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FREQUENCY, TYPES, AND RISK FACTORS OF ANEMIA IN PEDIATRIC INFLAMMATORY BOWEL DISEASE

ÇOCUKLUK ÇAĞI İNFLAMATUAR BAĞIRSAK HASTALIKLARINDA ANEMİNİN SIKLIĞI, TÜRLERİ VE RİSK FAKTÖRLERİ

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ABSTRACT

Objective: Inflammatory bowel disease patients are prone to be anemic at diagnosis and follow-up. As it is a common extra-intestinal manifestation, its early identification and treatment are essential. We aimed to evaluate the frequency, types, and predictors of anemia and its treatment in pediatric inflammatory bowel disease patients.

Methods: The electronic records of pediatric IBD patients who attended our outpatient clinics between 1 April 2018 and 01 May 2019 were retrospectively evaluated. Patients who had the results of hemoglobin, hematocrit, mean corpuscular volume, iron indices, vitamin B12 level, folic acid level, reticulocyte count, C-reactive protein, and erythrocyte sedimentation rate at least once on a single day were included in the study. Laboratory results associated with anemia and disease activity index scores at three- and six-months follow-ups were recorded. Anemia was diagnosed according to WHO criteria in childhood. Anemia, risk factors, and management of anemia were determined.

Results: Forty patients were included in the study. At first evaluation, anemia was observed in 38.1% of Crohn's disease patients and 57.9% of ulcerative colitis patients. Iron deficiency anemia was the main type of anemia in both groups. The rate of anemia decreased at follow-up. Out of 40 patients, 21 had treatment at the initial evaluation. Active disease was the only predictor of iron deficiency anemia.

Conclusion: Anemia was common in pediatric inflammatory bowel disease patients, ranging between 25-47.5% during the 6-month follow-up in our study. Iron deficiency anemia was the main type of anemia. Having active disease was the only risk factor for anemia. The treatment of anemia and iron deficiency without anemia should be kept in mind in parallel with anti-inflammatory treatment.

Keywords: Anemia, inflammatory bowel disease, children, iron deficiency

ÖZ

Amaç: İnflamatuvar bağırsak hastalığı olan hastalar tanı ve takip sırasında anemik olmaya eğilimlidir. Anemi, yaygın bir ekstra-intestinal bulgu olduğundan, erken tanınması ve tedavisi önemlidir. Bu çalışmada pediatrik inflamatuar bağırsak hastalığı olan hastalarda aneminin sıklığını, tipini, risk faktörlerini ve tedavisini değerlendirmeyi amaçladık.

Yöntem: 1 Nisan 2018 ile 01 Mayıs 2019 tarihleri arasında polikliniğimize başvuran pediatrik İBH hastalarının elektronik kayıtları retrospektif olarak değerlendirildi. Hemoglobin, hematokrit, ortalama korpüsküler hacim, demirle ilgili belirteçler, B12 vitamini düzeyi, folik asit düzeyi, retikülosit sayısı, C-reaktif protein ve eritrosit sedimentasyon hızı sonuçlarına aynı gün içerisinde en az bir kez bakılmış olan hastalar çalışmaya dahil edildi. Üç ve altı aylık takiplerde anemi ile ilişkili laboratuvar sonuçları ve hastalık aktivite indeksi skorları kaydedildi. Çocukluk çağında anemi tanısı WHO kriterlerine göre konuldu. Anemi, risk faktörleri ve anemi tedavisi belirlendi.

Bulgular: Kırk hasta çalışmaya dahil edildi. İlk değerlendirmede Crohn hastalarının %38,1'inde, ülseratif kolit hastalarının ise %57,9'unda anemi gözlendi. Her iki grupta da ana anemi tipi demir eksikliği anemisiydi. Takiplerde anemi oranının azaldığı görüldü. Kırk hastadan 21'i ilk değerlendirmede tedavi aldı. Aktif hastalığa sahip olma demir eksikliği anemisinin tek risk faktörüydü.

Sonuç: Pediatrik inflamatuvar bağırsak hastalığı olan hastalarda anemi, 6 aylık takipte %25-47,5 arasında değişmekte olup, sık görülmektedir. Demir eksikliği anemisi aneminin ana tipiydi. Aktif hastalığa sahip olmak anemi için tek risk faktörüydü. Anti-inflamatuvar tedaviye paralel olarak anemi ve anemi olmaksızın demir eksikliğinin tedavisi de çocukluk çağı inflamatuvar bağırsak hastalığında akılda tutulmalıdır.

Anahtar Kelimeler: Anemi, inflamatuvar barsak hastalığı, çocuklar, demir eksikliği

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Introduction

Anemia is a frequently seen extra-intestinal manifestation of inflammatory bowel disease (IBD). Its prevalence in adult studies varies between 6% and 74%.[1,2] Studies evaluating the prevalence of anemia in pediatric IBD are scarce, but children are more likely to have anemia than adult IBD patients. This can be explained by a more extensive disease course and the tendency of children to anemia in general.[3,4]

In IBD patients, the main types of anemia are iron deficiency anemia (IDA) and anemia of chronic disease (ACD). Vitamin B12 deficiency, folic acid deficiency, drug-induced anemia, and hemolysis are other etiologic factors.[5,6]

It is not surprising to find a pediatric IBD patient anemic at diagnosis. However, anemia is reported during follow-up visits even during remission of pediatric IBD.[7] As IBD-related anemia is not found to be correlated with remission, it shouldn't be underestimated. Determining the etiology of anemia and starting the appropriate treatment is crucial as it affects growth and quality of life.[8]

This study aimed to examine the types of anemia, assess the connection between anemia and disease severity, and evaluate the treatment response to anemia in pediatric IBD.

Methods

The study was approved by the ethics committee of Kocaeli University Hospital (KÜ GOKAEK 2019/225) and were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. The electronic records of pediatric IBD patients who attended our outpatient clinics between 1 April 2018 and 01 May 2019 were retrospectively reviewed. Patients who had hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), iron indices, vitamin B12 level, folic acid level, reticulocyte count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) obtained at least once on a single day were included in the study. The first time including all these data was accepted as the initial evaluation. If the patients didn't have all these parameters on a single day, they were excluded from the study. Hb, hct, MCV, iron indices, CRP, and ESR levels of these patients were recorded at three-month and six-month follow-ups, if accessible. Patients with hemoglobinopathy disorders and those who had been administered blood transfusions were excluded from the study.

Clinical data (age, gender, disease type, age at diagnosis, disease duration, disease activity, disease location) and data associated with the therapy (current medications used for the treatment of IBD, medications used for treatment of anemic patients, and laboratory response to the treatment) were collected from the electronic medical records of patients. To evaluate disease activity, the Pediatric Crohn's Disease Activity Index (PCDAI) or the Pediatric Ulcerative Colitis Activity Index (PUCAI) scores of patients were calculated retrospectively from the electronic records at the initial evaluation, at three-month and six-month follow-ups.

Anemia was defined according to the World Health Organization's (WHO) criteria in childhood.[9] The level of inflammation was determining factor to define iron deficiency and anemia of chronic disease. A ferritin level of <30 μg/L, when CRP was <10 mg/L, or a ferritin level of <100 μg/L when CRP was ≥10 mg/L, was consistent with iron deficiency. Anemia of chronic disease was defined as a ferritin level of >100 μg/L and transferrin saturation (TfS) <%20 in the presence of biochemical (CRP ≥10 mg/L) or clinical evidence of inflammation.[10] B12 deficiency was defined as a level of <191 ng/L and folate deficiency as a level of serum folate <3.8 μg/L.

Iron sucrose infusion was given as intravenous therapy. IV iron requirement was calculated according to Ganzoni's formula.[11] For IV ferrous sulfate, the following calculation was used to determine the total iron deficit for initial repletion: total cumulative dose (mg) = [target Hb (12 g/dL) − actual Hb] × weight (kg) × 0,24 + [15 × weight (kg)]. To prevent adverse reactions, the maximum daily dose of iron sucrose was limited to 200 mg/day or 4mg/kg/day. It was diluted in 100 mL of normal saline and administered for 1 hour on each day.[12] Ferrous sulfate was the preferred oral iron formulation. Response to anemia treatment was evaluated by the change in hemoglobin levels three months and six months after the initial evaluation in those treated for more than one month.

Statistical Analysis

IBM SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The Shapiro-Wilk test was used to examine if a variable was normally distributed. Numerical variables were quoted as mean values±, standard deviation, and median (25th-75th percentile). Categorical variables were expressed as frequencies (percentages). Differences based on the evaluation time were evaluated depending on normality. When normal distribution for the variable was provided, one-way ANOVA was used for repeated measurements. If the normality wasn't provided, the variables were evaluated with Friedman's two-way analysis of variance. Binary logistic regression analysis was performed in order to determine risk factors for iron deficiency anemia. The relationship between categorical variables was evaluated by chi-squared and McNemar analyses. P values of <0.05 were considered significant for two-tailed tests.

Results

The number of IBD patients who met the criteria was 40. Of these patients, 21 (52.5%) were diagnosed with Crohn's disease and 19 (47.5%) with ulcerative colitis. The overview of the study is shown in Figure 1. The characteristics of the patients are given in Table 1. A

statistically significant difference was observed in gender between the two groups (p<0.001). There was a female predominance in patients with UC. Active disease according to PCDAI and PUCAI was higher in UC (57.9%) than in CD (42.1%) (p=0.350). Upper gastrointestinal system endoscopy was performed in 90.5% of CD patients. Of these patients, 7 (33.3%) had upper GI involvement. Among CD patients, 5 (23.8%) had colonic involvement, and 16 (76.2%) had ileocolonic involvement. CRP was significantly higher in patients with CD than in UC (p=0.036).

Anemia was observed in 8 (38.1%) of CD patients and 11 (57.9%) of UC patients at initial evaluation (Table 2). Anemia type mainly consisted of iron deficiency anemia in both groups. Mean hemoglobin levels were measured 12.5 ± 1.9 g/dl in CD and 11.2 ± 1.9 g/dl in UC at the beginning (p=0.04). There was a statistically significant difference between the groups in terms of ferritin (p=0.003). B12 was deficient in 4 of the CD patients and 1 of the UC patients. These patients had no anemia.

Table 3 shows the data related to anemia and disease activity for all IBD patients initially, at three months, and six months after the initial evaluation. The rate of anemia decreased gradually. Iron deficiency anemia was the primary type of anemia in each assessment. According to PCDAI or PUCAI, patients who have active disease decreased during follow-up.

Regarding possible risk factors of iron deficiency anemia, the diagnosis, the duration of the disease, the activity of the disease, having anti-TNF treatment, and early-onset IBD were evaluated. In the multivariate binomial logistic regression analysis, the activity of the disease was the only predictor of iron deficiency anemia (Table 4).

The management of anemia and iron deficiency was evaluated. Out of 40 patients, 21 had treatment at the first evaluation. This treatment consisted of oral iron (18/21, 85.7%), intravenous (iv) iron (2/21, 9.5%), combination therapy of oral iron, and B12 (1/21, 4.8%). At three months, 13 of the total patients (40.6%) had treatment for anemia or iron deficiency. Of these patients, 10 (76.9%) had oral iron therapy, and 3 (23%) had iv iron therapy.

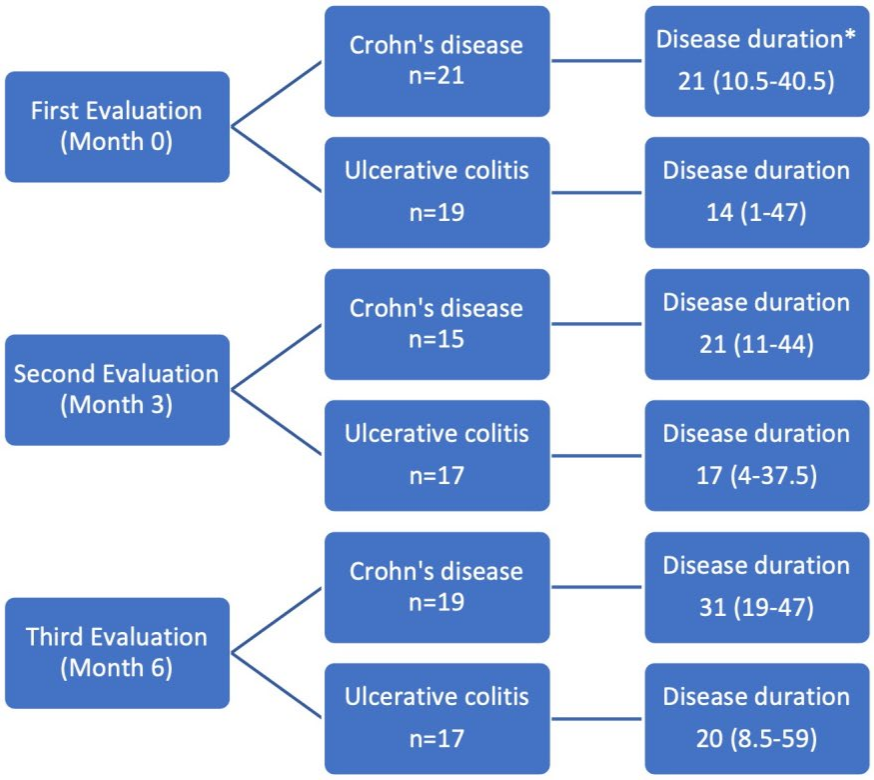

Figure 1. Overview of the study. *Median (Interquartile range)

Table 1. Characteristics of pediatric IBD patients at first evaluation

	Crohn's disease (n=21)	Ulcerative colitis (n=19)	P-value
Age, months; median (IQR)	188 (145.5-208.5)	188 (130-197)	0.537
Gender, females; n (%)	3 (15.8)	16 (84.2)	**<0.001**
Age at diagnosis, months; median (IQR)	163 (127.5-180.5)	170 (76-190)	0.830
Disease duration, months; median (IQR)	21 (10.5-40.5)	14 (1-47)	0.390
Height z-score, mean ± SD	0.55 ± 0.85	0.43 ± 1.18	0.137
Weight z-score, mean ± SD	0.71 ± 1.17	0.49 ± 1.33	0.580
BMI z-score, mean ± SD	-0.89 ± 1.42	-0.87±1.22	0.953
Disease activity			
	PCDAI	PUCAI	
Remission; n (%)	13 (61.9)	8 (42.1)	
Mild; n (%)	3 (14.3)	5 (26.3)	
Moderate; n (%)	5 (23.8)	3 (15.8)	
Severe; n (%)		3 (15.8)	
Active disease	8 (38.1)	11 (57.9)	0.350
Treatment			
5-aminosalicylic acid; n (%)		11 (57.9)	
Systemic corticosteroids; n (%)	2 (9.5)	2 (10.5)	
Azathioprine; n (%)	10 (47.6)	1 (5.3)	
Methotrexate; n (%)	2 (9.5)		
Anti-TNF; n (%)	5 (23.8)		
Exclusive enteral nutrition; n (%)	2 (9.5)		
Combination therapy*; n (%)	-	4 (21)	
None; n (%)	-	1 (5.3)	
C-reactive protein (mg/L), median (IQR)	7.49 (0.9-61.1)	1.1 (0.3-3.6)	**0.036**
Sedimentation (mm/h), median (IQR)	9 (5.5-32.5)	20 (7-35)	0.668
Albumin (g/dl), median (IQR)	4.1 (3.5-4.3)	4.1 (3.6-4.4)	0.688

BMI: Body mass index; IQR: Interquartile range; PCDAI: Pediatric Crohn's disease activity index; PUCAI: Pediatric ulcerative colitis activity index. Systemic corticosteroids consisted of methylprednisolone.
*Combination therapy consisted of 5-aminosalicylic acid and azathioprine, systemic corticosteroid and azathioprine, systemic corticosteroid and 5-aminosalicylic acid. Anti-tumor necrosis factor agent was infliximab.

Table 2. Characteristics and laboratory parameters of pediatric IBD patients related to anemia at first evaluation

	Crohn's disease (n=21)	Ulcerative colitis (n=19)	P-value
Anemia; n (%)	8 (38.1)	11 (57.9)	0.35
Hemoglobin (g/dl); mean ± SD	12.5 ± 1.9	11.2 ± 1.9	**0.04**
Hematocrit (%); median (IQR)	37.1 (33.5-41.7)	35.1 (31-37.4)	**0.041**
Mean corpuscular volume (fl); mean ± SD	76.4 ± 10.7	76 ± 7.86	0.79
Red cell distribution with, %; median (IQR)	15.3 (14-18.2)	16 (13.9-20)	0.573
Reticulocyte count (10^6/µL); median (IQR)	0.053 (0.038-0.070)	0.055 (0.045-0.070)	0.491
White blood cell count (10^3/ µL); median (IQR)	7.5 (6.35-9.97)	8.37 (6.88-11.5)	0.247
Platelet cell count (10^3/ µL); median (IQR)	384.4 ± 114.4	392.48 ± 143.91	0.846
Serum iron (µg/dl); median (IQR)	40 (19-65)	32 (17-59)	0.452
Ferritin (ng/ml); median (IQR)	29.3 (13.4-38)	9.9 (7.3-25.4)	**0.003**
TIBC (µg/dl); mean ± SD	336.6 ± 62.3	368.73 ± 50.7	0.086
Transferrin saturation (%); median (IQR)	13 (6-16.5)	8 (4-17)	0.196
Vitamin B_{12} (pg/ml); median (IQR)	273 (215.5-338)	310 (267-439)	0.078
Folate (ng/ml); median (IQR)	10.4 (6.8-13.8)	6.65 (5-8.2)	**0.027**
Anemia type			
Iron deficiency anemia (IDA); n (%)	6/8 (75)	10/11 (90.9)	
Anemia of chronic disease (ACD); n (%)	-	-	
IDA+ACD; n (%)	2/8 (25)	1/11 (9.1)	
B12/folate deficiency anemia	-	-	
Thiopurines	-	-	
Iron deficiency; n (%)	19/21 (90.5)	17/19 (89.5)	

IQR: Interquartile range, SD: Standard deviation, TIBC: Total iron binding capacity

Table 3. Characteristics and laboratory parameters related to anemia at first evaluation and at follow-up

	First evaluation	Three months later	Six months later	P-value
Anemia; n (%)	19/40 (47.5)	10/32 (31.3)	10/36 (25)	
Anemia type				
Iron deficiency anemia (IDA); n (%)	16/19 (84.2)	10/10 (100)	6/10 (60)	
Anemia of chronic disease (ACD); n (%)			2/10 (20)	
IDA+ACD; n (%)	3/19 (15.8)		2/10 (20)	
Iron deficiency; n (%)	36/40 (90)	23/32 (57.5)	29/36 (80.6)	
Hemoglobin (g/dl); mean ± SD	11.89 ± 1.99	12 ± 1.59	12.5 ± 1.74	0.056
Hematocrit (%); mean ± SD	35.89 ± 5.19	35.92 ± 4.16	37.74 ± 4.56	**0.018**
Mean corpuscular volume (fl); mean ± SD	76 ± 9.37	77.65 ± 9.2	79.56 ± 9.21	**0.005**
Serum iron (µg/dl); median (IQR)	33.5 (18.25-59.75)	52.5 (23.75-97.25)	54 (34-73.75)	0.288
Ferritin (ng/ml); median (IQR)	20.9 (8.6-36)	15.95 (10.67-30.3)	24.45 (13.8-36.8)	0.361
TIBC (µg/dl); mean ± SD	351.87 ± 59	337.69 ± 42.5	343.11 ± 53.29	0.541
Transferrin saturation (%); median (IQR)	8.5 (6-16.75)	14.5 (7-27)	17 (9.25-23.75)	**0.025**
ESR; median (IQR)	18.5 (6.25-32.75)	18 (8-23.25)	17 (8-22.75)	1
CRP; median (IQR)	2.6 (0.7-10.3)	2.58 (0.67-11.52)	2 (0.64-5.5)	0.547
Active disease; n (%)	19/40 (47.5)	14/32 (43.7)	11/36 (30.5)	

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, IQR: Interquartile range, SD: Standard deviation, TIBC: Total iron binding capacity

Table 4. Simultaneous Multivariate Binary Logistic Regression Analysis of Factors Predictive of Iron Deficiency Anemia Among Pediatric IBD Patients

	Odds ratio	95% CI	P-value
Diagnosis (vs. Crohn's disease)	1.832	0.336-9.998	0.484
Duration	0.980	0.947-1.014	0.244
Activity (vs. inactive disease)	11.553	2.289-58.295	**0.003**
Anti-TNF (vs. no anti-TNF)	0.850	0.055-13.242	0.908
Age group (vs. >120 months)	1.691	0.247-11.576	0.593

Anti-TNF: Anti-tumor necrosis factor

Discussion

In this study, the rate of anemia was 47.5% at the initial evaluation, decreasing to 31.3% at three months and 25% at six months. These rates were consistent with other studies evaluating anemia during follow-up in pediatric IBD.[13-18]

In these studies, the prevalence of anemia at diagnosis ranged between 54.9-77%.[14-17] One or two years after the diagnosis; the range was between 27.8-65%. Goodhand et al.[18] evaluated consecutive patients with IBD attending pediatric, adolescent, and adult outpatient clinics in April 2009. The prevalence of anemia was 70% in children and 42% in adolescents.[18] Unfortunately, because of the missing data, we weren't able to evaluate the prevalence of anemia at diagnosis.

Iron deficiency anemia was the most common type of anemia in each evaluation, which is compatible with previous studies.[15,17,18] Iron deficiency without anemia was even more common than any kind of anemia. These findings might be explained by poor iron intake, gastrointestinal bleeding, and increased disease activity. Anemia prevalence declined gradually at follow-up, probably due to the treatment of anemia and lower disease activity.

In this study, we also compared the characteristics of patients with ulcerative colitis and Crohn's disease. There wasn't a statistically significant difference in the anemia rate between groups. On the other hand, hemoglobin, hematocrit, and ferritin levels were significantly lower in ulcerative colitis patients, probably owing to higher disease activity indices and significant blood loss in UC. In a study by Aljomah et al.[13], ferritin was found to be lower in UC patients, too.

Iron therapy was given to 21 of the total patients. Of these patients, 15 had iron deficiency anemia, and 6 had iron deficiency without anemia. The percentage of anemic patients receiving iron therapy (78.9%) was higher than the percentages found in other studies.[14,15,17,18] But our sample size was smaller than the sample sizes in other studies. The treatment rate of iron-deficient patients without anemia was 30%. This lower rate of treatment made us think that treatment of iron deficiency was overlooked more than iron deficiency anemia. As pediatric gastroenterologists, we are probably more involved in putting the patient into remission. Besides, there might be a misconception that treating the patient with anti-inflammatory drugs will correct anemia simultaneously. There are other concerns mentioned in other studies. Goodhand et al.[18] suggested that there was no published evidence showing that oral iron improved the quality of life in pediatric IBD. Moreover, the side effects of oral iron and the risk of exacerbation caused by oral iron were other drawbacks mentioned in the literature.[1,15,18]

In our study, the therapy mainly consisted of oral iron. Only two patients had intravenous therapy at the first evaluation. They both had active inflammation. One of these patients had severe anemia. The other patient had anemia unresponsive to oral iron therapy. At three months, ten patients had oral iron, and three patients had iv iron therapy. These three patients had moderate anemia, which was unresponsive to oral iron. Iron supplementation and the decrease in disease activity might be accounted for the improvement in the anemia rate at follow-up. Both oral and iv iron therapy were well tolerated. No side effects were reported. Gisbert et al.[19]

reported in their study that iron treatment was safe and well-tolerated, and a beneficial impact on hemoglobin concentration and quality of life was observed in adult patients.

Simultaneous binary logistic regression analysis showed that active disease was the only factor predictive of anemia. It wasn't surprising as similar results have been reported in other studies.[16-18] Goodhand et al.[18] reported that the key determinants were the activity of the disease and being a pediatric patient as they compared the anemia prevalence between different age groups. Gerasimidis et al.[16] found that active disease was the strongest determinant of anemia at diagnosis and after one year of follow-up. In terms of disease activity, our study revealed that activity indices of IBH (PCDAI and PUCAI) were predictors of anemia. Interestingly, Aljomah et al.[13] reported that PCDAI and PUCAI were poor predictors of anemia, and the degree of anemia was consistent with inflammatory markers in their study.

Our study had some limitations. Because the study was retrospective, we weren't able to collect all the necessary data. We had to choose the first time, including information about hematologic parameters, inflammatory markers, and activity indices as the initial evaluation, which made our number of patients relatively small.

The key strength of this study is that it contains data describing the type of anemia and the relationship between activity indices and anemia. Additionally, it gives information about the treatment of anemia and anemia rate during follow-up visits.

In conclusion, this study confirms that anemia (especially iron deficiency anemia) and iron deficiency without anemia have high rates in each evaluation of pediatric IBD patients. Having a higher disease activity index was found to be a risk factor for anemia. As these results were consistent with other studies, pediatric gastroenterologists should raise their awareness of anemia and iron deficiency without anemia in patients with IBD. Anemia screening tests should be kept in mind each visit and should be done if needed. To provide a better quality of life, the treatment of anemia should be considered in parallel with anti-inflammatory treatment. However, further studies are required to figure out the treatment of anemia.

Ethical Approval

The study was approved by the ethics committee of Kocaeli University Hospital (KÜ GOKAEK 2019/225) and were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

NUA, EZ, AU: Concept-Design; EZ, AU: Supervision; NUA: Data Collection and/or Processing; NUA, AU: Analysis and/or Interpretation; NUA, EZ: Literature Review; NUA: Writer; EZ, AU: Critical Review

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