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Alimentary Tract

Anemia at the time of diagnosis of inflammatory bowel disease: Prevalence and associated factors in adolescent and adult patients

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ABSTRACT

Background: The prevalence, characteristic and determinants of anemia, at the time of inflammatory bowel disease (IBD) diagnosis have yet to be fully elucidated.
Methods: Retrospective cross-sectional study. Analytical data and disease characteristics obtained upon diagnosis of 1278 IBD patients [Crohn's disease/ulcerative colitis (CD/UC): 718/560] were collected.
Results: Anemia was present in 41.2% of patients at diagnosis (47% and 33.8% of CD and UC patients, respectively; $p < 0.001$), being severe in 5.5%. Iron deficiency anemia represented 69.6% of cases, with no differences between CD and UC. Female sex was the strongest risk factor for anemia in both CD and UC (OR 7.11; 95%CI 4.18–12.10 and 6.55; 95%CI 3.39–12.63, respectively), followed by elevated (≥2 mg/dL) C-reactive protein (OR 4.08; 95%CI 2.39–6.97 and 4.58; 95%CI 2.26–9.27, respectively). Current smoking was a risk factor for anemia in CD (OR 2.23; 95%CI 1.24–4.02), but a protective one in UC (OR 0.36; 95%CI 0.14–0.92). A penetrating CD behavior increased the risk of anemia (OR 3.34; 95%CI 1.36–8.21); in UC, anemia increased with disease extension (E2 + E3) (OR 1.80; 95%CI 1.13–2.86).
Conclusions: Female sex and disease activity are major determinants of anemia at IBD diagnosis. Anemia is associated with disease behavior in CD and with disease extension in UC.

1. Introduction

Anemia is the most common systemic complication and extraintestinal manifestation in inflammatory bowel disease (IBD) [1,2], significantly affecting the health-related quality of life (HRQoL) of patients [3,4] and their ability to work [5]. Anemia determines long-term disease outcomes, including the amount of treatment needed, hospital admissions [6], and the need for surgery in IBD population [7], all of which lead to substantial increases in health-care costs [8].

The reported prevalence of anemia in patients with IBD varies markedly from 6% to 74%, depending on the definition of anemia used, the moment of assessment, and the population studied [9]. Anemia presents more frequently in patients with Crohn's disease (CD) than in ulcerative colitis (UC) [10], and in hospitalized compared to outpatients [11]. Several factors underlie inter-study variations in the prevalence of anemia, including the lack of standardized definitions of anemia, the specific study populations considered, patients' sex [12], moment of assessment during the course of the disease [13], and the disease activity [14]. Together, these factors indicate that the prevalence of anemia changes throughout the natural history of IBD.

Several factors contribute to anemia in IBD, the most common types being iron deficiency anemia and anemia of chronic disease (ACD), which often overlap [15,16]. Vitamin B12 and folic acid

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deficiencies, along with the effects of pro-inflammatory cytokines, hemolysis, drug therapies, and myelosuppression, are also identified in a number of patients [1].

The heterogeneity of the populations and disease stages analyzed in most of the available literature and the varying criteria used to define anemia have limited our understanding of the prevalence and determining factors of this complex manifestation of IBD. Studying a more homogeneous population at a defined moment in the course of the disease should improve frequency estimates and provide valuable data for a better understanding of the determining factors. We thus undertook an evaluation of the overall prevalence of anemia in adult patients at the moment of IBD diagnosis, analyzing the influence of various patient and disease characteristics on the appearance of anemia.

2. Methods

2.1. Study design and data source

Between March 2015 and March 2016 we undertook a cross-sectional, multicenter study within the Ciudad Real province IBD working group, representing all adult IBD units in this region of Spain [17]. Patients over 13 years of age identified in the IBD unit databases of the participating hospitals with a diagnosis of IBD established according to standard clinical, endoscopic, histological, and radiological criteria [18,19] were retrospectively identified. Epidemiological and clinical data obtained at the time of diagnosis included patient age, sex, hospital of diagnosis, type and location of the disease according to the Montreal classification system, smoking habits at diagnosis, and the presence of extraintestinal manifestations at disease onset. The need for surgery during the disease course was also recorded. Patients with indeterminate colitis were excluded.

Only naïve patients with information available on hematological parameters recorded either at the moment of diagnosis or during the previous 3 months were included. Analytical parameters included hemoglobin; hematocrit; mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); serum ferritin, serum transferrin, iron levels; and transferrin saturation (TfS), whenever possible. Disease activity was measured in terms of C-reactive protein (CRP) serum concentration.

Anemia was considered as a binary outcome variable (yes/no) and defined according to sex- and age-specific hemoglobin and hematocrit cutoffs established by the WHO for Caucasian populations [20]. Thus, the minimum normal hemoglobin and hematocrit levels for non-pregnant adult women were 12 g/dL and 36%, respectively, while those for adult men were 13 g/dL and 39%, respectively. Anemia prevalence was calculated as the ratio of the number of anemic patients over the total number of patients included in the study.

The type of anemia at diagnosis was classified into one of the following 3 categories, defined according to the European Consensus on diagnosis of anemia in IBD [16] and expert definitions [21,22]: iron deficiency anemia, ACD, and anemia of mixed origin. Briefly, iron deficiency anemia was defined as a serum ferritin level <30 μg/L, TfS <20%, MCH <27 pg, or MCHC <31 g/dL. In cases of active inflammation (defined as CRP >2 mg/dL), serum ferritin levels <100 μg/L were considered an appropriate cut-off point [21,23]. Anemia of chronic disease was diagnosed as the presence of subnormal hemoglobin levels, increased concentration of CRP (≥2 mg/dL), and characteristic alterations of iron homeostasis with serum ferritin levels >100 μg/L and TfS levels <20% [24]. Anemia of mixed origin was defined as serum ferritin levels between 30 and 100 μg/L.

Severe anemia was arbitrarily defined as a hemoglobin value <10 g/dL [10,13,25]. Accordingly, adult patients with hemoglobin concentrations lower than their sex cutoff for the definition of anemia but above 10 g/dL were classified as mildly anemic.

2.2. Statistical analyses

Results for continuous variables are expressed as the mean and SD or as the median and interquartile range (IQR); qualitative variables are presented as absolute and relative frequencies. The χ^2-test (Fisher's exact test, where appropriate) or Student's t-test were used to compare qualitative and quantitative variables, respectively. Odds ratios (OR) with 95%CIs were calculated for significant variables. A significance level of 0.05 was used throughout. Logistic regression was performed separately for CD and UC. Analyses and summaries were carried out with the PASW statistical program (version 18.0; SPSS Inc., Chicago, Illinois).

2.3. Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki principles. The registries supporting this study were approved by the local ethics or research committees at the participating centers.

3. Results

3.1. Subject characteristics

1278 patients diagnosed with IBD between 1960 and 2016 had analytical information available; 718 (56.2%) patients presented with CD and 560 (43.8%) with UC. The median age at IBD diagnosis was 38.8 years (IQR 16.9; range 13–90). CD patients were younger [36 (16.4; 13–56)] than UC [42.5 (16.9; 13–90)] ($p < 0.001$).

Age groups at the moment of diagnosis were as follows: A1 (≤16), 6.4% of patients; A2 (between 17 and 40), 53.4% of patients; and A3 (disease onset >40), 40.2%. Table 1 shows patients characteristics at the moment of diagnosis.

Regarding CD, an ileal disease (L1) was present in 255 patients (37.2%); in 161 patients (23.5%), CD presented with a colonic involvement (L2). An ileocolonic disease was diagnosed in 265 patients (38.7%) while isolated upper digestive tract CD (L4) was present in only four patients (0.6%) (Table 1). In terms of disease behavior, 444 patients (64.8%) presented with an inflammatory (B1) pattern, 164 patients (23.9%) had a stricturing disease (B2), and the remaining 77 patients (11.2%) a penetrating disease (B3).

At diagnosis, proctitis (E1) was present in 21.6% of UC patients. A left-sided UC (E2) was found in 48.2% of patients and an extensive UC (E3) in 30.2% (Table 1).

Extraintestinal manifestations at IBD diagnosis were present in 170 patients (24.7%) with CD and 62 patients (12.1%) with UC ($p < 0.001$), with pelvic/perirectal abscesses, skin disorders, and osteoarticular manifestations appearing significantly more often in CD patients (Table S1). Extraintestinal manifestations were independent of anemia in both CD and UC patients (Table 2). Patients who presented with anemia tended to require surgery during the course of the disease more often than non-anemic patients (7.2% *vs.* 4.6%, respectively), in both CD (10.3% *vs.* 8.2%) and UC (1.6% *vs.* 0.8%) (not statistically significant). In contrast, extraintestinal manifestations at disease onset were associated with increased risk of undergoing surgery during the course of the disease: 16% of IBD patients with extraintestinal manifestations at diagnosis underwent surgery compared to 5% of those with no extraintestinal manifestations. This association was observed for CD (18.8% *vs.* 89%) and for UC (8.2% *vs.* 0.4%) ($p < 0.001$ for all comparisons). Pelvic/perirectal abscesses at diagnosis were the best predictor of

Table 1
Demographics and clinical characteristics of IBD patients.

		n (%)			p
		IBD overall	Crohn's disease	Ulcerative colitis	
N		1278	718	560	–
Age [Mean (SD) (range)]		38.8 (16.9; 13–90)	36 (16.4; 13–56)	42.5 (16.9; 13–90)	p < 0.001
Sex (male/female)		685 (53.6)/593 (46.4)	370 (51.5)/348 (48.5)	315 (56.3)/245 (43.7)	p = 0.093
Smoking habit	No	719 (68.2)	388 (62.3)	331 (76.6)	p < 0.001
	Yes	213 (20.2)	164 (26.3)	49 (11.3)	
	Former smoker	123 (11.7)	71 (11.4)	52 (12)	
Age at diagnosis (A)	A1	81 (6.4)	59 (8.3)	22 (4)	p < 0.001
	A2	671 (53.4)	413 (58.4)	258 (46.9)	
	A3	505 (40.2)	235 (33.2)	270 (49.1)	
Disease location (L)	L1	–	255 (37.2)	–	–
	L2	–	161 (23.5)	–	–
	L3	–	265 (38.7)	–	–
	L4	–	4 (0.6)	–	–
Disease behavior (B)	B1	–	444 (64.8)	–	–
	B2	–	164 (23.9)	–	–
	B3	–	77 (11.2)	–	–
Disease extension (E)	E1	–	–	110 (21.6)	–
	E2	–	–	246 (48.2)	–
	E3	–	–	154 (30.2)	–

Table 2
Baseline characteristics of patients with and without anemia at inflammatory disease diagnosis: bivariate analyses.

		IBD overall n (%)		p	Crohn's disease n (%)		p	Ulcerative colitis n (%)		p
		Anemia	No anemia		Anemia	No anemia		Anemia	No anemia	
Mean age (SD)		38.9 (18.5)	40.3 (16.5)	0.254	36.8 (18.3)	37.4 (15.8)	0.711	42.6 (18.2)	43.3 (16.7)	0.713
Sex	Male	125 (34.5)	365 (68.9)	<0.001	78 (33.1)	187 (70.3)	<0.001	50 (37)	178 (67.4)	<0.001
	Female	243 (65.5)	165 (31.1)		158 (66.9)	79 (29.7)		85 (63)	86 (32.6)	
Age at diagnosis (A)	A1	29 (7.9)	24 (4.6)	0.116	20 (8.5)	18 (6.8)	0.540	9 (6.7)	6 (2.3)	0.096
	A2	183 (49.7)	275 (52.4)		124 (53)	153 (57.5)		59 (44)	122 (47.1)	
	A3	156 (42.4)	226 (43)		90 (38.5)	95 (35.7)		66 (49.3)	131 (50.6)	
Disease location (L)	L1				88 (37.9)	110 (43)	0.230			
	L2				54 (23.3)	55 (21.5)				
	L3				90 (38.8)	88 (34.4)				
	L4				0	3 (1.2)				
Disease behavior (B)	B1				153 (66.2)	188 (73.4)	0.068			
	B2				48 (20.8)	50 (19.5)				
	B3				30 (13)	18 (7)				
Disease extension (E)	E1							22 (17.2)	65 (27.1)	0.002
	E2							55 (43)	119 (49.6)	
	E3							51 (39.8)	56 (23.3)	
CRP concentration	>2 mg/dL	161 (52.1)	100 (23.1)	<0.001	112 (55.7)	67 (29.9)	<0.001	49 (45.4)	33 (15.6)	<0.001
	<2 mg/dL	148 (47.9)	333 (76.9)		99 (44.3)	157 (70.1)		59 (54.6)	176 (84.2)	
Any complication at IBD diagnosis		69 (19.2)	85 (17.1)	0.437	53 (22.8)	62 (24.1)	0.739	18 (12.5)	23 (9.6)	0.387
Pelvic/perirectal abscesses		21 (5.8)	18 (3.6)	0.125	18 (7.8)	17 (6.6)	0.624	3 (2.3)	1 (0.4)	0.123
Ocular disease		1 (0.3%)	5 (1%)	0.410	1 (0.4%)	3 (1.2%)	0.626	0	2 (0.8%)	0.545
Skin disorders		11 (3.2%)	11 (2.3%)	0.415	9 (4%)	10 (4%)	0.999	2 (1.7%)	1 (0.4%)	0.264
Venous thromboembolic disease		0	2 (0.4%)	0.512	0	1 (0.4%)	0.999	0	1 (0.4%)	0.999
Sclerosing cholangitis		3 (0.8%)	2 (0.4%)	0.655	2 (0.9%)	0	0.225	1 (0.8%)	2 (0.8%)	0.999
Osteoarticular manifestation		42 (12.4%)	65 (13.7%)	0.609	30 (13.6%)	45 (18.3%)	0.172	12 (10.2%)	20 (8.7%)	0.652
Smoking habit at diagnosis		98 (30.3%)	137 (32.2%)	0.580	69 (32.5%)	98 (42.6%)	0.029	29 (26.1%)	39 (20%)	0.215
Surgery during disease course		26 (7.2%)	23 (4.6%)	0.108	24 (10.3%)	21 (8.2%)	0.406	2 (1.6%)	2 (0.8%)	0.613

IBD: inflammatory bowel disease; CRP: C-reactive protein; A: age at diagnosis; A1: ≤16 years old; A2: between 17 and 40 years of age; A3: >40 years old. L: disease location (for Crohn's disease); L1: ileal disease; L2: colonic disease; L3: ileocolonic disease; L4: upper gastrointestinal tract disease. B: disease behavior (for Crohn's disease); B1: inflammatory disease; B2: stricturing disease; B3: penetrating disease. E: disease extension (for ulcerative colitis); E1: ulcerative proctitis E2: left-sided ulcerative colitis; E3: extensive disease.

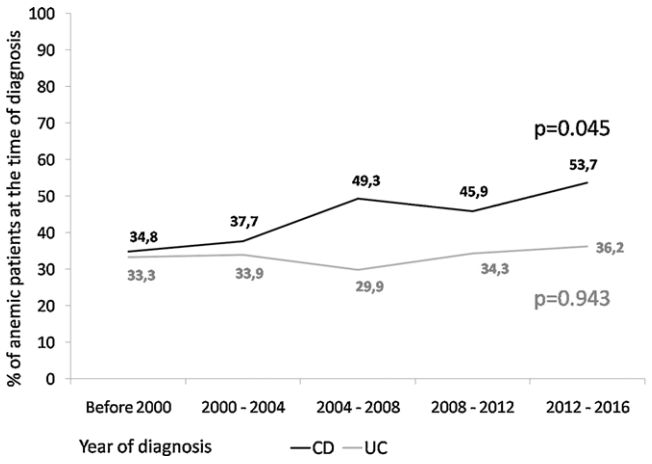

Fig. 1. Variations in the prevalence of anemia overtime for patients with Crohn's disease (CD) and ulcerative colitis (UC) at the moment of disease diagnosis.

surgery, both in IBD overall (27.6% *vs.* 6.1%) and specifically in CD (29.6% *vs.* 9.8%) ($p < 0.001$). Elevated serum CRP values were also higher among patients with extraintestinal manifestations at IBD diagnosis (44.4 *vs.* 24.5%; $p = 0.012$).

Smoking (both current and former) was more frequent in patients with CD (37.7%) than in those with UC (23.4%) ($p < 0.001$) (Table 2). Smoking was associated with UC at the time of diagnosis in the subgroup of patients with severe anemia ($p = 0.046$).

3.2. Basic hematological profile and prevalence of anemia at IBD diagnosis

The mean ± SD hemoglobin concentration at IBD diagnosis was 13.4 ± 2.0 g/dL, being lower in CD (13.1 ± 2.0 g/dL) than in UC (13.7 ± 2.0 g/dL) ($p < 0.001$). Overall, 371 IBD patients (41.2%) presented with anemia at diagnosis; a higher prevalence was found in CD (47%) than in UC patients (33.8%) ($p < 0.001$).

After analyzing case series divided into five year periods, prevalence of anemia significantly increased in CD over time ($p = 0.045$) but remained unchanged in UC (Fig. 1). The age–sex stratified prevalence of anemia at the time of IBD diagnosis was estimated for the age strata 16 to >65 years. Overall, patients with CD aged between 26 and 65 had a lower risk for anemia than patients between 16 to 25 years, and those >65 ($p < 0.01$) (Fig. 2A). These differences were more marked for male patients ($p = 0.039$). In UC patients, we found no significant association between age and anemia (Fig. 2B).

Proportionally, more women than men presented with anemia at the moment of IBD diagnosis (65.5% *vs.* 34.5%). This was also observed independently for CD and UC ($p < 0.001$ for all comparisons) (Table 2). Severe anemia (Hb <10 g/dL) was present in 6% and 5% of patients with CD and UC, respectively (p = ns).

Iron deficiency anemia was the predominant type in IBD (69.6%). ACD represented the second cause, present in 20.1% of IBD patients, while anemia of mixed origin presented in 10.4% of patients at diagnosis. No differences in the distribution of types of anemia were noted between CD and UC (Table 3).

Hemoglobin, hematocrit, MCV, MCH, MCHC, and iron levels were all significantly lower in CD compared to UC; however, CRP concentrations were higher in CD ($p < 0.001$). No differences in serum ferritin, serum transferrin, or TfS levels were observed between the two diseases (Table 3).

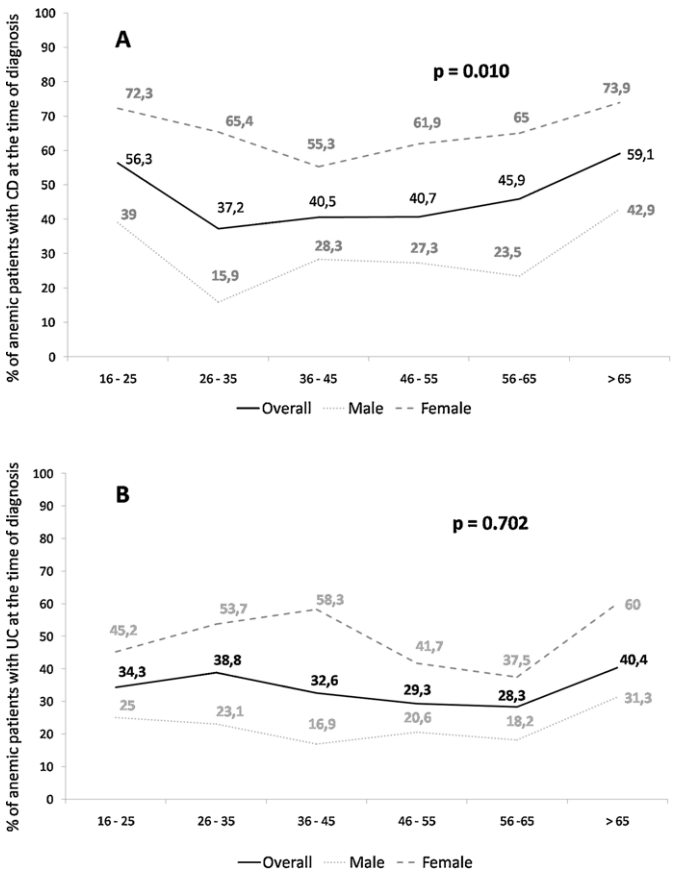

Fig. 2. Prevalences of anemia for the different age groups of patients with (A) Crohn's disease and (B) ulcerative colitis for the different age groups classified by gender.

Table 4
Factors associated with anemia by logistic regression in patients with Crohn's disease and ulcerative colitis at the moment of diagnosis.

	Odds ratio	95% confidence interval	p
Crohn's disease			
Female gender	7.11	4.18–12.10	<0.001
Elevated (≥2 mg/dL) C-reactive protein	4.08	2.39–6.97	<0.001
Penetrating disease behavior (B3)	3.34	1.36–8.21	0.009
Current smoking	2.23	1.24–4.02	0.007
Ulcerative colitis			
Female gender	6.55	3.39–12.63	<0.001
Elevated (≥2 mg/dL) C-reactive protein	4.58	2.26–9.27	<0.001
Disease extension (E2/E3)	1.80	1.13–2.86	0.013
Current smoking	0.36	0.14–0.92	0.032

3.3. Associations and determinants of anemia at IBD diagnosis

Bivariate analyses demonstrated a significantly higher proportion of anemia in IBD women compared to men, irrespective of disease type or age. Disease activity, defined as serum CRP concentrations ≥2 mg/dL, was higher in CD than in UC ($p < 0.001$) as well as in anemic compared to non-anemic patients, in IBD overall, CD and UC ($p < 0.001$ for all comparisons) (Table 4).

No differences in the prevalence of anemia were observed when small intestine location (L1 + L3) was compared to exclusive colonic location (L2) in CD. In contrast, anemia was more common in CD patients with a penetrating (B3) compared to a non-penetrating (B1 + B2) disease behavior (13% *vs.* 7%, respectively) ($p = 0.028$). Patients with a penetrating disease also exhibited higher serum CRP values than those with non-penetrating disease (5.59 ± 6.49

Table 3
Prevalence of anemia and hematological profile at the time of diagnosis in patients with inflammatory bowel disease.

	n (%)			p
	IBD overall	Crohn's disease	Ulcerative colitis	
Anemia	371 (41.2)	236 (47)	135 (33.8)	p < 0.001
Severe anemia (Hb <10 g/dL)	50 (5.5)	30 (6)	20 (5)	0.549
Type of anemia				
Iron deficiency anemia	215 (69.6)	144 (71.3)	71 (66.4)	p = 0.487
Anemia of chronic disease	62 (20.1)	40 (19.8)	22 (20.6)	
Anemia of mixed origin	32 (10.4)	18 (8.9)	14 (13.1)	
Hemoglobin (g/dL) [mean (SD; range)]	13.4 (2; 6.1–19.6)	13.1 (2; 6.1–18)	13.7 (2; 6.1–19.6)	<0.001
Hematocrit (%)[mean (SD; range)]	40 (5.6; 18.5–58)	39.3 (5.7; 18.5–54)	40.8 (5.6; 20.5–58)	<0.001
RBC $\times 10^{12}$ [mean (SD; range)]	4.6 (0.6; 2–6.3)	4.6 (0.6; 2–3.6)	4.6 (0.6; 2.7–5.9)	0.358
MCV (fL) [mean (SD; range)]	86.5 (6.9; 48.6–110)	85.3 (7.2; 48.6–103)	88 (6.2; 52.3–110)	<0.001
MCH (pg) [mean (SD; range)]	29.1 (3.8, 12.4–90.3)	28.6 (3.6; 12.4–75)	29.8 (4.1; 15.3–90.3)	<0.001
MCHC (g/dL) [mean (SD; range)]	33.4 (1.5; 14.1–47.7)	33.3 (1.5; 14.1–37)	33.5 (1.5; 20.5–47.7)	0.024
Serum iron (μg/dL) [mean (SD); range)]	61 (37.6; 1–294)	56.1 (36.8; 1–294)	67.2 (38.3; 3–240)	<0.001
Serum ferritin (μg/L) [mean (SD; range)]	119.7 (165.4; 1–1551)	119.3 (153.1; 1–1551)	120.3 (181; 1–1474)	0.935
Serum transferrin (mg/dL) [mean (SD; range)]	247.6 (63.8; 72–417)	243 (65.8; 72–399)	254.8 (60; 89.3–417)	0.097
Transferrin saturation (%) [mean (SD; range)]	19.8 (12.1; 0.4–61)	18.6 (11.6; 1.9–56.2)	21.9 (12.8; 0.4–61)	0.110
C-reactive protein (mg/dL) [mean (SD; range)]	3.2 (5.1; 0–32)	3.8 (5.5; 0–32)	2.4 (4.5; 0–32)	<0.001

vs. 3.67 ± 5.43; p = 0.033). The proportion of CD patients with serum CRP ≥2 mg/dL was also higher for penetrating than for non-penetrating disease behavior (59.5% *vs.* 40.6%; p = 0.019).

For UC, the prevalence of anemia significantly increased with disease extension at diagnosis, being higher for left-sided and extensive disease than for proctitis (p = 0.002).

A logistic regression was performed separately for CD and UC to determine the exact contribution of various factors in anemia. For CD, anemia was significantly associated with female sex (OR 7.11; 95%CI 4.18–12.10; p < 0.001); current smoking (OR 2.23; 95%CI 1.24–4.02; p = 0.007); elevated serum CRP (OR 4.08; 95CI 2.39–6.97; p < 0.001); and penetrating disease behavior (OR 3.34; 95%CI 1.36–8.21; p = 0.009).

For UC patients, anemia at disease diagnosis was associated with female sex (OR 6.55; 95%CI 3.39–12.63; p < 0.001), elevated CRP serum levels (OR 4.58; 95%CI 2.26–9.27; p < 0.001), and disease extension (E2/E3 compared to E1) (OR 1.80; 95%CI 1.13–2.86; p = 0.013). Current smoking was clearly identified as a protective factor (OR 0.36; 95%CI 0.14–0.92; p = 0.032); former smoking showed no significant effect on determining anemia at UC diagnosis.

Severe anemia was not associated with patient or disease characteristics at IBD diagnosis, except for smoking in UC.

4. Discussion

This study found that anemia was present in 41.2% of IBD patients attended in reference units in a region of Spain, with no differences in age categories according to Montreal classification system. Our results show anemia as the most prevalent systemic manifestation of IBD, even at the very moment of diagnosis. Almost half of CD patients and one-third of those with UC in our cohort suffered from anemia at disease diagnosis, in agreement with previously reported figures for incident IBD cases [26,27]. Treating IBD reduces the frequency of anemia [28] throughout the course of the disease, but a significant proportion of patients remain anemic even several years after being diagnosed [10,14].

The relationship between anemia and IBD has been intensively investigated, but not at IBD diagnosis, the prevalence and determinants of it having been scarcely assessed. To date, only a handful of retrospective cohorts that included incident CD or UC cases have dealt with this topic [7,26], showing comparable results. Our research includes almost twice as many patients as any of the previous studies and covers IBD cases diagnosed over a period of more than 50 years. The prevalence of anemia in CD progressively increased over the years, but remained stable in UC, despite significant advances in diagnosis and management of IBD. These results are in agreement with those reported in previous pediatric research [13], but should be used cautiously due to retrospective data collection.

Anemia at diagnosis showed significant variation across patient ages or age groups, with a lower risk in CD patients aged between 25 to 64 compared to younger and older subjects, and especially among males. A recent meta-analysis of cross-sectional studies including outpatient populations at tertiary hospitals throughout Europe [10] also showed that male patients between 30 and 64 seemed to have a significantly lower risk for anemia than younger or older patients, while for women, the prevalence was virtually equal at every stage of life. This coincidence in the higher risk of anemia in younger and older male patents both at the time of CD diagnosis and over time requires further research on additional age- and sex-related factors that come into play from IBD diagnosis throughout the course of the disease. Anemia was significantly higher in CD than in UC, which is in strong agreement with most of the previous research [10,14,28,29].

Iron deficiency anemia represents the most common type of anemia in IBD at diagnosis, with no significant differences between CD and UC. These results contrast with those from prior research conducted in western Hungary [29] and focused on extraintestinal manifestations, which described a higher proportion of iron deficiency anemia in CD. However, it provided no information regarding the diagnostic criteria of anemia. Iron deficiency anemia as a consequence of intestinal bleeding, dietary restrictions, or malabsorption is recognized as the most prevalent one in IBD at all stages [9,15]. An additional feature of our study was the assessment of the severity of anemia at IBD diagnosis: only 5.5% of patients had severe anemia (representing 13.5% of all anemic patients), without differences between CD and UC.

In the absence of full-blown anemia, iron deficiency itself lowers the perceived HRQoL in IBD patients [30]. We showed that serum iron levels were significantly lower in CD patients. Other biochemical parameters related to iron deposits, such as serum transferrin and TfS, were also lower in CD compared to UC. However, no differences were observed in serum ferritin levels between the two diseases, limiting the diagnostic value of this acute phase reactant.

Multivariate analyses demonstrated that female sex and disease activity were the determinant factors significantly associated with anemia at IBD diagnosis for both CD and UC patients. Previous studies assessing the prevalence and associated factors of anemia throughout the course of IBD have also found that female

sex [14,31,32] and disease activity [26,32] were independent risk factors. CRP levels have been proposed as a predictor of oral iron supplementation unresponsiveness [30]. This marker may thus be useful in identifying IBD patients who can benefit from first-line treatment with *i.v.* administration of iron [34].

The finding that tobacco consumption is an independent risk factor for anemia in CD, but a protective one in UC at disease onset is novel. Although smokers develop compensatory polycythemia as a result of the carbon monoxide in cigarette smoke [35], multivariate analysis clearly identified tobacco as a risk factor for anemia at CD diagnosis. Indeed, current smoking was associated with a two-fold prevalence of this complication among CD patients. On the contrary, tobacco protected UC patients from developing anemia. Strong evidence links smoking with IBD onset risk, clinical course [36], and disease outcomes [37], with opposite effects in CD and UC [38]. To our knowledge, the association of current smoking with increased risk of anemia in CD and reduced risk in UC has not been described before, adding to the body of evidence for the differing effects of tobacco in CD and UC. However, we failed in identifying potential effects of smoking cessation on anemia presentation at IBD diagnosis.

We also examined whether IBD location or extension could impact on the prevalence of anemia. Risk of anemia was not increased in CD small intestine location (L1 + L3) compared to colonic (L2). For UC, the prevalence of anemia significantly increased with the extension of the disease, suggesting that anemia in IBD appears to be more a consequence of intestinal bleeding rather than iron malabsorption.

A penetrating disease (B3) was a significant risk factor for anemia in CD compared to inflammatory (B1) and stricturing (B2) behavior. Higher CRP levels observed in B3 compared to B1 + B2 (5.59 *vs.* 3.67; p = 0.033) along with the higher proportion of patients with elevated CRP levels among the B3 group (59.5% *vs.* 40.6%; p = 0.019) suggest disease activity as an explanation.

In order to reduce selection bias, our study exhaustively included all IBD patients attending gastroenterology/IBD units of participating public regional hospitals who had available laboratory records. This broad coverage along with the absence of private healthcare resources potentially ensured the inclusion of the majority of IBD diagnosed patients in the region. Still, the external validity of our results should be studied further as we cannot assume our region is representative of the entire IBD population.

The retrospective nature of the analytical data collection represents a limitation. However, recovering archived well identified analytical data reduced subjectivity. We assessed widespread used analytical values, thereby reducing the risk of bias in the results obtained. Disease activity was measured exclusively by CRP, since clinical activity indexes were not available or could not be accurately calculated for every patient. Finally, our study provides no data on pediatric onset IBD, but the prevalence of anemia at diagnosis in these patients has recently been published [13] and mostly agrees with our adolescent and adult data.

Anemia represents a frequent complication of IBD from the very moment of diagnosis, affecting up to half of patients with CD and one third of UC of all ages. Its main cause is iron deficiency. Female sex and disease activity are significant risk factors, while smoking exerts opposite effects in CD and UC. Penetrating disease behavior and disease extension are additional risk factors in CD and UC, respectively. Finally, advances in IBD diagnosis and management over the past few decades had no significant impact on the prevalence of anemia at IBD onset.

Conflict of interest

None declared.

Authorship

Guarantor of the article: Alfredo J Lucendo.

Disclaimers

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2016.12.005.

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