Prevalance And Types of Anemia in Inflammatory Bowel Diseases in Sanliurfa Region
Şanlıurfa Yöresi İnflamatuvar Bağırsak Hastalıklarında Anemi Sıklığı ve Tipleri

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Summary
Objective: Anemia is a common hematological complication that adversely affects the clinical course of the diseases. In his study, it was aimed to evaluate the anemia status of inflammatory bowel disease (IBD) patients.
Material and Methods: This is a retrospective, cross sectional study. Files of 202 IBD patients were evaluated. They were divided into four groups according to anemia types. IBM SPSS.22 program was used for statistical analysis.
Results: The majority of 202 patients were female (51.48%). Majority of them (74.75%) were diagnosed with ulcerative colitis. Of the Crohn's disease patients, 35.29% had ileal involvement and 39.08% of the ulcerative colitis patients had proctitis. Low iron levels were found in 69.79% of patients. 41.58% of the patients had also vitamin-mineral deficiency
Conclusion: Low iron levels and vitamin-mineral deficiencies were found in the majority of patients. It can be said that early diagnosis and treatment of anemia and deficiencies is an important approach to protect and improve health of IBD patients.
Keywords: Anemia, Crohn's disease, inflammatory bowel disease, iron deficiency, ulcerative colitis

Özet
Amaç: Anemi, hastalıkların klinik seyrini olumsuz etkileyen yaygın bir hematolojik komplikasyondur. Bu çalışmanın amacı inflamatuar barsak hastalığı (İBH) olan hastalarda anemi durumunu değerlendirmektir.
Gereç ve Yöntem: Bu bir retrospektif, kesitsel çalışmadır. 202 İBH'lı hasta dosyası değerlendirildi. Hastalar anemi tiplerine göre dört gruba ayrıldılar. İstatiksel analiz için IBM SPSS.22 programı kullanıldı.
Bulgular: 202 hastanın çoğunluğu (%51,48) kadındı. Çoğunluğu (%74,75) ülseratif kolit tanısı almıştı. Crohn hastalarının %35,29'unda ileal tutulum ve ülseratif kolit hastalarının %39,08'inde proktit şeklinde bağırsak tutulumu vardı. Hastaların toplam %69,79'unda düşük demir seviyeleri olup %41,58'inde vitamin-mineral eksikliği de olduğu görüldü.
Sonuç: Hastaların çoğunda düşük demir seviyeleri ve vitamin-mineral eksiklikleri bulundu. Anemi ve vitamin mineral eksikliklerinin erken teşhis ve tedavisinin İBH hastalarının sağlığını korumak ve iyileştirmek için gerekli ve önemli bir yaklaşım olduğu söylenebilir.
Anahtar Kelimeler: Anemi, Crohn hastalığı, inflamatuar bağırsak hastalığı, demir eksikliği, ülseratif kolit

Introduction

Inflammatory bowel diseases (IBD) is a chronic, inflammatory disease group of unknown etiology, which can be accompanied by extraintestinal organ involvement as well as involving the digestive system with periods of exacerbation and recovery. IBD includes ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. Today, IBD has become a global disease (1). The incidence and prevalence of the disease may vary according to geographical region and ethnic groups, and the mean prevalence has been reported to be 1-15/100000. In an epidemiological study conducted in Turkey, the incidence of CD was around 2/100000 and that of UC was 4/100000 (2).

Anemia is a hematological complication that can be seen in IBD, impairing the patient's quality of life and

increasing hospitalization rates. The incidence of anemia in IBD varies between 8.8% and 73.7% (3). Although there are many factors that can cause anemia, Iron deficiency anemia (IDA) and anemia of chronic disease (CDA) are reported to be as the most common types of anemia in IBD (4,5,6).

Early diagnosis and treatment of anemia, which negatively affects quality of life and increases hospitalization rates in IBD patients, is an important approach to protect and improve health of this group of patients. In this study, it was aimed to determine the incidence, types and affecting factors of anemia in IBD patients in Sanliurfa region.

Material and Methods

This cross sectional, retrospective study includes outpatients and hospitalized patients who applied to the Gastroenterology Clinic of Harran University Medical Faculty Hospital. Patients, who admitted between January 2011 and June 2021 were divided into two classes as UC and CD. Disease involvement sites were classified according to the Montreal classification (7). In cases with CD; ileal involvement was named as (L1), colon involvement (L2), ileocolonic involvement (L3) and upper GIS involvement was named as (L4). In UC patients; rectal involvement was called as (E1), left colon involvement up to splenic flexure as (E2) and pancolitis exceeding splenic flexure was called as (E3).

Anemia frequency and anemia types in IBD patients were determined by examining the files of the patients. Exclusion criterias were being younger than 18 years of age, being pregnant, being diagnosed with uncertain colitis, radiation colitis, malignancy and insufficient file data. Age, gender, type of IBD, age of the disease, site of involvement, treatment, use of immunosuppressive agents, use of steroids, disease situation, presence of complications, were recorded. The type and etiology of anemia, if any, were detected.

Hb values less than 13 g/dl in men and less than 12 g/dl in women were accepted as anemia, as in the WHO criteria (8). Classification of anemia in IBD patients were made according to the European Anemia Consensus criteria and they were divided into 4 groups as IDA, CDA and

mixed (IDA+CDA) anemia (9). Anemias other than these 3 main groups were defined as "other anemias".

Data were evaluated using the SPSS 22.0 statistical package program. The conformity of the variables to the normal distribution was examined by Q-Q plot and Kolmogrov-Smirnov tests. Number (n), percentage (%), mean, standard deviation (SD), minimum-maximum (min-max) and median values were used in the evaluation of the data. When comparing the data of two independent groups for a certain variable, Student's-t test was used for normally distributed data and Mann-Whitney U test was used for non-normally distributed data. Binary Logistic Regression was used in multivariate analysis. Significance was accepted as $p<0.05$, and the results were evaluated within the 95% confidence interval.

Ethics committee approval was gained from Harran University Faculty of Medicine Ethical Committee report with 01/21th numbered session (E-76244175-050.04.04-4561), dated 04.01.2021.

Results

The records of 288 newly diagnosed IBD patients were accessed. A total of 86 patients, 2 of whom had undetermined colitis, 2 of whom had malignancy, 3 under 18 years of age, and 79 of whom anemia parameters could not be reached, were not included in the study. Evaluation was performed on a total of 202 patients. Of the 202 patients, 104 (51.48%) were female and 98 (48.51%) were male (Table 1). The rate of patients with UC was 74.75% (n=151) and of CD was 25.25% (n=51).

Table 2 shows the correlation of blood parameters with UC and CD. There was no significant difference between UC and CD according to the mean blood parameters of the patients. Vitamin B12 level was found to be significantly lower in CD than in UC (p= 0.006).

Table 3 shows the distribution of the affected intestinal regions in UC and CD's. Majority of them (74.75%) were diagnosed with ulcerative colitis. Of the Crohn's disease patients, 35.29% had ileal involvement and 39.08% of the ulcerative colitis patients had proctitis.

Table 4 shows the correlation between gender and anemia in UC and CD Anemia was found in 89 (44.06%) of patients. The frequency of anemia was higher in women than men in IBD disease, and there

was a significant correlation between anemia and gender in favor of female gender (p=0.009). No significant correlation was found between gender and presence of anemia in CD (p=0.382). A significant correlation was found between gender and anemia in UC patients (p=0.011) in favor of female gender (p=0.011). IDA was found in 61 (68.54%) of the anemic patients. There was no megaloblastic anemia among the anemia detected in IBD patients (Table 5).

Table 1: *Distribution of ulcerative colitis and Crohn's disease by gender*

Group	Gender	(n)	(%)
Crohn's disease	Female	21	41.17
	Male	30	58.83
Ulcerative colitis	Female	83	54.97
	Male	68	45.03

Table 2: *Correlation of ulcerative colitis and Crohn's disease with blood parameters*

Blood parameters*	CD (n=51) mean±SD	UC(n=151) mean±SD	IBD(n=202) mean±SD	p
Hb (g/dl)	12,53±2,20	12,07±2,39	12,18±2,34	0,230
Htc (%)	40,45±6,18	39,11±6,76	39,44±6,63	0,213
	medium (min-max)	medium (min-max)	medium (min-max)	p
MCV (fL)	82,0 (63,6-99,0)	83,0 (49,0-108,0)	82,0 (49,0-108,0)	0,858
WBC (10³/uL)	8,0 (2,6-31,0)	8,0 (1,6-29,0)	8,0 (1,6-31,0)	0,785
PLT (10³/uL)	321,0 (190,0-832,0)	330,0 (107,0-970,0)	325,0 (107,0-970,0)	0,466
Iron (mcg/dl)	28,0 (2,0-419,0)	37,0 (5,0-257,0)	36,5 (2,0-419,0)	0,166
TIBC(mcg/dl)	295,0 (17,0-458,0)	301,0 (24,0-560,0)	298,0 (17,0-560,0)	0,992
Ferritin (ng/ml)	36,0 (1,5-586,0)	19,0 (0,0-1100,0)	20,5 (0,0-1100,0)	0,072
B12 vit(pg/ml)	269,0 (180,0-595,0)	318,0 (8,0-2258,0)	301,5 (8,0-2258,0)	**0,006**
Folate (pg/ml)	7,6 (2,9-16,0)	7,0 (1,8-25,0)	7,03 (1,8-25,0)	0,814
Sedimentation	19,0 (2,0-63,0)	22,0 (2,0-110,0)	21,0 (2,0-110,0)	0,308
CRP (mg/dl)	1,49 (0,0-21,0)	0,53 (0,0-33,39)	0,595 (0,0-33,39)	0,071

Hb:Hemoglobin, Htc:Hematocrit, MCV:Mean corpuscular volüm, WBC:White blood cells, PLT:Platelet, CRP:C-reactive protein, CD: Crohn's disease, UC:Ulserative colitis, IBD: Inflammatory Bowel Disease

Table 3. *Involvement status of intestinal regions in ulcerative colitis and Crohn's disease*

	intestinal regions*	(n)	(%)
Crohn's Disease	L1	18	35.29
	L2	9	17.65
	L3	22	43.14
	L4	2	3.92
Total		**51**	**100.00**
Ulserative Colitis	E1	59	39.08
	E2	38	25.16
	E3	54	35.76
Total		**151**	**100.00**

In CD patients; Ileal involvement (L1), colonic involvement (L2), ileocolonic involvement (L3) isolated upper GIS involvement (L4). In UC patients; rectal involvement (E1), left colon involvement up to splenic flexure (E2), pancolitis in those exceeding splenic flexure (E3)

Table 4. *Correlation between gender and anemia in Ulcerative colitis and Crohn's disease*

Group	Gender	Non-anemic	Anemic	Total	p
Crohn's disease	female	10 (47.62)	11 (52,38)	21 (100,00)	0,382
	male	18 (60.00)	12 (40,00)	30 (100,00)	
	Total	28 (54.90)	23 (45,10)	51 (100,00)	
Ulcerative colitis	female	39 (46,99)	44 (53,01)	83 (100,00)	**0,011**
	male	46 (67.65)	22 (32,35)	68 (100,00)	
	Total	85 (56.29)	66 (43,71)	151 (100,0)	
Inflamattory bowel diseases	female	49 (43.36)	55 (61,79)	104 (100,00)	**0,009**
	male	64 (56.64)	34 (38,21)	98 (100,00)	
	Total	113 (55.94)	89 (44,06)	202 (100,00)	

Table 5. *Anemias and vitamin-mineral deficiency rates in inflammatory bowel diseases patients*

	CD		UC		Total	
Anemias	**n**	**%**	**n**	**%**	**n**	**%**
IDA	17	33,33	44	29,14	61	30,19
CDA	2	3,92	6	3,97	8	3,96
IDA+CDA (mixt type)	1	1,96	6	3,97	7	3,46
The other types of anemia	3	5,88	10	6,62	13	6,44
Deficiencies						
Iron deficiency	15	29,41	47	31,13	62	30,69
Vitamin B12 deficiency	1	1,96	1	0,66	2	0,99
Folate deficiency	3	5,88	6	3,97	9	4,46
Iron and folate deficiency	3	5,88	7	4,64	10	4,95
Iron and B12 deficiency	0	0,00	1	0,66	1	0,50
Patients without anemia and vitamin deficien	6	11,76	23	15,23	29	14,36
Total	5	100,00	15	100,00	20	100,00

IDA: Iron deficiency anemia, CDA: Chronical disease anemia CD: Crohn's disease, UC: Ulcerative colitis

Presence of anemia in women was found to be significantly higher than in men (p=0.009). A highly significant correlation was found between female gender and IDA (p=0.001) but there was no significant correlation in terms of gender with CDA, mixed and other types of anemia (table 6). There was no significant difference between CD and UC in terms of anemia types. There was no significant correlation in CD between the involved intestinal region and anemia types. Both IDA and CDA were significantly higher in UK patients with pancolitis involvement (p=0.003; 0.037, respectively) (table 6). According to the correlation between disease activation and anemia types, IDA rate was significantly higher in clinically active patients (p=0.031) (table 6).

Table 6. *Correlation of anemia types between gender, involved intestinal region and presence of active disease in IBD patients*

*		IDA (n,%)	CDA (n,%)	IDA+CDA (n,%	Other (n,%)	Total (n,%)
Gender	Female	42(40,38)	3(2,88)	4(3,84)	6(5,77)	55(52,88)
	Male	19(19,39)	5(5,10)	3(3,06)	7(7,14)	34(34,69)
	P	**0,001**	0,488	1,000	0,691	**0,009**
Disease group	CD	17(33,34)	2(3,92)	1(1,96)	3(5,88)	23(45,10)
	UC	44(29,14)	6(3,97)	6(3,97)	10(6,62)	66(43,71)
	P	0,573	1,000	0,682	1,000	0,863
Involved intestinal region **UC**	E1	8(13,56)	0(0,00)	2(3,39)	5(8,47)	15(25,42)
	E2	14(36,84)	1(2,63)	2(5,26)	2(5,26)	19(50,00)
	E3	22(40,74)	5(9,26)	2(3,70)	3(5,55)	32(59,26)
	P	**0,003**	**0,037**	0,892	0,763	**0,001**
Involved intestinal region **CD**	L1	5(27,78)	0(0,00)	0(0,00)	1(5,55)	6(33,34)
	L2	4(44,44)	0(0,00)	0(0,00)	1(11,11)	5(55,55)
	L3	8(36,36)	2(9,10)	1(4,50)	1(4,54)	12(54,54)
	L4	0(0,00)	0(0,00)	0(0,00)	0(0,00)	0(0,00)
	P	0,606	0,433	0,719	0,886	0,279
Active disease	Yes	5(13,88)	0(0,00)	0(0,00)	5(13,88)	10(27,78)
	No	56(33,73)	8(4,82)	7(4,22)	8(4,82)	79(47,59)
	P	**0,031**	0,355	0,356	0,059	**0,030**

IDA: Iron deficiency anemia, CDA: Chronical disease anemia, UC: Ulcerative Colitis, CD: Crohn's Disease. IBD: inflammatory bowel disease

Discussion

Anemia, which is common in the community, accompanies IBD and negatively affects the clinical course of the disease and the life quality. Early diagnosis and treatment of anemia is one of the important steps to improve health in patients with IBD. In this study, it was observed that the number of patients diagnosed with UC was approximately 3 times higher than CD (UC/CH:3.7/1 in women; UC/CH:2.2/1UC in men). The ratio of female patients in UC and male patients in CD was higher. The presence of anemia was found to be significantly higher in the younger age group, in women, and in those with a shorter follow-up period.

According to the literature, UC disease is 3 times more than CD in the Turkish population; CD is more common in the north-west of Turkey, and UC in the eastern regions (2). In the study, similar to the literature, UC (74.75%) patients were found 3 times (25.25%) more than CD. In a study conducted by Uyanıkoğlu et al. the results of colonoscopy in the Şanlıurfa region were evaluated and similar frequencies were reported (UC: 7%; CH: 2.5%) (10). In the study conducted by Kaya et al. with 102 participants, unlike the study, the rate of participants with a diagnosis of CD (52%) was higher than that of UC (48%) (11). In the study of Bengi et al., different from the study, it was reported that the rate of participants followed up with a diagnosis of CD (55.2%) was higher than UC (48.8%) (12). These two different studies are from the western regions of Turkey, and it is thought that sociocultural and geographical differences may have affected the results.

It has been reported in the literature that UC and CD are more common in males (2,11). Wozniak et al., on the other hand, observed that there was a female predominance in CD, and there was no difference in the incidence of UC between the gender (13). In the study, similar to the studies conducted in Turkey, although male (58.83%) predominance was observed in CD, UC was more common in females (54.97%). Kaya et al. also reported similar results (11,14,15). The significantly higher presence of anemia in IBD in women can be explained by the effect of menstrual bleeding on women of reproductive age. According to the WHO, the prevalence of anemia in non-pregnant women (30.2%) in the Turkish population was reported to be

considerably higher than in men (12.7%). In the study, according to disease subtypes, the rate of anemia in UC was found to be significantly higher in women (53.01%) than in men (32.35%), but no significant correlation was found in CD.

In the study of Wozniak et al., while ileocolonic (67.31%) involvement was most common in CD patients, involvement as pancolitis (52.83%) was more common in UC (13). In the study of Bengi et al. (12), the most common involvement was as ileal type (48.2%) in CD and left colon invovement (41.0%) in UC. In the study of Duman et al., colonic (49.5%) involvement was most common in CD and proctitis (53.0%) in UC (17). In the presented study, the most common involvement in CD was ileocolonic type (43.14%), while the most common involvement in UC was rectal (39.08%); no significant difference was observed between CD and UC in terms of age and disease follow-up. Similar results were reported in the studies of Duman et al. and Özkılıç et al (17,18).

In a retrospective study conducted by Atuğ et al. in a tertiary care hospital in Istanbul; there were no significant difference between UC and CD in terms of Fe, ferritin, Hgb, Htc, MCV and transferrin saturation levels, while B12 vit and folate levels were found to be significantly lower in CD compared to UC (19). In the study, similar to other studies, no significant difference was found between UC and CD in terms of blood parameters associated with anemia, but only vitamin B12 was found to be significantly lower in CD than in UC. This can be explained by the fact that B12 absorption occurs from the ileum and ileal involvement is more common in CD.

According to the literature, the incidence of anemia in IBD patients ranges from 6% to 94% (14,20,21,22,23). Bengi et al. reported anemia rate as 51.6% in IBD patients in their studies (12). According to the study results, anemia is seen in 44.06% in IBD, which is consistent with the literature. It is thought that the wide range in the frequency of anemia reported in the literature may be due to the use of different reference values in the definition of anemia in related studies and the sociodemographic, clinical and genetic characteristics of the patients (24).

In the study, UC patients with pancolitis and left colon involvement were found to have significantly more anemia. In another study,

similar to this, it was found that there was a significant increase in the incidence of anemia as the spread of the disease increased in UC, but there was no relationship between the site of involvement and anemia in CD (12). The reason why more anemia is seen in parallel with the excess of involved areas in UC may be due to increased inflammation burden and intestinal tissue loss.

In IBD patients, IDA is the most common anemia, followed by CHA and mixed type anemia (11,25, 26,27). Mixed anemia with IDA and CCA was first mentioned in the literature in patients with rheumatoid arthritis (28). In the study of Kalaycı et al., IBD patients were classified into three groups as non-anemic, IDA, and CHA. They reported that CHA was more common in UC and CD than IDA, different from other studies in the literature and with a very high rate (29). It is thought that this may be due to the longer follow-up period of the disease in IBD patients. In the study of Duman et al., it was observed that the rate of mixed type anemia was much higher than CHA (13.2% vs 36.8%) (17). In the study, IBD was found to be the most common (68.54%) in patients with anemia in IBD. Rates of CHA and mixed anemia (8.99%; 7.86%) were also found to be similar to some studies (12). There are different results in terms of CHA and mixed anemia rates in the literatüre. These differences may be due to the lack of a standard method for classifying anemia types and the lack of a common laboratory criterion for mixed anemia. In the study, the rate of 'other anemia' that is not classified as IDA, CHA, mixed type anemia and megaloblastic anemia was found to be higher (14.61%). Due to retrospective study design, the etiology cannot be fully elucidated because of the insufficient data, but it is estimated that drug-induced anemia is in this group. It is noteworthy that, similar to the literature, there were no patients diagnosed with megaloblastic anemia among IBD patients (11,13).

Although there are studies reporting that the incidence of IDA is higher in UC than CD (11,30); in the study, the rate of IDA was higher in CD. Similarly, in a multicenter, prospective, observational study conducted by Blumenstein et al. in Germany, IDA was found to be higher in CD. In their studies, mixed type anemia was seen more frequently than CDA (31).

In Kulnigg and Gasche's review on the management of anemia in CD; the rate of iron deficiency varies between 36% and 90% (32). Kaya et al. (11) found the rate of iron deficiency as 43.9% in patients who were not anemic and this rate was found to be higher in UC than in CD (63.2% vs. 27.3%). When patients with IDA and CHA+DEA were included; patients with iron deficiency without anemia, more than 50% of the total patients had low iron levels regardless of the diagnosis of anemia. Similarly, in a study conducted in Brazil, the incidence of low iron levels in IBD patients was found to be 50%, although it was higher in UC than in CD (53.5% vs. 45.4%) (15). In the study, iron deficiency was found in 73 (36.14%) patients, vitamin B12 deficiency in 3 individuals, and folic acid deficiency in 19 individuals, without being anemic in all IBD patients. The ratio of all patients with IDA, mixed anemia and iron deficiency without anemia diagnosis was 69.79%, and iron deficiency was observed in approximately two-thirds of the patients. Although IDA is the most common type of anemia in IBD patients, this study revealed that the rate of iron deficiency, which has not yet affected the Hb level and has not developed anemia, is also quite high.

It has been reported that, 5.6-38% of patients with CD had vitamin B12 deficiency (33,34,35,36,37). In the study of Battat et al. (38), vitamin B12 deficiency in CD was detected in 10.4% of the participants. In their study, ileal resection was performed in 36% of patients with CD, and especially resection more than 20 cm poses a risk for vitamin B12 deficiency. In the presented study, there were 3 patients with vitamin B12 deficiency, and although 17.64% of CD patients had a history of surgical resection, data on bowel resection length were insufficient.

Conclusion

Anemia is an important health problem in patients with IBD, as it is the most common extraintestinal finding. This study is the first to reveal the frequency and types of anemia in IBD in the Şanlıurfa region. In the study, it was observed that patients with IBD had anemia with a rate of 44.05%, including IDA, CHA, mixed anemia and other anemia, and vitamin-mineral deficiency at a rate of 41.8%. Low iron level, which was not reflected in anemia, was the most common (36.14%) deficiency condition detected in IBD

patients. When patients with IDA, IDA+CHA and patients with low iron levels although not within the limits of anemia, were evaluated collectively, iron deficiency was detected in 69.79% of the patients. In the light of these results; early recognition and treatment of anemia, iron and vitamin deficits in IBD patients is an important approach to maintaining and improving health.

Limitations

Due to the retrospective nature of the study, data on treatment for these deficiencies and the severity of the disease were insufficient. The fact that the criteria used in the classification of anemia has not yet been unified, may have an impact on reporting different results from similar studies in the literature. In addition, there were not enough diagnostic tests to detect mixed anemia. Due to the retrospective nature of this study, it was insufficient to elucidate the etiology of anemia in the 'other anemia' group.

Conflict of interest:
The authors declare no conflicts of interest.

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