Turk J Gastroenterol *2016; 27: 143-8*

Incidence rate of anemia in inflammatory bowel diseases

BOWEL

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Original Article

ABSTRACT

Background/Aims: To determine the incidence rate and distribution of anemia types over time from an Inflammatory Bowel Disease (IBD) patient cohort spanning 18 years.

Materials and Methods: Between January 1995 and November 2013, the University Hospital digital databases as well as hard copies of patients' files were reviewed retrospectively. IBD patients with at least one complete blood count (CBC) report were included in this study.

Results: We obtained 941 IBD patients' records; 375 (39.9%) patients were diagnosed with Crohn's disease (CD), and 566 (60.1%) patients had ulcerative colitis (UC). Anemia was detected in 548 (58.2%) patients. Female patients were more frequently anemic than male patients (68.4% vs. 49.7%, p=0.001). The frequency of anemia was slightly higher in patients with CD (62.1%) than in patients with UC (55.7%) (p=0.04). The incidence rate of anemia for the entire IBD patient cohort was calculated as 103.45 per 1,000 patient-years. The correlation between the age of the IBD disease and the presence of anemia exhibited a high correlation coefficient of Pearson's r=0.702.

Conclusion: This is the first study to report the incidence rate of anemia (103.45 per 1,000 patient-years) in a long-term cohort of IBD patients.

Keywords: Anemia, inflammatory bowel disease, Crohn's disease, ulcerative colitis

INTRODUCTION

Inflammatory bowel diseases (IBD) are relapsing and remitting chronic intestinal disorders with extra-intestinal manifestations (EIM). IBD predominantly consist of two different clinical forms: Crohn's disease (CD) and ulcerative colitis (UC) (1,2).

Anemia is a common complication in IBD and has a known negative impact not only on quality of life and but also on the ability to work (3,4). Thus, the detection and treatment of anemia in IBD patients deserves careful consideration with regards to the approach (5). Anemia of chronic disease (ACD) and iron deficiency anemia (IDA) are major causes of anemia in IBD patients (5,6). Vitamin B_{12} and/or folate deficiency and drug-induced bone marrow suppression may represent other important contributing factors (7). In cross-sectional studies of IBD series, anemia was reported over a very wide range, from 6% to 74% (8,9). Indeed, the frequency of anemia differs among IBD patient populations and is dependent on hospitalization, IBD type, and remission status. Anemia has been reported to be more frequent in hospitalized patients and CD patient groups but less frequent in patients with clinical remission. In a recent review, the mean prevalence of anemia in an IBD patient population was 17% (16% in outpatients and 68% in hospitalized patients), with anemia occurring more frequently in patients with CD than in patients with UC (5,8). However, scarce information is available regarding the incidence rate of anemia over time in IBD cohorts. The anemia prevalence of Turkish IBD patients is also unknown.

The main aim of this study was to determine the incidence rate and distribution of anemia types over time in an IBD patient cohort spanning 18 years from a single tertiary center in Turkey.

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Received: January 8, 2016 **Accepted:** February 19, 2016
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2016.16011

MATERIALS AND METHODS

Study design, population, and data collection

This study was performed in a tertiary IBD center in Istanbul, which is the largest city in Turkey with a population of approximately 15 million. This IBD center receives patients from all over Turkey.

This study was performed with a retrospective design. The study was conducted in both outpatient clinics and hospitalized patients. The cohort in this study included both naive and treated patients during 18 years of follow-up. IBD patients who had at least one complete blood count (CBC) report were included in the study. Unclassified IBD patients and patients younger than 18 years were excluded from the study. IBD diagnoses were established with endoscopic, histological, and radiographic procedures, according to the current guidelines (10). The University Hospital digital databases as well as hard copy patient files were reviewed retrospectively from January 1995 to November 2013. Data regarding the gender, age at diagnosis, IBD type, location, behavior, age of disease, and time period of clinical follow-up were recorded for each patient.

Definition of variables

The diagnostic criteria for anemia consisted of the minimum hemoglobin (Hb) and hematocrit levels specified by the WHO (World Health Organisation) and ECCO (European Crohn's and Colitis Organisation) consensus reports (11,12). Hb levels <13 g/dL in men and <12 g/dL in non-pregnant women were accepted as anemic. Hb level <10 g/dL in both sexes was accepted as severe anemia. A ferritin level <30 ng/mL was accepted as iron deficiency (ID) (13). Patients with low Hb (men <13 g/dL and women <12 g/dL), a transferrin saturation (TfS) <20% and ferritin concentration <30 ng/mL were classified as having iron deficiency anemia (IDA). Patients with anemic Hb levels with TfS levels below 20% and ferritin levels above 100 ng/mL were classified as having anemia of chronic disease (ACD). However, those with anemic Hb levels with TfS levels below 20% and ferritin level >30 ng/mL and <100 ng/mL were classified as having ACD with absolute iron deficiency (ID). Severe anemia was defined as a (Hb) level <10 g/dL. We did not evaluate the usage and effect of iron and/or vitamin replacement therapies.

Data related to anemia were recorded for all patients. The clinical follow-up time of all patients was also recorded and transformed to patient-years. We searched for patients with complete blood count (CBC) results, including the lowest value for Hb and/or hematocrit during the entire clinical follow-up period. Simultaneous (within a period of 1 week of the CBC report) test results for ferritin, iron, total iron binding capacity, and other anemia-related tests were also recorded, and transferrin saturation (TFs) values were calculated. Patients with simultaneous test results for all three tests were defined as "patients for whom the full anemia work-up had been performed." However, we also recorded the reports of patients with absent test sets. For all IBD patients, we searched not only for the lowest Hb (g/dL) and/or lowest hematocrit (%) but also the lowest mean corpuscular volume (MCV) (fL), lowest iron (µg/dL), lowest ferritin (ng/mL), lowest TFs (%), lowest folic acid (ng/mL), and lowest vitamin B12 (pg/mL) values. Patients who had all of the appropriate test results for the anemia work-up, i.e., "patients for whom the full anemia work-up had been performed," were included in the analysis of the distribution of anemia types. In the absence of any of these three tests, the patient was excluded from the second analysis.

Biostatistics

The statistical methods of this study were reviewed by a biomedical statistician from Marmara University. Continuous, normally distributed data were calculated as the mean±SD, and non-parametric data were calculated as the median with minimal and maximal values. A significant p-value was accepted at less than 0.05. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) 20.0 software (SPSS Inc.; Chicago, IL, USA) for Windows. The age and gender distributions of the groups were analyzed with unpaired Student's t-tests, one-way analysis of variance (ANOVA), and Chi-square tests.

Ethics

The regional ethics committee (Marmara University School of Medicine Ethics Committee, approval date: March 05, 2012 and approval no: B.30.2.MAR.0.0.MEK/240) approved the study. The confidentiality of patient identity and records was maintained using guidelines from the Turkish Ministry of Health. The study was performed according to the Declaration of Helsinki.

RESULTS

We identified 941 IBD patient CBC records, and of these patients, 434 (46.1%) were women and 507 (53.9%) were men. The mean age was 44.5±14.8 years. Three hundred and seventy-five patients (39.9%) had CD, and 566 (60.1%) had UC. Anemia was detected in 548 (58.2%) patients. Female patients were more frequent anemic than male patients in the whole IBD group (68.4% vs 49.7%, p=0.001). The frequency of anemia was slightly higher in patients with CD (62.1%) than in patients with UC (55.7%) (p=0.04). Severe anemia, i.e., an Hb level <10 g/dL, was found in 60 patients (6.4%). However, we did not determine any predictor or risk factor for severe anemia.

The mean total clinical follow-up time of the patients was 5.63±4.47 years (1–18 years). The total follow-up time of all 941 patients was 5,297 patient-years. The incidence rate of anemia for the entire cohort of IBD patients was calculated as 103.45 per 1,000 patient-years. The incidence rates of anemia in UC (315 patients, 3,147 patient-years: 100.09 per 1,000 patient-years) and CD (233 patients, 2,150 patient-years: 108.37 per 1,000 patient-years) were also calculated.

Pearson's correlation test was applied for the duration of IBD disease and the presence of anemia. A high Pearson's coeffi-

Table 1. Patient characteristics and laboratory values

Values (mean±standard deviation)	All IBD patients (n=941)	Crohn's disease patients (n=375)	Ulcerative colitis patients (n=566)	p-value CD/UC
Gender (female/male)	434/507	189/186	245/321	0.032[a]
Age at diagnosis of IBD (years)	44.5±14.8	41.4±13.8	46.5±15.1	<0.001[a]
Age of the disease	5.6±4.5	5.7±4.3	5.6±4.6	0.584
Extent of Ulcerative Colitis (UC); n, (%)				
Proctitis (E1)		n: 128, (22.7%)		
Left-sided colitis (E2)		n: 200, (35.4%)		
Extensive colitis (E3)		n: 238, (41.9%)		
Location of Crohn's Disease (CD); n, (%)				
Ileal (L1)		n: 121, (32.3%)		
Colonic (L2)		n: 45, (12. 0%)		
Ileocolonic (L3)		n: 209, (55. 2%)		
Behavior of Crohn's disease (CD); n, (%)				
Nonstricturing-nonpenetrating (B1)		n: 200, (53.3%)		
Stricturing (B2)		n: 79, (21.1%)		
Penetrating (B3)		n: 96, (25.6%)		
Perianal involvement		n: 32, (8.5%)		
Lowest hemoglobin (g/dL)	11.9±2.1	11.7±2.12	11.9±2.0	0.130
Lowest hematocrit (%)	35.6±6.5	31.2±6.9	35.9±6.2	0.159
Lowest MCV (fL)	81.5±9.3	80.9±10.0	82.0±8.6	0.195
Lowest iron (µg/dL)	55.3±37.9	53.4±41.7	56.8±34.7	0.396
Lowest ferritin (ng/mL)	49.0±74.0	56.6±83.8	43.2±64.9	0.092
Lowest transferrin saturation (%)	16.2±12.2	15.6±13.1	16.6±11.6	0.569
Lowest folic acid (ng/mL)	9.2±7.0	8.3±4.9	9.9±8.3	0.014[a]
Lowest vitamin B_{12} (pg/mL)	352.9±221.4	326.4±226.3	373.9±215.7	0.023[a]

[a]p<0.05

CD: Crohn's disease, UC: ulcerative colitis; IBD: inflammatory bowel diseases

cient of r=0.702 indicated the presence of a good positive correlation.

For anemic patients in whom the iron, TFs, and ferritin reports were available, data is further analyzed for the distribution of the anemia type. Out of the 548 anemic patients, only 201 patients fulfilled the criteria of full anemia work up while the remaining 347 anemic IBD patients did not have records of the necessary essential anemia work-up tests.

Out of the 201 anemic patients who underwent full anemia work-up, IDA was diagnosed in 59.7% (n: 120) of patients diagnosed with IDA. There were 10 patients (4.9%) described as having ACD and 29 patients (14.4%) as having ACD with absolute ID. These patients' characteristics and laboratory values are shown in Table 1, and the frequencies of anemic types are shown in Table 2.

Folic acid levels were found to be below the laboratory cut-off point for only one patient in the UC group and three patients in the CD group. Out of the 566 UC patients 36 (6.4%) and out of 375 CD patients 53 (14.1%) had low vitamin B_{12} levels (p=0.01 significant). Thus, the incidence rate of vitamin B_{12} deficiency in our 18-year IBD cohort was calculated as 16.80 per 1,000 patient-years.

DISCUSSION

The incidence of IBD in a Turkish population from the referral center was reported to be 4.4/100,000 and 2.2/100,000 for UC and CD, respectively (13). The IBD incidence is lower than that in North and West Europe but close to that reported in the Middle East and Asia. However, IBD has been more frequently encountered in Turkey in recent years, and insufficient studies have been performed regarding the epidemiology of IBD in Turkey.

Table 2. Frequencies of anemia and anemic types in IBD patients

	IBD all (f/m)	CD (f/m)	UC (f/m)	p value
Total number of patients screened (n)	941 (434/507)	375 (189/186)	566 (245/321)	0.03[b]
Total number of patients diagnosed with anemia (n)	548 (296/252)	233 (141/92)	315 (155/160)	0.04[b]
Percentage of patients diagnosed with anemia out of the total number of screened patients (%)	58.2 (68.2/9.7)	62.1 (74.6/ 49.5)	55.7 (63.3/ 49.8)	-
Full anemia work-up performed IBD patients (n)	201 (115/86)	88 (54/34)	113 (61/52)	-
IDA (n)	120 (75/45)	47 (32/15)	73 (43/30)	0.10
(%)	59.7	53.4	64.6	
ACD (n)	10 (5/5)	5 (2/3)	5 (3/2)	0.65
(%)	4.9	5.7	4.4	
ACD+ID (n)	29 (16/13)	21 (13/8)	8 (3/5)	0.01[b]
(%)	14.4	23.9	7.1	
TFs >20% (n)	42 (19/23)	15 (7/8)	27 (12/15) 0.23	
(%)	20.9	17.0	23.9	

[b]p<0.05

CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel diseases; f: female; m: male; IDA: iron deficiency anemia; ACD: anemia of chronic disease; ACD + ID: anemia of chronic disease with absolute iron deficiency; TFs >20%: patients with transferrin saturation greater than 20%

The prevalence of anemia in IBD patients has been reported to range from 6%, equal to the prevalence of anemia in the normal population of Sweden, to 74% in actively hospitalized patients (8,9). This wide variation is most likely due to differences in the definition of anemia, the study populations (hospitalized patients vs. out-patients), and health systems between countries.

In a meta-analysis from six studies, including 2,192 patients from European countries, the overall prevalence of anemia in patients with IBD was reported as 24%, and more than half of anemic patients (57%) were classified as having IDA. The prevalence of anemia in patients with IBD was relatively comparable in Germany, Norway, Spain, Sweden, and Switzerland (range, 18%–25%) (14).

However, little is known regarding the incidence rate of anemia over time in IBD cohorts. The incidence rate is defined as the number of new patients or cases per population at risk in a given time period. If the sum of the patient-time of the population at risk is taken as the denominator, then this is referred to as the patient-time incidence rate or incidence density rate (15). Theoretically, a study from an IBD patient cohort reporting the incidence rate may express the effect of anemia better than reports obtained from cross-sectional designed studies. Cross-sectional studies provide a picture of a specific time point but cannot give results over a time period; thus, it is difficult to estimate the frequency of new cases of anemia due to different causes.

To the best of our knowledge, this is the first study to determine the incidence rate of anemia in a long-term patient cohort. This study was performed in a cohort of Turkish patients with IBD treated at a specialized tertiary referral center in the Western part of Turkey. We found that nearly two-thirds (58.2%) of our IBD patients had experienced an anemic episode at least once during their clinical follow-up period. A high correlation coefficient of Pearson's r=0.702 was found between the duration of the IBD disease and the presence of anemia. This result indicates that the cumulative diagnosis of anemia increases with IBD disease duration. Thus, the higher rate of anemia identified in our cohort is likely due to this cumulative phenomenon when compared to cross-sectional prevalence studies from many other European countries (16-20). However, this increased rate of anemia may also be due to other factors; for instance, some of our patients were referrals and, thus, more complicated patients gathered in our cohort. The higher anemia frequency in patients treated at university hospitals may also be related to the higher proportion of IBD patients with active and/or severe disease at university hospitals. Lastly, some differences in anemia frequency between different IBD centers may be attributed to different health systems operating in different countries; for example, the prevalence of anemia in Italian and Greek IBD patients was found to be higher than that in other Northern European countries (17,18).

We found the rate of anemia to be slightly higher in patients with CD than in those with UC (62.1% vs. 55.7%, p=0.004). This finding is consistent with results obtained in a recent meta-analysis from Europe (14). It is well known that chronic intestinal blood loss via the ulcerated mucosal surface and retention of iron in the reticulo-endothelial system causes anemia in both disease entities. Moreover, patients with CD in the upper gastrointestinal region have the potential risk of reduced iron absorption, resulting in iron-deficiency anemia, potentially accounting for this difference (8).

One weakness of this study is that the observational data were collected from patient laboratory records retrospectively; thus, a structured appraisal of disease activity using activity indices was not possible. As a result, it was difficult to evaluate if the presence of anemia was associated with disease activity. Relationship between anemia and immune-suppressive treatment was not evaluated. Ideally, it would have been better if we had collected data related to the history of drug usage, disease-related surgery, and accompanying diseases (i.e., celiac disease), which may all affect the anemic status. Studying prospective cohorts to determine the cumulative prevalence of anemia will not be easy and cheap but it should be considered for future studies, particularly in tertiary focused IBD centers.

One other important weakness of our retrospective study was the low ratio of patients who had fulfilled the rigid criteria of having a full anemia work-up performed within one week of finding the lowest Hb value. Only 36.7% of all anemic patients (201/548) had fulfilled this rigid endpoint. However, most of the other patients had reports of anemia work-ups, although they were not within one week or lacked at least one of the three essential tests—serum iron, TFs, and ferritin.

Although only one-third of all anemic patients in our cohort (201/548) fulfilled these criteria, the results of these 201 anemic patients demonstrate that ACD+ID was more frequent in the CD patient group than in the UC group (23.9% vs. 7.1%, p=0.01). However, although not statistically significant, IDA was more frequent in the UC patient group than in the CD group (64.6% vs. 53.4%, p=0.10). Our results confirmed the conclusions obtained from a recent meta-analysis, indicating that anemia was more prevalent in CD than in UC. We also confirmed that ACD was more common in CD and IDA was more common in UC (14).

In conclusion, to the best of our knowledge, this is the first study to report the incidence rate of anemia (103.45 per 1,000 patient-years) using real-life data from an 18-year cohort of IBD patients. We found that more than half (58.2%) of our IBD patients had experienced an anemic episode at least once during their clinical follow-up period. Thus, our results suggest that anemia expands its negative impact on IBD patients over time and thus must be carefully screened and treated as needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University School of Medicine.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.A, H.A.; Design - O.A. Supervision - N.İ., H.A.; Resources - Ö.A., H.T.K., M.B.; Materials - Ö.A., H.T.K., M.B.; Data Collection and/or Processing - Ö.A., H.T.K., M.B.; Analysis and/or Interpretation - Ö.A., H.T.K., H.A.; Literature Search - Ö.A., H.T.K., M.B.; Writing Manuscript - Ö.A., H.T.K., H.A.; Critical Review - N.İ., H.A.

Acknowledgements: We would like to thank IBD Nurse Saadet İlhan for her help during the search and extraction of related data the patients' hard copy files. We are also thankful to Güray Can, MD from Edirne University for his unconditional help regarding the statistics of the manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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