Persistent or Recurrent Anemia Is Associated With Severe and Disabling Inflammatory Bowel Disease

Ioannis E. Koutroubakis, Claudia Ramos–Rivers, Miguel Regueiro, Efstratios Koutroumpakis, Benjamin Click, Robert E. Schoen, Jana G. Hashash, Marc Schwartz, Jason Swoger, Leonard Baidoo, Arthur Barrie, Michael A. Dunn, and David G. Binion

Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

BACKGROUND & AIMS: **Anemia is a common manifestation of inflammatory bowel disease (IBD) that can greatly affect patients' quality of life. We performed a prospective study of a large cohort of patients with IBD to determine if patterns of anemia over time are associated with aggressive or disabling disease.**

METHODS: **We performed a longitudinal analysis of demographic, clinical, laboratory, and treatment data from a registry of patients with IBD at the University of Pittsburgh Medical Center from 2009 through 2013. Patients with a complete follow-up evaluation (at least 1 annual visit with laboratory results) were included. Anemia was defined by World Health Organization criteria. Disease activity scores (the Harvey–Bradshaw Index or the ulcerative colitis activity index) and quality-of-life scores (based on the short IBD questionnaire) were determined at each visit; laboratory data, including levels of C-reactive protein and erythrocyte sedimentation rates, as well as patterns of IBD-related health care use, were analyzed.**

RESULTS: **A total of 410 IBD patients (245 with Crohn's disease, 165 with ulcerative colitis; 50.5% female) were included. The prevalence of anemia in patients with IBD was 37.1% in 2009 and 33.2% in 2013. Patients with IBD and anemia required significantly more health care and had higher indices of disease activity, as well as a lower average quality of life, than patients without anemia ($P < .0001$). Anemia (persistent or recurrent) for 3 or more years was correlated independently with hospitalizations ($P < .01$), visits to gastroenterology clinics ($P < .001$), telephone calls ($P < .004$), surgeries for IBD ($P = .01$), higher levels of C-reactive protein (in patients with ulcerative colitis, $P = .001$), and a higher erythrocyte sedimentation rate ($P < .0001$). Anemia was correlated negatively with quality-of-life scores ($P < .03$).**

CONCLUSIONS: **Based on a longitudinal analysis of 410 patients, persistent or recurrent anemia correlates with more aggressive or disabling disease in patients with IBD.**

Keywords: Quality of Life; C-Reactive Protein; Erythrocyte Sedimentation Rate; Crohn's Disease; Ulcerative Colitis.

See editorial on page 1767.

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders characterized by a variable clinical course. CD often has a progressive pattern from inflammatory to more complicated disease with stenoses or fistulae.[1] UC may become more extensive with time, increasing the possibility of colectomy or cancer.[2] IBD patients who manifest an aggressive disease course characterized by frequent relapses, persistent inflammatory activity, a need for intensified medical treatment, and/or surgical management recently were defined as having severe or disabling disease.[3]

There is a lack of reliable and universally accepted biomarkers that predict the disease course in IBD. Moreover, the assessment of disease activity in IBD is difficult.[4,5] Concerning the use of biomarkers in the management and prognosis of IBD, C-reactive protein

Abbreviations used in this paper: **CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; Hb, hemoglobin; HBI, Harvey–Bradshaw index; IBD, inflammatory bowel disease; IV, intravenous; OR, odds ratio; SIBDQ, short inflammatory bowel disease questionnaire; UC, ulcerative colitis; UCAI, ulcerative colitis activity index.**

Most current article

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2015.03.029

(CRP) and fecal calprotectin are the most widely used, but both have several limitations and are far from ideal. Because of the shortcomings of clinical and biochemical indices, endoscopic evaluation and assessment of mucosal healing is becoming increasingly important in the clinical management of IBD patients.[6]

Anemia is an important complication and/or extraintestinal manifestation of IBD, which is present in one third of the IBD patients, resulting in a significant impact on their quality of life. Several recent studies have focused on the prevalence, pathophysiology, and treatment of anemia in IBD[7–11]; however, the data on anemia and its course over time in the outpatient clinic setting as a potential marker of disabling disease are limited. A recent study of 62 uncomplicated CD patients showed that low hemoglobin or hematocrit levels were independent predictors of the first complication or CD-related surgery.[12] Persistent anemia is common in IBD,[13] but its potential role in disease stratification is unknown.

The aim of this study was to investigate if the presence and duration of anemia in IBD patients followed up longitudinally correlated with a clinical pattern of aggressive/disabling disease.

Patients and Methods

The characteristics of the consented, prospective, longitudinal, natural history registry of patients with IBD at the University of Pittsburgh Medical Center have been described previously.[14] In addition to demographic information, the registry houses temporally organized prescription, endoscopic, pathologic, radiologic, laboratory, and other clinical data regarding health care use of enrolled patients and is updated routinely through Information Technology support. De-identified longitudinal data were used in the analysis from patients with a definitive IBD diagnosis according to established criteria. Patients who were seen during the 5-year period from January 1, 2009, to December 31, 2013, and who had complete follow-up evaluation, defined as at least 1 annual visit during this period with laboratory evaluations, were included. Demographic, clinical, and laboratory data prospectively collected from clinic visits and information from electronic medical record–based computer searches and manual confirmation of information were recorded. Complete blood count data, disease activity scores, biochemical markers of inflammation and anemia, and patterns of medication use were monitored prospectively in all patients. Patterns of health care use such as emergency department (ED) or GI clinic visits, telephone calls to the IBD office, and hospitalizations also were recorded prospectively. Disease location and behavior in CD and extent of bowel involvement in UC was classified according to the Montreal classification.[15] The disease activity also was evaluated prospectively using clinical activity scores such as the Harvey–Bradshaw index (HBI) for CD[16] and the ulcerative colitis activity index (UCAI) for UC.[17] Prospectively collected health-related quality of life, as measured by the validated short IBD questionnaire (SIBDQ),[18] also was analyzed. The average scores of the HBI, UCAI, and SIBDQ, as well as the CRP and erythrocyte sedimentation rate (ESR) 5-year measurements, were calculated and used in the analysis.

Anemia was defined as a hemoglobin (Hb) level less than 13 g/dL in men and a Hb level less than 12 g/dL in nonpregnant women based on World Health Organization criteria.[19] IBD patients were divided into 3 groups: patients without anemia (group A), patients with anemia for 1 or 2 (consecutive or not) years (group B), and patients with anemia for 3 (consecutive or not) or more years (group C). Persistent anemia was considered the absence of hematopoietic response (normal Hb level) after treatment, and recurrent anemia was considered the response to treatment followed by a decrease of Hb level. Patients with other important diseases that may manifest with anemia such as renal or heart failure, cirrhosis, and malignancies were excluded from the analysis. Information on possible iron supplementation for anemic patients was characterized using electronic records. Proportions of patients treated for anemia at the time of the evaluation with oral or intravenous (IV) iron were recorded.

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

Statistical Analysis

Data are presented either as means $\pm$ SD for continuous, normally distributed variables, or as medians and range for nonparametric data. The Kolmogorov–Smirnov test was used to evaluate distribution normality. Differences between groups were evaluated using the Student t test for parametric continuous data and the Mann–Whitney U test for nonparametric continuous data. Data from contingency tables were analyzed using chi-squared analysis. Correlation with Spearman rho (r) was used for assessing the relationship between anemia status and biomarkers or disease activity indices. A logistic regression analysis was used to adjust for potential confounders. In the final model, the dependent variable was the presence of persistent anemia, and the covariates were those with significance less than 0.1 in the univariate analysis. P values less than .05 were considered statistically significant.

Results

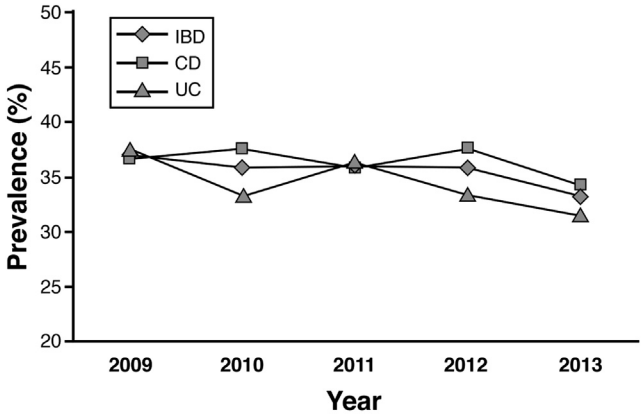
A total of 421 IBD patients met the inclusion criteria of complete follow-up evaluation with at least 1 annual visit including complete blood count and biomarker (CRP and ESR) evaluation. Eleven cases were excluded owing to uncertain IBD diagnosis or because of the presence of other diseases related to the manifestation of anemia. In the final study population there were 245 patients with

CD and 165 patients with UC. The demographic and clinical data of the IBD patients included in the study are presented in Table 1.

The prevalence of anemia was 37.1% (CD, 36.7%; UC, 37.6%) in 2009, with a small decrease in 2013 to 33.2% (CD, 34.3%; UC, 31.5%). The prevalence of anemia per year in IBD patients is presented in Figure 1. No significant differences between CD and UC or the time periods of the study concerning the prevalence of anemia were found ($P > .05$). The burden of anemia as expressed by years with anemia of the IBD patients is presented in Figure 2. A total of 137 IBD patients (33.4%) were without anemia at any time (group A), 140 IBD patients (34.1%) had anemia for 1 to 2 years (group B), and 133 patients (32.5%) had anemia for 3 or more years (group C). The median number of measurements with a normal Hb value was 12 (range, 5–48) in group A, 11 (range, 3–36) in group B, and 9 (range, 0–29) in group C. The median number of Hb measurements with low values were 0 in group A, 2 (range, 1–17) in group B, and 12 (range, 3–150) in group C. Among patients in group C, 30 (23.6%) had persistent anemia (no measurement with normal Hb) and 103 (77.4%) had recurrent anemia (measurements with low and normal Hb level). Twenty-four patients (80%) with persistent anemia and 78 patients (75.7%) with recurrent anemia had active disease (HBI or UCAI > 4). Iron supplementation at any time was administered to 167 patients (131 oral, 36 IV). Folate or vitamin B12 deficiency was found in 4 and 7 cases with anemia, respectively. CD patients with a history of surgery (149) were receiving vitamin B12 replacement. No cases with myelodysplastic syndrome were observed.

Table 1. Demographic and Clinical Characteristics of Inflammatory Bowel Disease Patients Included in the Study

Diagnosis	CD	UC	Total IBD
Patients, n (%)	245 (59.8)	165 (40.2)	410 (100)
Median age, *y* (range)	39 (17–79)	43 (15–83)	40 (15–83)
Female sex, n (%)	137 (55.9)	70 (42.4)	207 (50.5)
Smoking, yes, n (%)	102 (41.6)	63 (38.2)	165 (40.2)
Median disease duration, *y* (range)	13 (0–63)	10 (0–70)	11 (0–70)
Montreal classification for UC			
Proctitis, E1, n (%)		14 (8.6)	
Left-sided colitis, E2, n (%)		59 (35.6)	
Extensive colitis, E3, n (%)		92 (55.8)	
Montreal classification for CD			
Inflammatory, B1, n (%)	99 (40.4)		
Stricturing, B2, n (%)	92 (37.6)		
Penetrating, B3, n (%)	54 (22.0)		
Perianal, p, n (%)	57 (23.3)		
Ileum, L1, n (%)	58 (23.7)		
Colon, L2, n (%)	49 (20.0)		
Ileocolon, L3, n (%)	132 (53.9)		
Upper GI, L4, n (%)	6 (2.4)		
Use of immunomodulators, n (%)	113 (46.1)	53 (32.1)	166 (40.0)
Use of biologics, n (%)	94 (38.4)	20 (12.1)	114 (27.8)
History of surgery for IBD, n (%)	149 (60.8)	46 (27.9)	195 (47.6)



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

Figure 1. Prevalence of anemia in inflammatory bowel disease patients over the 5-year period.

IBD patients without anemia during the 5 years were found to have significantly lower clinical or biochemical activity scores (average values for the 5 years), and lower rates of health care use (ED or GI clinic visits, telephone calls, and hospitalizations), as well as a higher SIBDQ score compared with patients with anemia (for all parameters, $P < .0001$). IBD patients from group C had significantly higher clinical or biochemical activity scores (average values for the 5 years), and higher rates of health care use (ED or GI clinic visits, telephone calls, and hospitalizations), as well as a lower SIBDQ score compared with patients from groups A and B (Table 2). The prevalence of complicated disease (stricturing or penetrating) was higher in CD patients from groups C (61.7%) and B (58.9%) compared with CD patients from group A (48.6%), but the difference was not statistically significant ($P = .07$). The prevalence of extensive UC was significantly higher in group C (58.5%) compared with groups A (38.3%) and B (37.9%) ($P = .004$).

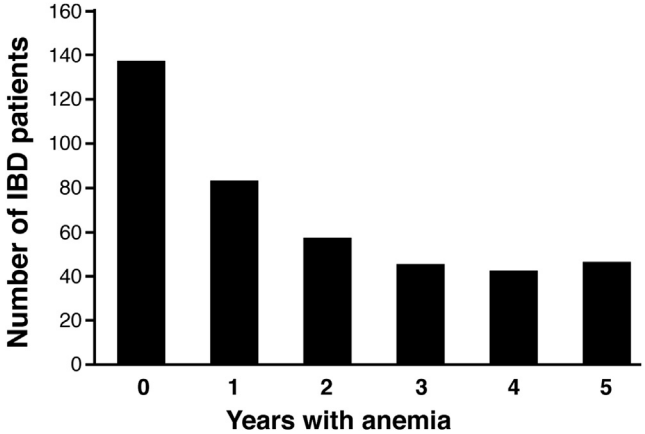


Figure 2. The burden of anemia, as expressed by years with anemia, of the inflammatory bowel disease patients included in the study.

Table 2. Activity Indices, Quality-of-Life Scores, and Health Care Use in Inflammatory Bowel Disease Patients in Relation to Anemia Status

Parameter	Group A[a]	Group B[b]	Group C[c]	*P* value
5-year average CRP, median, *mg/L* (range)	0.2 (0.02–5.2)	0.5 (0.02–9.5)	1.1 (0.02–23.5)	<.001
5-year average ESR, mean ± SD, *mm/h*	14.7 ± 8.5	18.8 ±12.0	34.1 ± 20.8	<.0001
5-year average HBI for CD, median (range)	2.0 (0–17)	3.3 (0–23)	5.7 (0.4–21.8)	<.001
5-year average UCAI for UC, median (range)	1.7 (0–13)	3.0 (0–13)	5.3 (0–28)	.001
5-year average SIBDQ, median (range)	58 (22.7–69.8)	52.4 (26.5–70)	47.2 (18.2–67.3)	<.001
Telephone calls, median (range)	13 (0–95)	17 (0–157)	28 (0–288)	<.001
Emergency department visits, median (range)	0 (0–52)	1 (0–79)	4 (0–78)	<.0001
GI department visits, median (range)	8 (0–29)	11 (0–81)	12 (0–107)	<.001
Hospitalizations, median (range)	0 (0–7)	1 (0–27)	3 (0–27)	<.0001

[a]Patients without anemia.
[b]Patients with anemia for 1–2 years.
[c]Patients with anemia for ≥3 years.

Concerning the use of IBD medications, patients from group C had significantly lower use of thiopurines (azathioprine or mercaptopurine) compared with group A patients ($P = .008$), but the use of methotrexate or biologic agents was similar among groups (Table 3). In 7 cases (5 CD, 2 UC) with persistent anemia, erythropoietic growth factors (2 epoetin alfa, 5 darbepoetin alfa) also were administered. Blood transfusions occurred rarely (4% of the patients) and were given in cases with a Hb less than 7 g/dL (17 patients: 5 in group B and 12 in group C).

In the Spearman correlation the anemia status of the IBD patients was correlated significantly with the CRP level ($r = 0.37$; $P < .0001$), ESR ($r = 0.46$; $P < .0001$), SIBDQ ($r = -0.29$; $P < .0001$), ED ($r = 0.41$; $P < .0001$) or GI clinic ($r = 0.13$; $P = .007$) visits, telephone calls ($r = 0.26$; $P < .0001$), hospitalizations ($r = 0.49$; $P < .0001$), and history of a surgery for IBD ($r = 0.25$; $P < .0001$). Anemia status also was correlated significantly with HBI ($r = 0.32$; $P < .0001$) in CD patients and with UCAI ($r = 0.34$; $P < .0001$) in UC patients. No association with diagnosis (CD vs UC), sex, smoking status, or disease duration was found ($P > .05$).

Table 4 shows the factors associated with persistent/recurrent anemia in the logistic regression analysis. After adjustment, the parameters that were found to be associated with persistent/recurrent anemia in the final model were ESR ($P < .0001$), SIBDQ ($P = .03$), GI clinic visits ($P = .001$), telephone calls ($P = .004$), hospitalizations ($P = .01$), and surgery for IBD ($P = .01$). Logistic regression analysis of only CD patients showed similar results but in contrast to univariate analysis showed no correlation of persistent/recurrent anemia with HBI (odds ratio [OR], 1.04; 95% confidence interval [CI], 0.94–1.15; $P = .38$). Logistic regression analysis in UC patients showed further significant correlation of persistent/recurrent anemia with UCAI (OR, 1.22; 95% CI, 1.03–1.44; $P = .002$) and with CRP level (OR, 2.54; 95% CI, 1.31–4.92; $P = .006$).

Table 3. Use of Medications and History of Surgeries in Inflammatory Bowel Disease Patients in Relation to Anemia Status During the Evaluation

Medication	Group A[a]	Group B[b]	Group C[c]	*P* value
Azathioprine or mercaptopurine, n (%)	57 (41.6)	47 (33.6)	34 (25.6)	.008[d]
Methotrexate, n (%)	6 (4.4)	13 (9.3)	13 (9.8)	.14
Biologics, n (%)	32 (23.4)	45 (32.1)	37 (27.8)	.48
Oral iron, n (%)	5 (3.6)	10 (7.1)	20 (15.0)	.002[d]
IV iron, n (%)	0 (0)	4 (2.9)	10 (7.5)	.003[d]
History of IBD surgery, n (%)	39 (28.5)	74 (52.9)	82 (61.6)	<.0001[d]

[a]Patients without anemia.
[b]Patients with anemia for 1–2 years.
[c]Patients with anemia for ≥3 years.
[d]Group A vs group C.

Discussion

In this study we found that patients with IBD and anemia and particularly those with persistent or recurrent anemia required significantly more health care and had higher indices of disease activity, as well as lower average quality of life, than patients without anemia.

Table 4. Determinants of Persistent/Recurrent Anemia in Inflammatory Bowel Disease Patients in the Adjusted Analysis

Independent variables	OR (95% CI)	*P*
CRP level, *mg/L*	1.08 (0.88–1.33)	.45
ESR level, *mm/h*	1.08 (1.06–1.11)	<.0001
SIBDQ	0.97 (0.94–0.99)	.03
ED visits	0.99 (0.93–1.05)	.73
GI clinic visits	0.93 (0.89–0.97)	.001
Telephone calls	1.02 (1.01–1.04)	.004
Hospitalizations	1.20 (1.04–1.39)	.01
History of surgery for IBD	2.15 (1.17–3.98)	.01

The prevalence of anemia in IBD according to systematic reviews ranges from 6% to 74%.[9,20] A recent meta-analysis of European studies showed an overall anemia prevalence of 27% for CD and 21% for UC.[11] Two recent Scandinavian studies showed a significant decrease of the prevalence of anemia in IBD during the disease course.[21,22] In contrast, Wiskin et al[13] showed that 30% of pediatric IBD patients had persistent anemia 2 years after diagnosis.

Our study showed that one third of IBD patients had anemia at any time during the study period. These prevalence rates are similar to previous reports, but in marked contrast we found only a small decrease in the prevalence of anemia in IBD patients over time (37.1% in 2009 and 33.2% in 2013), despite IBD treatment and iron supplementation. IBD-related therapy was not significantly different in patients with anemia compared with those without anemia with the exception of thiopurines. The more frequent use of thiopurines in patients without anemia compared with patients with anemia may be related to differences in the tolerability of these medications in patients with anemia.

Several clinical and serologic markers have been investigated extensively in IBD for disease stratification, diagnostic association, and, to a lesser degree, for disease prognostication. Although red cell parameters have been linked to the diagnosis of anemia or to IBD activity,[23] little attention has been given to the presence of anemia as a marker of disease severity or disease course prediction. Rieder et al[12] recently showed that the presence of anemia in CD patients could serve as an independent predictor of disease-related complications or surgeries. Our study showed that anemia is correlated significantly with disease severity and outcome. The presence of persistent/recurrent anemia was found to be associated significantly with all the examined parameters of IBD-related health care use. There is evidence that IBD patients with disabling disease have significantly higher health care use and cost compared with IBD patients with mild disease or those in remission.[14,24,25] We also found a significant association between anemia status and disease activity measured by clinical activity indices (HBI or UCAI) and biochemical markers (CRP and ESR). The presence of persistent/recurrent anemia was correlated significantly with all of these parameters in the univariable analysis. However, in the multivariable analysis the statistical significance remained only for ESR. Multivariate analysis in UC patients showed significant correlation of persistent/recurrent anemia with UCAI and CRP whereas in CD no significant association between persistent/recurrent anemia and HBI or CRP was found. These rather unexpected differences between UC and CD could be related to variations in the type of anemia (iron deficiency vs anemia of chronic disease), which unfortunately we were not able to investigate more thoroughly in the present study. The higher rates of IBD-related surgeries in CD, which often include small-bowel resection, also could contribute to the difference between UC and CD. Persistent/recurrent anemia was found in our study to be associated significantly with a history of IBD-related surgeries, which are known to be more common in patients with severe disease. Finally, we found that in our study population, IBD patients with anemia had significantly decreased quality-of-life scores as measured by the SIBDQ compared with patients without anemia. The presence of persistent/recurrent anemia independently was correlated negatively with the mean SIBDQ. Several previous studies already have established that disease severity is a major factor in the reduction of quality of life among IBD patients.[24–26]

Our results also suggest that anti-TNF therapy, despite its significant beneficial effects on disease activity and clinical outcomes, has only a modest effect on anemia. Data on the therapeutic effect of anti-TNF treatment on anemia in IBD patients are limited. A recent pediatric study in accordance with our results showed no significant differences in Hb levels between responders and nonresponders to anti-TNF treatment.[27] Moreover, we recently showed that anemia in IBD patients who are receiving anti-TNF treatment often persists and remains a significant manifestation of IBD even after 1 year of treatment.[28]

The suggested criteria for the definition for disabling disease in IBD include hospitalization for flare-up or complications, presence of disabling chronic symptoms, need for immunosuppressive therapy or intestinal resection, or perianal surgery.[3] The present study showed that persistent/recurrent anemia independently is correlated significantly with parameters considered characteristics of disabling disease such as hospitalizations, continued active disease, and IBD-related surgeries. Based on these results, the presence of persistent/recurrent anemia could be considered to be associated with disabling disease and probably as an important parameter in therapeutic decisions for IBD patients. Disabling disease is certainly the result of active and complicated IBD, but according to our findings the presence of anemia and especially of persistent/recurrent anemia could serve as a marker for the appropriate management, possibly preventing a disabling course. Our results also emphasize that anemia should not be neglected in the general management of IBD patients and the appropriate treatment for anemia should be administered. We also found that IBD patients with persistent/recurrent anemia more often have active, extensive, and complicated disease, obviously as a secondary manifestation. Based on these observational data we cannot support that treatment of anemia alone has any potential independent influence on the disease course, but future prospective case-controlled studies are needed. IBD patients with persistent anemia should have a complete evaluation to characterize the type of anemia and exclude other causes of anemia. First-line treatment in these cases should be IV iron replacement followed by erythropoiesis-stimulating agents in patients with persistent anemia and characteristics of anemia of chronic disease.

This study had several strengths but it also had some limitations. First, the study was conducted in a tertiary center and the study population might not be representative of the overall US or international IBD general population. Biases related to the referral centers and selection of more severe IBD patients could be involved. Second, the absence of enough data on the iron status of IBD patients did not permit investigation of possible differences concerning the type of anemia or to clarify how many patients have characteristics of anemia of chronic disease, which is useful information for their treatment.

In summary, anemia status in IBD patients may serve as a biomarker for assessment of disease severity and may be predictive of clinical outcome. The presence of persistent/recurrent anemia in IBD is correlated independently with parameters associated with disabling disease and with worse health-related quality of life. Persistent/recurrent anemia for 3 or more years could be used as an objective marker of disabling disease in IBD, helping to identify patients who need more aggressive management. Future studies in other tertiary or population-based cohorts should validate these results.

References

1. Munkholm P, Langholz E, Davidsen M, et al. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995;30:699–706.
2. Langholz E, Munkholm P, Davidsen M, et al. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994;107:3–11.
3. Blonski W, Buchner AM, Lichtenstein GR. Clinical predictors of aggressive/disabling disease: ulcerative colitis and Crohn disease. Gastroenterol Clin North Am 2012;41:443–462.
4. Levesque BG, Sandborn WJ, Ruel J, et al. Converging goals of treatment for inflammatory bowel disease, from clinical trials and practice. Gastroenterology 2015;148:37–51.
5. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007; 132:763–786.
6. Walsh A, Palmer R, Travis S. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. Gastrointest Endosc Clin N Am 2014; 24:367–378.
7. Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. Ann Gastroenterol 2013;26:104–113.
8. Oustamanolakis P, Koutroubakis IE, Kouroumalis EA. Diagnosing anemia in inflammatory bowel disease: beyond the established markers. J Crohns Colitis 2011;5:381–391.
9. Kulnigg S, Gasche C. Systematic review: managing anemia in Crohn's disease. Aliment Pharmacol Ther 2006;24:1507–1523.
10. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis 2007;13:1545–1553.
11. Filmann N, Rey J, Schneeweiss S, et al. Prevalence of anemia in inflammatory bowel diseases in European countries: a systematic review and individual patient data meta-analysis. Inflamm Bowel Dis 2014;20:936–945.
12. Rieder F, Paul G, Schnoy E, et al. Hemoglobin and hematocrit levels in the prediction of complicated Crohn's disease behavior – a cohort study. PLoS One 2014;9:e104706.
13. Wiskin AE, Fleming BJ, Wootton SA, et al. Anaemia and iron deficiency in children with inflammatory bowel disease. J Crohns Colitis 2012;6:687–691.
14. Ramos-Rivers C, Regueiro M, Vargas EJ, et al. Association between telephone activity and features of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2014; 12:986–994.
15. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19(Suppl A):5–36.
16. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1:514.
17. Kozarek RA, Patterson DJ, Gelfand MD, et al. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. Ann Intern Med 1989;110:353–356.
18. Jowett SL, Seal CJ, Barton JR, et al. The short inflammatory bowel disease questionnaire is reliable and responsive to clinically important change in ulcerative colitis. Am J Gastroenterol 2001;96:2921–2928.
19. World Health Organization, UNICEF, UNU. Iron deficiency anemia: assessment, prevention and control. Report of a joint WHO/UNICEF/UNU consultation. Geneva, Switzerland: World Health Organization, 1998.
20. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. Am J Med 2004;116(Suppl 7A):44S–49S.
21. Høivik ML, Reinisch W, Cvancarova M, et al. Anaemia in inflammatory bowel disease: a population-based 10-year follow-up. Aliment Pharmacol Ther 2014;39:69–76.
22. Sjöberg D, Holmström T, Larsson M, et al. Anemia in a population-based IBD cohort (ICURE): still high prevalence after 1 year, especially among pediatric patients. Inflamm Bowel Dis 2014;20:2266–2270.
23. Oustamanolakis P, Koutroubakis IE, Messaritakis I, et al. Measurement of reticulocyte and red blood cell indices in the evaluation of anemia in inflammatory bowel disease. J Crohns Colitis 2011;5:295–300.
24. Gibson PR, Weston AR, Shann A, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. J Gastroenterol Hepatol 2007;22:1306–1312.
25. Gibson PR, Vaizey C, Black CM, et al. Relationship between disease severity and quality of life and assessment of health care utilization and cost for ulcerative colitis in Australia: a cross-sectional, observational study. J Crohn's Colitis 2014; 8:598–606.
26. Kalafateli M, Triantos C, Theocharis G, et al. Health-related quality of life in patients with inflammatory bowel disease: a single-center experience. Ann Gastroenterol 2013;26: 243–248.
27. Assa A, Hartman C, Weiss B, et al. Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. J Crohns Colitis 2013;7:369–376.
28. Koutroubakis IE, Ramos–Rivers C, Regueiro M, et al. The influence of anti-TNF agents on hemoglobin levels of patients with inflammatory bowel disease. Inflamm Bowel Dis 2015;21:1587–1593.

Reprint requests
Address requests for reprints to: David G. Binion, MD, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, 200 Lothrop Street, Presbyterian University Hospital Mezzanine Level, C Wing, Pittsburgh, Pennsylvania 15213. e-mail: binion@pitt.edu; fax: (412) 648-9378.

Conflicts of interest
These authors disclose the following: Ioannis Koutroubakis has served on the consulting/advisory boards for AbbVie and MSD; Miguel Regueiro has served as a consultant for AbbVie, Janssen, Shire, Takeda, and UCB; and David Binion has served on the consulting/advisory boards for AbbVie, Janssen, Cubist, Salix, UCB Pharma, and has received financial support from Janssen. The remaining authors disclose no conflicts.

Funding
Supported by a sabbatical salary from the Medical Faculty, University of Crete, Greece (I.K.), a National Institute for Diabetes and Digestive and Kidney Diseases grant (5T32DK063922-10 to B.C.), and by grant W81XWH-11-2-0133 from the US Army Medical Research and Material Command (M.D. and D.G.B.).