Anemia in a Population-based IBD Cohort (ICURE): Still High Prevalence After 1 Year, Especially Among Pediatric Patients

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Background: Prevalence of anemia in patients with inflammatory bowel disease (IBD) is uncertain because of scarcity of population-based studies. The aim of this study was to evaluate prevalence of anemia in a population-based cohort of newly diagnosed patients with IBD to identify risk factors for anemia and to describe contemporary anemia-specific treatment during the first year.

Methods: All patients with ulcerative colitis or Crohn's disease in the IBD Cohort of Uppsala Region cohort (n = 790) and hemoglobin levels at the time of diagnosis were eligible for inclusion. The WHO definition of anemia was used.

Results: Seven hundred forty-nine (95%) of the patients with IBD were included. Five hundred eighty of 749 (77%) patients had measured hemoglobin levels at 12-month follow-up. The prevalence of anemia at the time of diagnosis was 227/749 (30%). After 1 year, it was 102/580 (18%). Anemia was more common among newly diagnosed patients with Crohn's disease compared with ulcerative colitis (42% versus 24%, $P < 0.0001$), but after 1 year, there was no difference (18% versus 18%, P = NS). Children had more often anemia compared with adults, both at diagnosis and after 1 year (diagnosis: 55% versus 27%, $P < 0.0001$; follow-up: 28% versus 16%, $P < 0.05$). Anemia was associated with colonic engagement in Crohn's disease and the extent of inflammation in ulcerative colitis. Only 46% of patients with anemia were treated with iron supplementation or blood transfusion.

Conclusions: The overall prevalence of anemia in patients with IBD at the time of diagnosis was high. A large proportion was still anemic after 1 year. Children were more at risk compared with adults. More efforts are needed to treat patients with anemia.

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Key Words: anemia, inflammatory bowel disease, Crohn's disease, ulcerative colitis, epidemiology

Anemia is an early symptom of inflammatory bowel disease (IBD), not merely a complication.[1,2] Despite increased focus on identifying anemia and treating it with better disease control and iron supplementary treatment, the prevalence in the IBD group is still uncertain. Previous studies reports disparate prevalence from 6% to 74%, mainly because of the different patient materials included.[1,3–7] High prevalence was frequently seen in hospitalized patients or at referral centers, whereas cross-sectional studies at outpatient clinics reported lower prevalence. The definition of anemia also varied between different studies. To the best of our knowledge, only a few previous population-based study including children and adults have reported on prevalence of anemia at diagnosis and follow-up.[8,9]

The aim of this study was to evaluate the prevalence of anemia in a population-based cohort of newly diagnosed patients with IBD and to identify risk factors for maintaining or developing anemia and to describe contemporary treatment practice during the first year when intravenous iron supplementation is available.[10]

MATERIALS AND METHODS

Six hospitals participated in the ICURE study (the IBD Cohort of Uppsala Region). In Uppsala County, all patients with IBD were prospectively identified during 2005–2009 and in the remaining 3 counties (Dalarna, Södermanland, and Åland) during 2007–2009. The mean population in the study region was 305,381 in 2005–2006 and 642,117 in 2007–2009. A total of 790 patients were diagnosed with either ulcerative colitis (UC, n = 526) or Crohn's disease (CD, n = 264) resulting in an average incidence of 20.0/1,00,000 per year for UC and 9.9/1,00,000 per year for CD, age-adjusted for the Swedish population.[11,12]

In this study, all UC and CD patients in the ICURE study with measured hemoglobin (Hb) levels within 3 months before or at the time of diagnosis, but before treatment, were eligible for inclusion in group 1. From the patients in group 1, all patients with Hb levels both at diagnosis and after 12 ± 3 months were

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included in group 2. If there were more than 1 measured Hb level in the time period, the Hb closest to the time of diagnosis and the 12-month follow-up was chosen.

The WHO definition of anemia was used in the study (children 0–4 yr: Hb < 110 g/L; 5–11 yr: Hb < 115 g/L; 12–14 yr: Hb < 120 g/L, women ≥15 yr: Hb < 120 g/L, and men ≥15 yr: Hb < 130 g/L).[13] An Hb level <100 g/L was considered as severe anemia, regardless of age or gender. An Hb level consistent with anemia but ≥100 g/L was considered as moderate anemia. Data regarding Montreal classification,[14] treatment, and laboratory findings were collected.

Statistics

All data analysis were performed using the software STATISTICA (version 10; 2011; StatSoft Inc., Tulsa, OK; http://www.statsoft.com). Depending on the characteristics of the data, continuous variables are presented as means and SDs or medians and interquartile range.

Differences between groups were evaluated using Student's *t* test for parametric continuous data (age, hemoglobin levels, and change in hemoglobin levels) and Mann–Whitney U test for nonparametric continuous data (CRP). Data from contingency tables were analyzed using χ^2 test or Fisher's exact *P* test for tables with

TABLE 1. Demographics at Diagnosis

	UC (n = 495), n (%)	CD (n = 254), n (%)	*P*
Age at diagnosis, yr			0.0015
Mean (SD)	39.4 (19.6)	35.1 (19.4)	
Median (IQR)	35.0 (23.0–54.0)	31.0 (19.0–47.0)	
Gender, women/men	221/274 (44.6/55.4)	131/123 (51.6/48.4)	0.0721
Montreal classification for UC			
E1 (proctitis)	149 (30.1)		
E2 (left-sided colitis)	154 (31.1)		
E3 (extensive colitis)	159 (32.1)		
E unknown (E2 or E3)	33 (6.7)		
S1 (mild)	250 (50.5)		
S2 (moderate)	198 (40.0)		
S3 (severe)	46 (9.3)		
Montreal classification for CD			
B1 (inflammatory)		194 (76.4)	
B2 (stricturing)		35 (13.8)	
B3 (penetrating)		25 (9.8)	
p (perianal)		22 (8.7)	
L1 (ileal)		74 (29.1)	
L2 (colonic)		122 (48.0)	
L3 (ileocolonic)		58 (22.8)	
L4 (upper GI)		40 (15.7)	
C-reactive protein at diagnosis (n = 599), mg/L			<0.0001
Mean (SD)	22.2 (42.8)	44.9 (61.3)	
Median (IQR)	5.0 (5.0–15.0)	18.0 (5.0–61.0)	
Hemoglobin at diagnosis (n = 749), g/L			<0.0001
Mean (SD)	132.0 (20.0)	123.9 (21.5)	
Median (IQR)	134.0 (122.0–146.0)	127.5 (110.0–140.0)	
Hemoglobin at 1 yr (n = 580), g/L			0.0076
Mean (SD)	136.2 (16.6)	133.3 (13.6)	
Median (IQR)	138.0 (127.0–149.0)	134.0 (125.0–143.0)	
Change in Hb from diagnosis to 1-yr follow-up (n = 580), g/L			0.0017
Mean (SD)	5.3 (17.9)	10.4 (20.2)	
Median (IQR)	3.0 (−5.0 to 12.0)	6.0 (−3.0 to 23.0)	

IQR, interquartile range.

small measured counts ($n \leq 5$) and expected counts ($n \geq 5$). McNemar's χ^2 test was used for paired contingency tables (anemia at diagnosis and follow-up). P values <0.05 were considered statistically significant. All tests were 2-sided.

Ethical Considerations

This study was approved by the local Ethics Committee at Uppsala University, Sweden.

RESULTS

Of the 790 UC and CD patients in the ICURE study, Hb level at diagnosis was measured in 749 individuals (UC, n = 495; CD, n = 254), and these were included in group 1. Hb level after 12 months was measured in 580 of the individuals in group 1 (UC, n = 381; CD, n = 199), and these subjects were included in group 2.

An analysis of the patients included in group 1 but not in group 2 revealed a significantly higher proportion of ulcerative proctitis (E1) patients compared with left-sided (E2) or extensive (E3) UC and a higher proportion of mild symptoms (S1) compared with moderate symptoms (S2) in the UC subgroup. Otherwise, the excluded patients and the included patients did not differ with regards to gender, age, prevalence of anemia at diagnosis, or other Montreal criteria.

Prevalence

Demographic data and Montreal classification at the time of diagnosis are presented in Table 1. The prevalence of moderate and severe anemia at diagnosis and after 12 months is presented in Table 2. At the time of diagnosis, the prevalence of anemia in the whole cohort was 227/749 (30.3%), and after 12 months, the prevalence was 102/580 (17.6%). Anemia was less common among patients with UC compared with CD at diagnosis (UC, 24.4%; CD, 41.7%, $P < 0.0001$). At the time of follow-up, there was no difference between the 2 groups (UC, 17.6%; CD, 17.6%, $P = 0.9994$). Children younger than 17 years were more prone to anemia compared with adults, both at diagnosis and after 1 year (Table 3).

Among the patients with anemia at diagnosis, 57/185 (30.8%) still suffered from anemia after 1 year, whereas 45/395 (11.4%) of patients without anemia at diagnosis developed anemia during follow-up. The prevalence of anemia at diagnosis and after 1 year for patients in group 2 is presented in Figure 1 (UC, stratified by extent and CD, stratified by location).

In patients with UC, extent of inflammation in the colon correlated significantly to the prevalence of anemia at diagnosis (E1 versus E2, $P = 0.0354$; E2 versus E3, $P = 0.0001$; E1 versus E3, $P < 0.0001$), but after 1 year, these differences had disappeared. In patients with CD, inflammation located in the colon was a significant risk factor for anemia at diagnosis compared with patients with pure ileal engagement (L1 versus L2, $P = 0.0086$; L2 versus L3, $P =$ not significant; L1 versus L3, $P = 0.0037$). After 1 year, the only significant difference in anemia prevalence was between ileal and ileocolonic CD (L1 versus L3, $P = 0.0439$). The extent or prevalence of colonic inflammation were high among children compared with adults (extensive UC: children 64.9%, adults 32.0%, $P = 0.0001$; colonic CD: children 93.2%, adults 66.2%, $P = 0.0003$).

TABLE 2. Anemia at Diagnosis and After 1 Year

	Total, n (%)	UC, n (%)	CD, n (%)	*P*
Group 1 (baseline, n = 749)				
At diagnosis				
No anemia	522 (69.7)	374 (75.6)	148 (58.3)	<0.0001
Moderate anemia	150 (20.0)	83 (16.8)	67 (26.4)	0.0019
Severe anemia	77 (10.3)	38 (7.7)	39 (15.4)	0.0011
Group 2 (follow-up, n = 580)				
At diagnosis				
No anemia	395 (68.1)	282 (74.0)	113 (56.8)	<0.0001
Moderate anemia	125 (21.6)	68 (17.8)	57 (28.6)	0.0027
Severe anemia	60 (10.3)	31 (8.1)	29 (14.6)	0.0157
At 1-yr follow-up				
No anemia	478 (82.4)	314 (82.4)	164 (82.4)	0.9994
Moderate anemia	90 (15.5)	57 (15.0)	33 (16.6)	0.6085
Severe anemia	12 (2.1)	10 (2.6)	2 (1.0)	NA

Comparison between patients with UC and CD.
NA, not applicable.

TABLE 3. Anemia Among Children (<17 yr) Versus Adults (≥17 yr)

	n (%)	*P*
Anemia at diagnosis		
All		<0.0001
Children	45/82 (54.9)	
Adults	182/667 (27.3)	
UC		0.0025
Children	17/38 (44.7)	
Adults	104/457 (22.8)	
CD		0.0012
Children	28/44 (63.6)	
Adults	78/210 (37.1)	
Anemia at 1-yr follow-up		
All		0.0152
Children	20/72 (27.8)	
Adults	82/508 (16.1)	
UC		0.7581
Children	7/36 (19.4)	
Adults	60/345 (17.4)	
CD		0.0013
Children	13/36 (36.1)	
Adults	22/163 (13.5)	

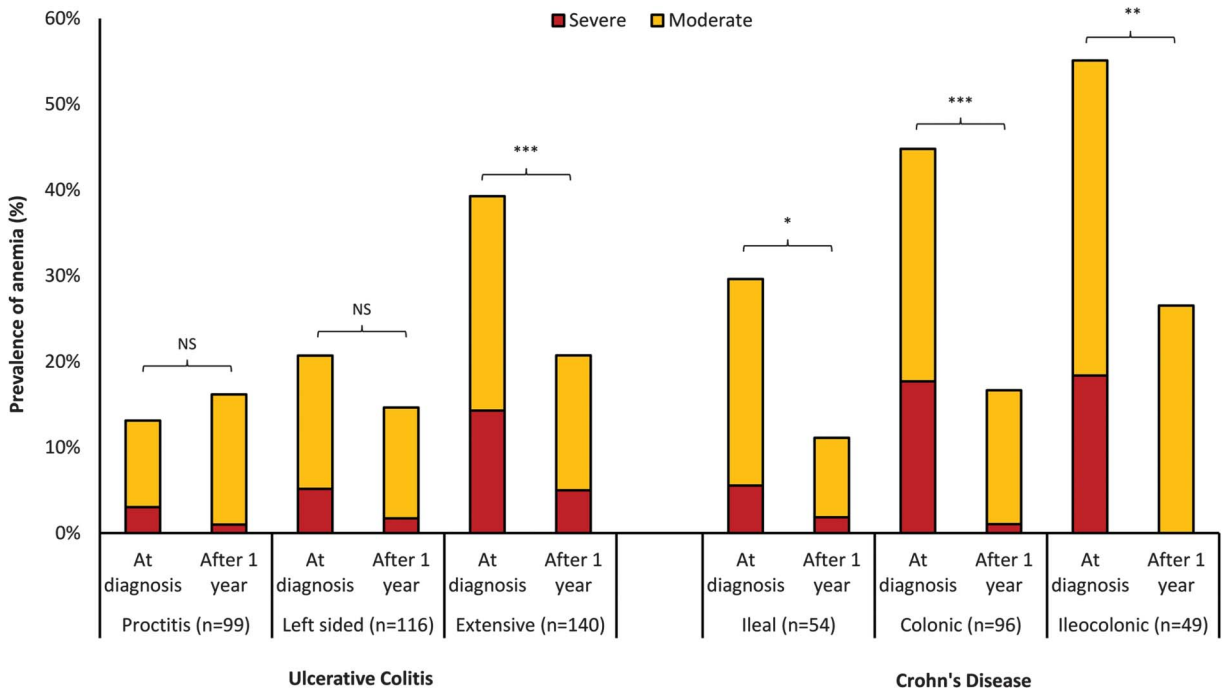

FIGURE 1. Prevalence of anemia at diagnosis and after 1 year. UC (n = 355), CD (n = 199). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. NS, not significant.

Medical Treatment

During the first year, 73.7% of the patients were treated with 5-aminosalicylic acid, 68.9% with steroids, 22.2% with antimetabolites (thiopurine analogs or methotrexate), and 6.8% with anti-tumor necrosis factor (TNF)–α antibodies. There were no gender differences in medical treatment. A significantly higher proportion of the patients with UC were treated with 5-aminosalicylic acid compared with patients with CD (UC, 97.0%; CD, 28.3%; $P < 0.0001$), whereas a significantly higher proportion of patients with CD were treated with steroids (UC, 64.0%; CD, 78.3%; $P = 0.0001$), antimetabolites (UC, 12.1%; CD, 41.7%; $P < 0.0001$) and anti-TNF-α antibodies (UC, 5.1%; CD, 10.2%; $P = 0.0077$) compared with patients with UC.

Patients with anemia after 1 year were more often treated with steroids and/or anti-TNF antibodies compared with patients without anemia (steroids: 85/102 versus 142/478, $P = 0.0074$; anti-TNF antibodies: 16/102 versus 32/478, $P = 0.0028$).

During the first year after diagnosis, 119/580 (20.5%) patients received anemia-specific treatment (oral iron supplementation: 8.8%; intravenous iron: 5.0%; and blood transfusion: 6.2%). Among patients with either anemia at diagnosis or follow-up, 105/230 (45.7%) were treated with iron or transfusion. There was no difference between children and adults regarding anemia treatment nor was there any difference between men and women.

DISCUSSION

Anemia is a common complication to IBD both at onset and after the first year of disease. In this population-based cohort, almost one-third (30.3%) of all patients had anemia at the time of diagnosis. Severe anemia was common among the newly diagnosed patients (10.3%). A substantial proportion of the patients still had anemia after 1 year (17.6%), even if severe anemia was uncommon (2.1%). Ten patients in the ICURE cohort had anemia as the only symptom of their IBD.

In the IBSEN study where data were collected 15 years earlier than this study, similar results were presented for anemia at diagnosis and after 1 year.[8] This is disheartening because the medical armamentarium has changed radically during the last decades without improving the prevalence of anemia at the time of follow-up. More effort is needed not only to identify low hemoglobin levels but also to aim specific treatment towards the underlying problem, i.e., iron deficiency with or without inflammation.[15] In this study, the majority of the patients with anemia at diagnosis or follow-up did not receive any specific treatment (iron or blood transfusion) despite current guidelines.[16]

We found that in patients with UC, the prevalence of anemia increased in parallel with the extent of the inflammation in the colon. Likewise, colonic engagement with or without ileal involvement in patients with CD was a risk factor for anemia.

Children younger than 17 years were more vulnerable with a high prevalence both at diagnosis and follow-up compared with adults. This could be attributed to a high presence of colonic engagement among children. Data on population-based anemia prevalence at diagnosis among children are scarce, but in a study from Scotland, 72% were anemic at diagnosis and 61% still anemic after 1 year (this study: 55% and 28%, respectively).[17] At a tertiary pediatric center in Southampton, United Kingdom, 75% of the children were anemic at diagnosis and 30% at follow-up 2 years later.[18]

The observation that 30.8% of the patients with anemia at diagnosis suffered from the same condition at follow-up calls for attention.[9] Anemia at follow-up could reflect a more aggressive disease as indicated by the higher proportion of steroid and/or anti-TNF use. However, failure to identify anemia at diagnosis may lead to inadequate efforts to correct it side-by-side with anti-inflammatory treatment.

One weakness of this study is the lack of laboratory data characterizing the type of anemia. A previous Swedish study has reported that in the majority of patients in a mixed IBD population with various disease duration, the etiology of anemia is iron deficiency and/or anemia of chronic disease and that <5% can be contributed to vitamin B12 or folic acid deficiency.[15] The correlation between prevalence of anemia and colonic engagement suggests that inflammation and bleeding are the 2 major causes of anemia in this study. This is further supported by the notion that patients with CD with pure ileal disease (L1) had the lowest anemic prevalence. Furthermore, patients with CD had higher C-reactive protein levels compared with UC as a sign of greater systemic inflammatory activity, contributing to the higher degree of anemia in the CD patient group.

Because the study was observational and data were collected from patient records, a structured appraisal of disease activity through activity indices was not possible. It is therefore difficult to evaluate if presence of anemia at follow-up was associated with disease activity or lack of antianemic treatment only.

Another weakness is the lack of Hb levels at follow-up, resulting in a loss of 23% of the patients. The analysis of attrition disclosed that the loss of cases consisted mainly of patients with ulcerative proctitis with mild symptoms and that the 12-month follow-up results must be interpreted in accordance with these findings.

The strength of this study is the population-based design including all patients with IBD, adults and children in a well-defined geographic area and time period and the use of modern treatment. It describes the problem of anemia in patients with IBD in a clinical setting and reveals the need for improvement of the anemia-specific treatment.

In conclusion, this population-based study found a high prevalence of anemia in patients with IBD both at diagnosis and after 1 year. Children younger than 17 years were more likely anemic compared with adults. Anemia was strongly associated with the extent of inflammation in the colon in patients with UC and the presence of colonic engagement in patients with CD. The majority of the patients with anemia did not receive any iron supplementation therapy or blood transfusion.

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