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Five-year period prevalence and characteristics of anemia in a large U.S. inflammatory bowel disease cohort

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Abstract

Background—Anemia is a common manifestation of inflammatory bowel disease (IBD) but its prevalence in the U.S. is not well defined. Aim of this study was to determine the prevalence and characteristics of anemia in IBD patients who were followed in a U.S. referral center.

Methods—Demographic, clinical, laboratory and treatment data from a prospective, consented longitudinal IBD registry between the years 2009-2013 were analyzed. Disease activity was evaluated using Harvey-Bradshaw index (HBI) in Crohn's disease (CD) and ulcerative colitis (UC) activity index (UCAI) in UC as well as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Anemia was defined based on the World Health Organization criteria.

Results—A total of 1821 IBD patients [1077 with CD, 744 with UC, median age 43.8 years, 51.9% female] were included. The 5-year period prevalence of anemia in IBD patients was 50.1%, (CD: 53.3% vs UC: 44.7%, P =0.001). In multivariate logistic regression analysis anemia was associated with surgery for IBD [odds ratio (OR) 2.77 95% confidence inderval (CI) (2.21-3.48) P<0.0001)], female gender (OR 1.29 95% CI 1.04-1.61 P=0.02), CRP (OR 1.26 95%CI 1.16-1.37 P<0.0001), ESR (OR 1.02 95%CI 1.01-1.03 P=0.0002) and use of biologics (OR 2.00 95%CI 1.58-2.52 P=0.0001) or immunomodulators (OR 1.51 95%CI 1.21-1.87 P=0.0003). Iron replacement therapy was administered to 46.8% of the anemic patients.

Conclusions—Anemia has a high period prevalence in IBD patients followed at a tertiary center. Anemia is more common in CD than in UC, is associated with disease activity and in current practice is undertreated.

Keywords

anemia; Crohn's disease; prevalence; ulcerative colitis

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Introduction

Anemia is a common complication and/or extraintestinal manifestation of inflammatory bowel disease (IBD) with an important impact on patients' quality of life (1-3). The point prevalence of anemia in IBD varies enormously among studies and ranges from 6% up to 74% due to differences in the definition and subgroup of patients examined (4-10). The prevalence of anemia appears to be lower in outpatients when compared to hospitalized IBD patients (10). A recent meta-analysis of European studies with 2192 patients, mainly treated in tertiary referral centers, showed an overall prevalence of anemia of 27% [95% confidence interval (CI), 19–35] for Crohn's disease (CD) and 21% (95% CI, 15–27) for ulcerative colitis (UC) (11). Most existing data describes point prevalence, whereas the period prevalence of anemia in IBD patients is largely unknown. The period prevalence represents how many IBD patients will develop anemia over a given time period. Awareness of this variable will help physicians appreciate the size of the problem and identify patients that may need treatment.

The most common types of anemia in IBD are iron deficiency anemia (IDA), anemia of chronic disease (ACD) or inflammatory anemia (12), and mixed anemia (both IDA and ACD). IDA in IBD is the result of chronic blood loss from the gastrointestinal tract and reduced iron uptake from the enterocyte. ACD is caused by chronic inflammation, which through a cytokine-mediated mechanism leads to a decreased iron level in the circulation with a subsequent limited availability of iron to the erythroid cells.

For the sufficient evaluation of the anemia in IBD, the minimal required blood tests are a complete blood count, C-reactive protein (CRP) level, and serum ferritin. In the absence of signs of inflammation (normal CRP levels), iron deficiency is defined by serum ferritin <30 μg/L. Under inflammatory conditions (high CRP levels) where serum ferritin levels can be high despite depleted iron stores, the ferritin level of 100 μg/L has been suggested as an appropriate cut-off point differentiating IDA from ACD (12).

Anemia in IBD is usually correlated with more extensive and active disease, treatment of which is important for the management of anemia. Iron supplementation is recommended for all IBD patients with IDA. The use of oral iron has certain limitations in IBD such as poor tolerance and the possible worsening of intestinal damage (12). Intravenous (IV) iron preparations are usually better tolerated and preferably used especially for patients with active bowel disease or severe anemia (12).

The aim of this study was to determine the period prevalence and characteristics of anemia in a large US cohort of outpatients with IBD, to identify risk factors for developing anemia and to describe contemporary treatment modalities in IBD patients with anemia.

Materials and methods

The IBD Center at the University of Pittsburgh Medical Center (UPMC) maintains a consented, prospective, longitudinal natural history registry of IBD patients. The name of the registry is The UPMC IBD Research Registry and the data is prospectively collected by the physicians during routine clinical encounters. All clinical encounters have standardized

collection of clinical measurements. There is also clinical data from all clinical encounters occurring within the UPMC network system. These clinical data is pulled quarterly from the medical records by the Center for Assistance in Research Using the eRecord (CARe) team and delivered to the research group who then inspect, clean, organize and transform the data for analysis. This registry includes demographic, clinical, endoscopic, pathological, radiologic, laboratory and other clinical data of the enrolled patients and is updated routinely through Information and Technology support. De-identified longitudinal data from patients with a definitive IBD diagnosis based on established criteria was used in the analysis. Patients seen in the IBD clinic during the 5-year time period extending from January 1, 2009 to December 31, 2013 were included in this study. Prospectively collected demographic, clinical and laboratory data from clinic visits was utilized. Additional information was obtained with electronic medical record (EMR)-based computer searches and manual confirmation of the information. Complete blood count data, disease activity scores, biochemical markers of inflammation and anemia, and patterns of medication use were prospectively monitored in all patients.

Anemia was defined as a hemoglobin (Hb) <13 g/dL in men and Hb <12 g/dL in non-pregnant women based on WHO criteria (13). Patients with anemia during any of their follow up visits were included in the anemic group. Patients with Hb <10 g/dL, irrespective of gender were considered to have severe anemia. The laboratory data at the time when the Hb levels were the lowest was captured. A ferritin level of 100 ng/ml was used as a cutoff point of distinction between ACD and IDA or mixed anemia.

Disease location and behavior in CD and extent of bowel involvement in UC were classified according to the Montreal classification (14). The disease activity was also prospectively evaluated using clinical activity scores such as Harvey-Bradshaw index (HBI) for CD (15) and ulcerative colitis activity index (UCAI) for UC (16).

The proportions of patients treated for anemia at the time of the evaluation with either oral or IV iron were recorded.

Statistics

The Kolmogorov and Smirnov test was used to evaluate the distribution normality of the data. No parameters were normally distributed and they are reported as median and their minimum and maximum values. Differences between groups were evaluated using the Mann–Whitney U test for nonparametric continuous data. Data from contingency tables were analyzed using chi-squared tests. The period prevalence was calculated using the number of IBD patients who had anemia at any time during the 5 years of the study as the nominator and the total number of the IBD patients as denominator. The association between presence of anemia and the characteristics of IBD patients was examined by univariate and multivariate logistic stepwise regression analysis.. In the final model, the dependent variable was the presence of anemia and the covariates were those with significance <0.1 in the univariate analysis. P values <0.05 were considered statistically significant.

Ethical Considerations

The University of Pittsburgh's Institutional Review Board approved enrollment and participation of subjects in the research registry (PRO12110117).

Results

From a total of 1900 registered patients, 1821 had a definite IBD diagnosis and were included in the study. In 79 patients of the 1900, the diagnosis of IBD was uncertain or an alternative diagnosis was eventually made during follow up, and these patients were excluded. In the final study population there were 1077 patients with CD and 744 with UC The demographic and clinical data of the IBD patients included in the study are presented in Table 1. Table 2 shows the main laboratory findings at the time of the lower Hb of the included IBD patients. Patients with CD had significantly lower Hb values compared to patients with UC (P=0.002). Regarding CRP, erythrocyte sedimentation rate (ESR), and ferritin levels, no significant differences were found between CD and UC patients.

Prevalence

Anemia was found in 913 patients (574 CD, 339 UC). The median number of times that these patients had measurement of low Hb was 3 (1-150). The 5-year prevalence of anemia in IBD patients was 50.1% and it was higher in CD when compared to UC (53.3% vs 44.7%, P=0.001). Females had significantly higher prevalence of anemia compared to males (54.7% vs 45.3%, P<0.0001). In subgroup analysis the 14-44 year old females had significantly higher prevalence when compared to the 45-88 year old group (56.4% vs 50.2%, P=0.04). Severe anemia (Hb <10g/dL) was observed in 325 IBD patients (17.8%; 193 CD, 132 UC). The prevalence of severe anemia was 17.9% in CD and 17.7 % in UC. The prevalence of anemia in hospitalized IBD patients (calculation for all hospitalizations, some patients with more than one hospitalization) was 71.2% (73.4% for CD, 68.6% for UC).

Characteristics of anemia (in a subgroup of patients)

Serum ferritin levels were available in 287 (15.8%) IBD patients. In these patients ACD was found in 17.6% whereas IDA or mixed anemia was found in 82.4% of the anemic patients. Definite IDA with ferritin levels <30 ng/ml was observed in 46.5% of the anemic IBD patients with ferritin levels available. No significant difference concerning the type of anemia was found in patients with early disease (duration <2 years) compared to patients with late disease (duration >2 years) (ACD in 19.7% vs 15.9 %, P=0.56). Regarding other causes of anemia over the 5 year period, folate or vitamin B12 deficiency was found in 18 (1.0%) and 34 (1.9%) cases respectively. All CD patients with history of surgery were under vitamin B12 replacement. Only one case with myelodysplastic syndrome was observed.

Risk factors

Table 3 compares biomarker levels (CRP and ESR) and clinical disease activity scores (HBI and UCAI) between IBD patients with anemia and IBD patients without anemia. CD patients with colonic disease (L2) had lower but not significantly different median Hb values compared to patients with ileal disease (L1) (12.3g/L vs 12.5g/L, P=0.33). Similarly UC

patients with extensive UC (E3) had lower median Hb levels but not significantly different compared to proctitis and left sided colitis (E1 and E2 respectively) patients (12.4 g/L vs 12.6 g/L, P=0.22).

In univariable analysis (Table 4) Hb levels were significantly positively correlated with the diagnosis (CD vs UC) and negatively correlated with female gender, CRP, ESR, HBI/UCAI, use of immunomodulators, use of biologics, and history of IBD-related operations.

Table 5 shows the factors associated with anemia in the logistic regression analysis. After adjustment, the parameters that were found to be associated with anemia in the final model were female gender (P=0.02), surgery for IBD (P<0.0001), ESR (P=0.0002), use of biologics (P=0.0001), and use of immunomodulators (P=0.0003). Multivariate analysis of only CD patients showed similar results, but also correlation of anemia with HBI (OR 1.04 95% CI:1.01-1.07, P=0.01). Multivariate analysis in UC patients showed also similar results (with the exception of surgery for IBD) and correlation of anemia with UCAI (OR 1.05 95% CI:1.01-1.08, P=0.005). When we evaluated IBD patients with active inflammation, using cut-off points for CRP 0.7 mg/dL and for ESR 20mm/h logistic regression analysis showed that anemic IBD patients were more likely to have elevated CRP (2.3 times) or elevated ESR (1.9 times). Similarly anemic CD patients were more likely to have active disease (HBI>4, 1.6 times) and anemic UC patients were more likely to have active UC (UCAI>4, 1.8 times).

Treatment of anemia

Iron replacement was administered for anemia treatment in 427 out of the 913 anemic IBD patients (46.8%). Among these patients, 390 received oral iron, whereas 37 received IV iron. In patients with severe anemia 170 out of the 325 patients (52.3%) received iron replacement (148 oral, 22 IV iron). Ferrous sulfate (the most commonly used regimen was 100 mg twice daily for 20 weeks) was used as oral iron treatment in the majority of the cases (272, 69.7%) whereas iron sucrose (in a single doses of 200 mg once a week and according to total iron deficit) was the most common form of the IV iron regimens used (25, 67.6%). These were the treatment regimens used at the time of the evaluation with the lowest Hb levels.

Discussion

In this study we found that anemia has a high 5-year period prevalence in a large cohort of IBD patients who were followed prospectively in a U.S. referral center. Over half of the IBD patients were found to have anemia at least once during their follow-up. Recent studies conducted mostly in Europe, report that the point prevalence of anemia in IBD is between 20 and 40% (10,11). However, there is no data regarding the period prevalence in large cohorts of IBD patients.

The prevalence of anemia in the U.S. IBD population is still uncertain. In two systematic reviews 6 studies from the U.S are mentioned, but they are nearly four decades old (published between 1973-1977), with small number of mainly hospitalized patients, and contain enormous heterogeneity in the definition of anemia (11,17). The reported point prevalence of anemia in these cross-sectional studies ranged between 33% and 74% (18-23). Ershler et al utilized administrative claims data (1999–2001) from a U.S. population in order

to examine the economic impact that anemia has in a retrospective cohort of patients with various underlying diseases. They reported a prevalence of anemia in IBD of 12.9% (24). No prospective data on large series of IBD patients are available. The present study is the first large, prospective cohort study conducted in the U.S showing a 5-rear period prevalence of anemia in IBD patients of 50.1%. The novelty of this study is that evaluating the prevalence of anemia over time we have a more representative picture of the burden of anemia in IBD patients.

In this study, anemia was more common in CD than in UC. This is in concordance with the majority of the previous studies and the recent meta-analysis (Table 6) (10,11). A possible explanation of this difference is that in CD patients it is not only the blood loss that causes anemia, but also other mechanisms involved such as the systemic inflammation, which is usually more severe in CD than in UC and the iron malabsorption due to the proximal GI involvement. Females in our study had significantly higher prevalence rate of anemia compared to males. The difference was more remarkable in young females which can be explained by the blood loss during menstruation.

In a subgroup of IBD patients who had ferritin levels available (15.8%) the majority of the anemic patients were found to have IDA or mixed type of anemia whereas 17.6 % of them had ACD. There was no significant difference on the type of anemia among patients with early and late disease. These results as well as previously published data indicate that iron deficiency is the most important cause of anemia in IBD patients. In a recent systematic review and meta-analysis more than half of the anemic IBD patients (57%) were found to have IDA (11).

The presence of anemia was associated with several measures of disease activity. Hb levels were significantly negatively correlated with clinical and laboratory activity indices as well as with more aggressive medical treatment with immunomodulators or biologic agents and history of surgical CD-related treatment. In the multivariate analysis ESR, CRP, HBI, UCAI, surgery for IBD, use of immunomodulators or biologics all remained significantly associated with the presence of anemia. The most important risk factors for the development of anemia in IBD in this study were the female gender, active disease and history of surgery-related to IBD (in CD). The association of anemia with the use of immunomodulators or biologics could be attributed to the fact that the use of these medications reflects a more severe disease. It has been reported that the frequency of anemia in IBD is decreasing over time after the IBD diagnosis (25). However, our study did not demonstrate any association between Hb levels and disease duration.

Treatment of anemia has been reported to be associated with significant improvement of the health-related quality of life in IBD patients (26) but its necessity is still rather underappreciated. A recent systematic review and meta-analysis showed that IV iron treatment is better tolerated and more effective than oral iron treatment for anemia in IBD (27). In the present study, more than half of IBD patients with anemia did not receive any iron supplementation for anemia despite current guidelines. Moreover, in the majority of patients who did receive iron replacement (based on ferritin levels and/or low serum iron, MCV and expanded RDW) the iron was administered orally even in the cases with severe

anemia. These findings are in agreement with other recent reports on the management of IBD patients diagnosed with anemia. A recent study from 55 German gastroenterological centers showed that only 43.5% of anemic IBD patients were treated for anemia (28). In another study from 9 European countries the majority of IBD patients with anemia were treated with oral iron (67%) whereas only 28% received IV iron (29). This data in concordance with our study indicates that in clinical practice, most IBD patients with anemia either do not receive iron supplementation or receive oral iron despite the existing evidence and the international guidelines recommending IV administration as the preferred route (12, 27, 30). We should underline however, that this study was done before the recent approval of the newer IV iron formulation (ferric carboxymaltose) in the US.

The strengths of this study are the large number of IBD patients with a longitudinal follow up allowing us to calculate the 5-year period prevalence and to analyze the characteristics of anemia in IBD. The period prevalence approach of this study may demonstrate the magnitude of the problem and the burden of anemia in IBD patients better than cross-sectional studies. There are also some limitations of the present study. The most important one is that the study was conducted in a tertiary referral center and the study population might not be representative of the general U.S. or international IBD population. Since the study was conducted in a referral center, a potential bias of selection would explain the high prevalence of anemia compared to population based studies. Ferritin levels were available only in 15.7% of the patients and the results on the type of anemia may not completely represent the total IBD population.

In conclusion, this study showed a high 5-year period prevalence of anemia in a large cohort of IBD outpatients followed prospectively in a referral center. Half of the IBD patients presented with anemia at least once during their 5-year follow-up period. Female gender, active disease and history of IBD-surgery (in CD) are the most important risk factors for the development of anemia in IBD. Finally, in the current practice it seems that anemia in IBD is undertreated.

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Table 1

Demographic and clinical characteristics of inflammatory bowel disease patients (N 1821) included in the study

Diagnosis	CD	UC
Number (%)	1077 (59.0)	744 (40.7)
Median age (years, range)	39 (17-84)	43 (15-88)
Gender (females, %)	587 (54.5)	347 (46.6)
Race (whites, %)	1045 (97.0)	716 (96.2)
Current smokers (N, %) Ex-smokers (N, %) Never smokers (N, %)	236 (21.9) 206 (19.1) 635 (58.0)	95 (12.8) 186 (25.0) 463 (62.2)
Median disease duration (years, range)	12 (0-63)	10 (0-70)
Montreal classification for UC		
Proctitis (E1,N, %)		87 (11.7)
Left sided colitis (E2, N, %)		296 (39.8)
Extensive colitis (E3, N, %)		361 (48.5)
Montreal classification for CD		
Inflammatory (B1, N,%)	229 (21.3)	
Stricturing (B2, N,%)	547 (50.8)	
Penetrating (B3, N,%)	301 (27.9)	
Perianal (p, N,%)	252 (23.4)	
Ileal (L1, N,%)	251 (23.3)	
Colonic (L2, N,%)	224 (20.8)	
Ileocolonic (L3, N,%)	602 (55.9)	
Upper GI (L4, N,%)	76 (7.1)	
Surgery for IBD (N, %)	577 (53.6)	188 (25.3)
Use of immunomodulators (N, %)	483 (44.8)	227 (30.5)
Use of biologics (N, %)	293 (27.2)	80 (10.8)

CD, Crohn’s disease; IBD, inflammatory bowel disease; UC, ulcerative colitis

Table 2

Main laboratory data and disease activity scores of Crohn's disease and ulcerative colitis patients included in the study (evaluated at the time of lowest Hb levels)

Diagnosis	**CD**	**UC**	***P* value**
Median Hb (g/dL IQR)	12.1 (10.5-13.5)	12.5 (10.8-13.8)	0.002
Median CRP (mg/L, IQR)	0.42 (0.13-1.08)	0.33 (0.11-0.84)	0.29
Median ESR (1st h, IQR)	10 (6.0-17.0)	10 (6-19)	0.93
Median ferritin (ng/ml, IQR, results in 287 patients)	40.0 (14,3-67.8)	23.5 (13.8-70.0)	0.34
Median HBI (IQR)	4 (1-7)	--	--
Median UCAI (IQR)	--	3 (1-7)	--

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; Hb, hemoglobin, IQR: interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw index; UCAI, ulcerative colitis activity index

Table 3

Serum biomarkers and clinical disease activity indices in inflammatory bowel disease patients with anemia compared to those without anemia.

	IBD patients with anemia	IBD patients without anemia	*P* value
Median CRP (mg/L, IQR)	0.5 (0.2-1.7)	0.2 (0.1-0.6)	<0.0001
Median ESR (1st h, IQR)	12 (7-21)	8 (5-15)	<0.0001
Median HBI (for CD, IQR)	4 (2-8)	3 (1-6)	<0.0001
Median UCAI (for UC, IQR)	4 (1-10)	2 (0-5)	<0.0001

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; CRP, C-reactive protein; IQR: interquartile range; ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw index; UCAI, ulcerative colitis activity index

Table 4

Univariate logistic regression analysis demonstrating the relationship of anemia and selected characteristics of the inflammatory bowel disease patients

Characteristic	OR (95% CI)	*P*
Diagnosis (CD)	0.74 (0.62-0.88)	0.006
Age	0.99 (0.99-1.01)	0.75
Female gender	0.76 (0.63-0.91)	0.003
Disease duration	1.01 (0.99-1.02)	0.31
CRP	1.37 (1.26-1.49)	<0.0001
ESR	1.03 (1.02-1.04)	<0.0001
HBI	1.07 (1.04-1.10)	<0.0001
UCAI	1.07 (1.04-1.10)	<0.0001
Use of immunomodulators	1.51 (1.24-1.82)	<0.0001
Use of biologics	2.00(1.58-2.52)	<0.0001
Surgery for IBD	2.77 (2.28-3.35)	<0.0001

OD, odds ratio; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; HBI, Harvey-Bradshaw index; UCAI, ulcerative colitis activity index

Table 5

Determinants of anemia in inflammatory bowel disease patients in the multivariate logistic regression analysis

Variable	OR (95% CI)	*P*
Diagnosis	1.10 (0.89-1.37)	0.36
Female gender	1.29 (1.04-1.61)	0.02
CRP	1.26 (1.16-1.37)	<0.0001
ESR	1.02 (1.01-1.03)	0.0002
Use of immunomodulators	1.51 (1.21-1.87)	0.0003
Use of biologics	1.71 (1.31-2.24)	0.0001
History of surgery for IBD	2.77 (2.21-3.48)	<0.0001

OD, odds ratio; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease

Table 6

Prevalence of anemia in inflammatory bowel disease adult patients; results of recent studies using the World Health Organization criteria

Authors/year	Country	n	Diagnosis	Design	Prevalence (%)
Goodhand et al 2012 (6)	UK	124	IBD	Cross-sectional observational study of outpatients	40
Voegtlin et al 2010 (7)	Switzerland	241	IBD	Cross-sectional	21.2
Bager et al 2013 (8)	Six Scandinavian centers	300	IBD	longitudinal follow-up study	54.3***
Filmann et al 2014 (11)	5 European countries	2192	IBD CD UC	Metaanalysis	24 27 21
Høivik et al 2014 (4)	Norway	756	CD UC	Population based	48.8 20.2
Sjöberg et al 2014 (9)	Sweden	749	IBD CD UC	Population based	30 42 24
Koutroubakis et al 2015*	USA	1821	IBD CD UC	Registry study of outpatients	50.1** 53.3 44.7

*The present study;

**5-year period prevalence

***2-year period prevalence CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease