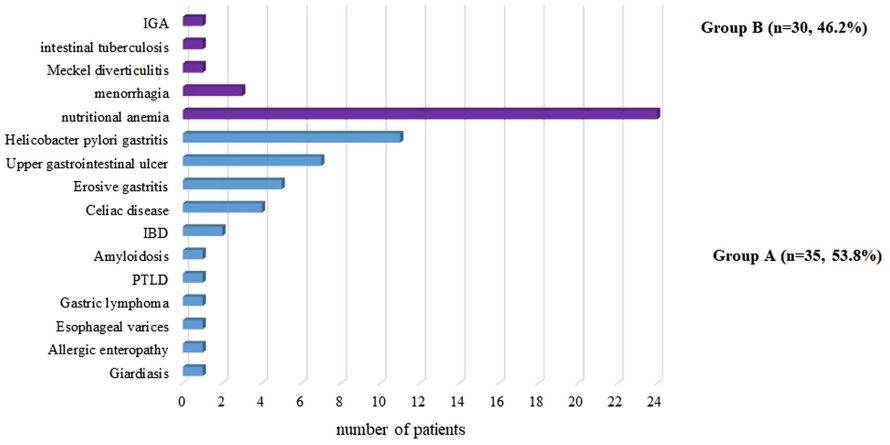


Figure 2. Final diagnosis of the patients with severe anemia (n = 65). Note that the patients with positive findings on endoscopic and/or histopathological examination is marked in blue (group A, n = 35, 53.8%), others were in purple (group B, n = 30, 46.2%). IBD, inflammatory bowel disease; IGA, Immerslund–Gräsbeck anemia; PTLD, post-transplant lymphoproliferative disorders.

reported in 75% and higher in patients with gastrointestinal bleeding and chronic diarrhea.[14]

Gulen et al[5] analyzed the diagnostic yield of UGE in the presence of IDA in older children and adolescents, and 56% of the patients had endoscopic and 47.7% of the patients had histological findings, and they suggest that *H. pylori* infection and other gastrointestinal system pathologies should be ruled out before iron deficiency treatment in older children and adolescents. Repo et al[4] reported that anemia increased the probability of being given a diagnosis in children undergoing endoscopic interventions, emphasizing its importance as an alarm symptom. However, diagnostic yields decrease in the absence of additional symptoms or laboratory abnormalities. Positive celiac serology, high calprotectin levels, increase in sedimentation rate, and hypoalbuminemia increase the diagnostic yields. Wang et al[15] reported that anemia was the most common laboratory finding in children undergoing UGE and/

Table 2. Comparison of Demographic, Clinical, and Laboratory Findings of 2 Groups

	Group A (n = 35)	Group B (n = 30)	*P*
Age, mean ± SD (year)	12.7 ± 3.8	11.4 ± 4.9	.24
Gender, female, n (%)	26 (74.3)	22 (73.3)	.9
Hemoglobin levels, g/dL, mean ± SD	6.3 ± 1.2	6.1 ± 1	.36
Anemia subgroup, n (%)			
Mix anemia	19 (54.3)	12 (40)	>.05*
IDA	15 (42.9)	16 (53.4)	
MBA	1 (2.8)	1 (3.3)	
CDA	0	1 (3.3)	
Accompanying symptoms, n (%)			
Chronic abdominal pain	12 (34.2)	7 (23.3)	>.05*
Chronic diarrhea	2 (5.7)	2 (6.6)	
Failure to thrive	4 (11.4)	2 (6.6)	
Vomiting	1	0	
Low ferritin, n (%) (<15 ng/mL)	28 (80)	25 (83.3)	.7
Low vitamin B_{12}, n (%) (<200 pg/mL)	17 (45.7)	12 (40)	.48
Low folic acid, n (%) (<3.1 µg/L)	6 (17.1)	2 (6.7)	.2
Thrombocytosis, n (%) (>450 000 × 10^3 µL)	9 (25.7)	5 (16.7)	.37
Thrombocytopenia, n (%) (<150 000 × 10^3 µL)	4 (11.4)	7 (23.3)	.2
Leukocytosis, n (%) (>15 000 × 10^3 µL)	2 (5.7)	1 (3.3)	1*
Leukopenia, n (%) (<4500 × 10^3 µL)	7 (20)	5 (16.7)	.72
Low MCV, n (%)	30 (85.7)	23 (76.6)	.34
Hypoalbuminemia, n (%) (<3.5 g/dL)	14 (40)	4 (13.3)	.01
High ESR, n (%) (>15 mm/h)	17 (48.5)	5 (16.6)	.006
High CRP, n (%) (>0.5 mg/L)	17 (48.5)	7 (23.3)	.03

CDA, chronic disease anemia; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FOB, fecal occult blood; IDA, iron deficiency anemia; MBA, megaloblastic anemia; MCV, mean corpuscular volume; SD, standard deviation. Categorical variables were compared using chi-squared test and *Fisher's exact test, and continuous variables were compared using Student's *t*-test.

Table 3. Sensitivity, Specificity, PPV, and NPV of Parameters for Predicting the Positive Endoscopic and/or Histopathologic Findings in Children with Severe Anemia

Parameters	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Hypoalbuminemia (<3.5 g/dL)	18	40	86.6	77.8	55.3
High ESR (>15 mm/h)	22	48.5	83.3	77.2	58.1
High CRP (>0.5 mg/L)	24	48.5	76.6	70.8	56.1
Hypoalbuminemia+high ESR	11	25.7	93.3	81.8	51.8
Hypoalbuminemia+high CRP	13	31.4	93.3	84.6	53.8
High ESR+high CRP	14	31.4	90	78.5	52.9
Presence of only 1 parameter	18	28.5	73.3	55.5	46.8
Presence of only 2 parameters	8	20	96.6	87.5	50.8
Presence of at least 1 parameter	36	71.4	63.3	69.4	65.5
Presence of at least 2 parameters	18	42.8	90	83.3	57.5
Presence of 3 parameters	10	22.8	93.3	80	50.9

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NPV, negative predictive value; PPV, positive predictive value.

or colonoscopy and up to 75% of the 20 subjects with anemia were found to have abnormal histology. It was also shown that the presence of anemia increased the diagnostic yield of UGE in children with chronic abdominal pain.[16] None of the studies in the literature addressed the diagnostic yield of endoscopy in patients with severe anemia. We found the diagnostic utility of endoscopic examinations to be considerably high (53.8%). The presence of hypoalbuminemia, high ESR, and high CRP were associated with increased diagnostic yield as in the previous studies.[3,17]

The most identifiable cause of severe anemia in our patient group was *H. pylori* gastritis. *H. pylori* is the most common chronic bacterial infection in humans, and approximately 80% of the population is in the carrier stage. The diseases such as chronic gastritis, atrophic gastritis, and peptic ulcer occur in only 20% of the colonized population.[18] Additionally, it has been determined that the manifestations of *H. pylori* infection in children may lead to protein-losing enteropathy, diarrhea, thrombocytopenia, malnutrition, and IDA.[19] There are some theories about the relationship between *H. pylori* and anemia. One of these theories is a bacteria-specific mechanism of anemia. The receptors on the outer membrane of *H. pylori* in the antrum acting as an iron sequestering focus receive and use iron for growth, and iron absorption impairs due to infection-associated changes in either lactoferrin or intragastric pH.[20] The other mechanisms of anemia in *H. pylori* infection are (i) iron loss due to chronic gastric ulcers and (ii) gastric hypoacidity and achlorhydria due to diffuse corpus gastritis, atrophic gastritis, and this causes decreased solubilization and absorption of non-hem iron.[21] In literature, *H. pylori* infection has also been correlated with the prevalence of iron deficiency and IDA in population-based studies.[22] In a study by UmaKiran et al.[23] 484 samples of children aged 5-12 years were studied and detected a 19% prevalence of *H. pylori* infection in the anemic group and 10.7% in the non-anemic group, which suggested an association between *H. pylori* and IDA. Similarly, previous studies showed an association between *H. pylori* gastritis, IDA, and also severe anemia.[24-26]

Nutritional anemia was the main cause of anemia in infants and children and becomes apparent due to inadequate intake of iron, folic acid, and vitamin B12. Iron deficiency and IDA are

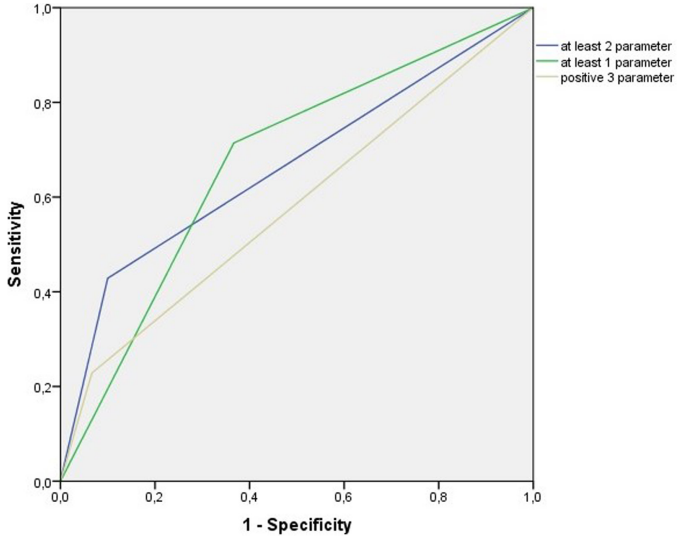


Figure 3. ROC of number of positive parameters for predicting positive endoscopic findings. AUROC for "at least 1 parameter positive", "at least 2 parameters positive," and "presence of 3 parameters" were 0.674 (95% CI: 0.540-0.807, $P < .05$), 0.664 (95% CI: 0.532-0.796, $P < .05$), and 0.581 (95% CI: 0.442-0.720, $P > .05$), respectively. AUROC, area under the receiver operating characteristic curve; ROC, receiver operating characteristic curve.

the major causes of nutritional anemia in children. It may stem from inadequate intake, poor intestinal absorption of iron necessary to supplement increased iron demand in the body during periods of active growth, and/or chronic loss of iron from the body. Diagnosis of IDA is made by the laboratory evaluation of Hg, hematocrit, MCV, and red cell distribution width, reticulocyte count, ferritin, peripheral blood smear, and stool for occult blood. An empirical trial of iron supplementation is recommended in children with mild anemia. But further evaluation including UGE and/or colonoscopy for the gastrointestinal loses or malabsorption is recommended in the presence of severe anemia or unresponsiveness to iron supplementation.[2] The diagnosis of nutritional anemia was definitely made in our study group by documenting the absence of gastrointestinal pathology in 24 patients (36.9%), and in fact, the diagnostic yield of endoscopic intervention in children with severe anemia increases to 90.7% after the exclusion of patients with severe anemia.

There are some limitations in our study as follows: (i) The lack of capsule enteroscopy in patients with normal UGE and colonoscopy because capsule enteroscopy is essential to rule out the small intestinal pathology in patients with anemia suggesting gastrointestinal origin. (ii) Lack of long-term follow-up of the children with nutritional anemia whether there is a response to iron supplementation or not. An advanced investigation may be needed in unresponsive patients. (iii) Our patient group only included the patients that were admitted to our unit or consulted us from the pediatric hematology unit. It must be kept in mind that there might be many other patients with severe anemia with other etiologies such as malignant diseases or hemolytic anemias. (iv) Retrospective nature of the study may cause some bias. Further prospective studies are needed to confirm or findings.

CONCLUSION

In conclusion, we recommend performing UGE and/or colonoscopy in patients with severe anemia with gastrointestinal symptoms that is associated with hypoalbuminemia, high ESR, and high CRP in order to rule out *H. pylori* gastritis, gastric ulcers, erosive gastritis, and other gastrointestinal pathologies.

Ethics Committee Approval: The study was approved by Ethics committee of Karadeniz Technical University (Approval no: 2018/260).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.S., M.Ç.; Design – M.Ç; Supervision – M.Ç.; Resources – G.P.S, B.G.; Materials – M.Ç; Data Collection and/or Processing – E.S., G.P.S.; Analysis and/or Interpretation – E.S., B.G.; Literature Search – B.G., A.B.; Writing Manuscript – M.Ç.; Critical Review – M.Ç.

Conflict of Interest: The authors have no conflict of interest to declare.

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