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Anaemia in Patients with Inflammatory Bowel Disease – A Nationwide Cross-Sectional Study

Francisco Portela[a, b] Paula Lago[b, c] José Cotter[b, f] Raquel Gonçalves[b, g] Helena Vasconcelos[b, h] Paula Ministro[b, i] Susana Lopes[b, d] Marta Eusébio[b, j] Henrique Morna[b, k] Marilia Cravo[l] Paula Peixe[b, m] Isabel Cremmers[b, n] Helena Sousa[b, o] João Deus[b, p] Maria Duarte[b, q] Fernando Magro[b, e] on behalf of CAPOR Investigators and GEDII

[a]Centro Hospitalar Universitário de Coimbra, Coimbra, [b]Grupo de Estudos da Doença Inflamatória Intestinal (GEDII), Almada, [c]Hospital Santo António, [d]Hospital São João, and [e]Department of Pharmacology and Therapeutics, Porto Medical School and Hospital São João, Porto, [f]Centro Hospitalar do Alto Ave, Guimarães, [g]Hospital de Braga, Braga, [h]Hospital Santo André, Leiria, [i]Centro Hospitalar Tondela Viseu, Viseu, [j]Hospital de Faro, Faro, [k]Hospital do Funchal, Funchal, [l]Hospital Beatriz Ângelo, Loures, [m]Hospital Egas Moniz, Lisboa, [n]Hospital de Setúbal, Setúbal, [o]Hospital de Portimão, Portimão, [p]Hospital Fernando Fonseca, Amadora, and [q]Hospital do Divino Espirito Santo, Ponta Delgada, Portugal

Key Words
Anaemia · Inflammatory bowel disease · Crohn's disease · Ulcerative colitis

Abstract
Background: Anaemia is the most common complication in patients with inflammatory bowel disease (IBD). This study aims to assess the prevalence of anaemia in IBD patients and to know its characteristics with regard to the main IBD clinical features. ***Methods:*** An observational cross-sectional multicentre study was conducted. We included all patients who had an appointment at the 15 participating centres during the period of 1 month, and who met the following selection criteria: age ≥18, diagnosis of IBD. Disease activity was evaluated by Harvey-Bradshaw Index (HBI) for Crohn's disease (CD), and by Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis (UC). ***Results:*** One thousand three hundred and thirteen patients, were included: 54.8% female, mean age 42.8 (interquartile range (25th–75th): 31–53 years), 59% had a diagnosis of CD, 39% of UC and 2% IBD unclassified. The median follow-up since diagnosis was 7 years. The ongoing treatment was aminosalicylates (63.1%), corticosteroids (11.6%), immunomodulators (36.4%) and anti-tumour necrosis factor (27.3%). Anaemia was identified in 244 patients, representing a prevalence of 18.6% (95% CI 16.6–20.9). A majority of cases (90%) have mild/moderate anaemia (mean haemoglobin 11.3 ± 0.8 g/dl). Anaemia was significantly higher in females (p = 0.006), but there were no differences between CDs (19.1%) and UCs (17.7%; p = 0.688). Anaemia

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E-Mail karger@karger.com
www.karger.com/dig

Francisco Portela
Serviço de Gastrenterologia
Centro Hospitalar e Universitário de Coimbra
Praceta Prof Mota Pinto. 3000 Coimbra (Portugal)
E-Mail fasportela@gmail.com

was more frequent in patients with active disease (HBI >4; SCCAI >2) than in those in clinical remission (33.6 vs. 15.6%, p < 0.001) and in patients on steroids (36.8%) vs. other treatments (p < 0.001). Only 47% of patients with anaemia were under any specific treatment (oral iron 67%; intravenous iron 41%). ***Conclusion:*** Anaemia was more frequent in patients with active disease and in those on corticosteroids. The treatment of anaemia still seems undervalued, whereas more than half of anaemic patients were not receiving any specific treatment and the use of oral iron prevails contrarily to current recommendations.

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic inflammatory conditions affecting the gastrointestinal tract. Intestinal manifestations, such as diarrhoea, abdominal pain and bleeding, are the main clinical features of these diseases. However, IBD is often complicated by manifestations that may be less apparent to the physician and the patient, such as malnutrition and anaemia [1].

Anaemia is currently recognised as one of the most common systemic complications of IBD [2, 3]. Its reported prevalence in IBD patients varies substantially depending on the definition of anaemia and the patient population considered (hospitalised vs. out-patients). Gasche [4] reported that one-third of patients with IBD are anaemic at any given time. Systematic reviews have reported an estimated prevalence of anaemia ranging from 6 to 74% [1, 5]. Gisbert and Gomollon [6] showed that the weighted mean prevalence of anaemia calculated from 22 studies was 17% (95% CI 16–18). When evaluating results stratified by out-patients and hospitalised patients, the weighted mean prevalence was 16 and 68%, respectively, underlining the importance of the population characteristics. In 2 recent papers, the prevalence of anaemia was reported to be 19% in an unselected outpatient population and 6% in a population-based cohort [7, 8].

Anaemia in IBD is associated with a reduced quality of life, and it negatively affects cognitive function and functional status [9, 10]. It is a co-morbid condition that is associated with other diseases (e.g. transfusion-associated hepatitis C) or even death [11], and needs adequate monitoring and treatment of the underlying, often multifactorial, causes [10, 12].

Anaemia in IBD has multiple causes, iron deficiency anaemia (IDA) being the most prevalent [13], but also including anaemia of chronic disease or a combination of both [3].

The therapeutic strategy for the treatment of anaemia in patients with IBD is essential in the management of this pathology and in the success of the therapeutic outcomes for patients. Due to the diversity of aetiologies, several treatment options were studied. For the main cause (IDA), the treatment options include oral or intravenous (IV) iron preparations, erythropoiesis stimulating agents supplemented with iron, and red blood cell transfusions.

The main aim of this study was to determine the prevalence of anaemia in a Portuguese cohort of IBD patients. Furthermore, this study assessed the clinical and socio-demographic profile of IBD patients with anaemia, and characterized the type, frequency and way of administration of anaemia treatment in this setting.

Materials and Methods

Study Design and Population

An observational cross-sectional multicentre assessment of IBD patients in 15 medical centres from southern, central and northern regions of Portugal was conducted. All patients attending one of those centres during a 1-month period, and who met the following selection criteria, were included: (a) age ≥18; (b) had a diagnosis of IBD; (c) gave their informed consent to participate in the study.

Data Collection

After obtaining informed consent, socio-demographic and clinical parameters were retrieved from all patients. Socio-demographic data included patients' age and gender. Clinical data encompassed the history of IBD (date of diagnosis, type of IBD, disease activity), IBD-associated comorbidities, presence of anaemia (date of diagnosis, type of anaemia), surgical background, previous and actual treatment for IBD (aminosalicylates, antibiotics, corticoids, immunomodulators or biologic therapy with anti-tumour necrosis factor (TNF)), anaemia-specific treatment (oral and IV iron preparations or red blood cell transfusions), and other simultaneous medications.

Disease activity was assessed through the Harvey-Bradshaw Index (HBI), a simplified version of the Crohn's Disease Activity Index [14], for patients with CD, and through the Simple Clinical Colitis Activity Index (SCCAI) [15] for patients with UC. Interpretation of disease severity scores were as follows: HBI ≤4 remission, HBI >4 active disease (HBI 5–7 mild disease; HBI ≥8 moderate/severe disease) [16], SCCAI ≤2.5 remission, SCCAI >2.5 active disease [17].

According to the definitions from the World Health Organization (WHO) [18], anaemia was defined as haemoglobin (Hb) levels <12 g/dl in nonpregnant women and <13 g/dl in men, both 15 years of age and above. Severe anaemia was considered for patients with Hb <10 mg/dl. Surgery was defined as any intra-abdominal procedure for active CD or a colectomy for UC.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 software. Continuous variables were described as medians and interquartile ranges, means and SD when appropriate, and categorical variables were described as numbers and (proportions with) percentages.

Exploratory analysis was performed using chi-square testing for categorical variables (or t tests for continuous variables) based on a 95% CI (2 sided). When it was not possible to use the t test for continuous variables, due to sample size, the corresponding non-parametric test was used. A p value of <0.05 was considered to be statistically significant.

A logistic regression analysis was performed to investigate whether the presence of anaemia was positively or negatively associated with exposure to several factors. OR were calculated for each of the considered variables, and ROC curves determined to assess the model's sensitivity and specificity.

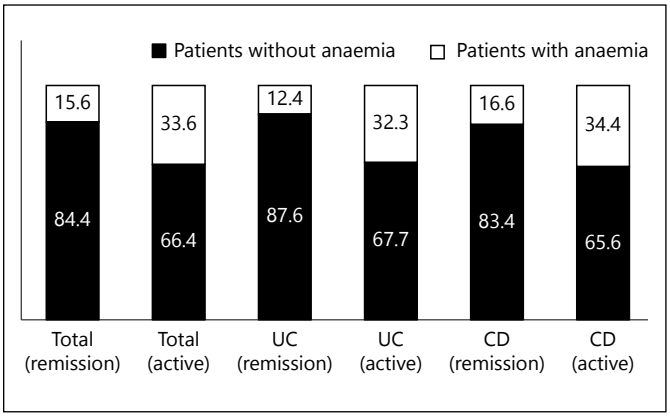

Fig. 1. Frequency of anaemia by disease activity. Active disease (HBI >4 or SCCAI >2.5); $p < 0.05$ for the differences between active and remission in total, UC and CD.

Results

A total of 1,313 patients (54.8% female vs. 45.2% male) with a mean age of 41 (interquartile range (25th–75th): 31–53 years) had criteria for inclusion and were enrolled in this study. Fifty nine per cent (n = 775) of patients had a diagnosis of CD, 39% (n = 512) patients had a diagnosis of UC, and 2% (n = 26) of patients had IBD unclassified. The median follow-up since diagnosis was 9 years, with no significant differences between CD and UC (table 1).

Data about disease activity showed that most patients (83%) were in clinical remission (HBI ≤4 or SCCAI ≤2.5). In total, among CD patients, 87.5% were in clinical remission, 8.6% had mild disease and 3.9% of the patients had a moderate/severe disease. Among UC patients, 66.1% were in clinical remission and 33.9% had active disease.

Disease-associated co-morbidities were reported in 32.6% of IBD patients with no significant differences between CD and UC patients (29.6 vs. 39.6%; p = 0.054). The most frequently observed co-morbidities were arterial hypertension, dyslipidaemia, diabetes and depression.

Anaemia was found in 244 patients, which represents a prevalence of 18.6% in this cohort. There were no statistically significant differences between affected patients in relation to type of IBD (19.1% prevalence of anaemia for CD patients vs. 17.7% for UC patients; p = 0.688) or in relation to mean age (44.1 years for anaemic patients vs. 42.3 years for patients without anaemia; p = 0.14). However, the same was not true concerning gender, with a significantly higher prevalence of anaemia in women than in men (21.5 vs. 15.5%; p = 0.006).

Among anaemic patients, a majority (90%) were classified as having mild anaemia (mean Hb 11.3 g/dl; SD 0.8) with only 10% with Hb <10 g/dl (mean Hb 8.8 g/dl; SD 0.5).

Table 1. Patients characteristics stratified by IBD type

	CD	UC
Patients, n (%)[1]	775 (59)	512 (39)
Age, years, mean (interquartile range; 25th–75th)	40.3 (29–49)	46.4 (34–58)
Female/male, %	54/46	55/45
Disease duration, years, mean (interquartile range; 25th–75th)	9.3 (3–13)	9.5 (3–13)
Hb, g/l, mean ± SD	11.3±1.0	11.1±1.1
Anaemia, %	19.1	17.7
Treatment (previous)		
5-ASA	570 (73.6)	427 (83.5)
Corticosteroids	527 (68.3)	278 (54.4)
Immunomodulators	333 (43.7)	126 (24.6)
Anti-TNF-α	79 (19.2)	40 (7.9)
Treatment (ongoing)		
5-ASA	363 (46.9)	444 (86.8)
Corticosteroids	93 (12.1)	58 (11.3)
Immunomodulators	369 (47.7)	101 (19.8)
Anti-TNF-α	259 (33.5)	92 (17.9)
Harvey-Bradshaw, mean ± SD	2.0±2.7	
SCCAI, mean ± SD		2.0±2.4

[1] 26 patients with IBD unclassified excluded from this table.

Anaemia was more frequent in patients with active IBD (HBI >4 or SCCAI >2.5) than in quiescent patients (33.6 vs. 15.6%, respectively; p < 0.001; fig. 1) and the Hb level showed a negative correlation with HBI (r = –0.216, p < 0.001) and SCCAI (r = –0.266, p < 0.001).

Concerning IBD treatment we found that prior surgery was not significantly associated with anaemia (19.7%; p = 0.456) but treatment with steroids (p < 0.001), immuno-

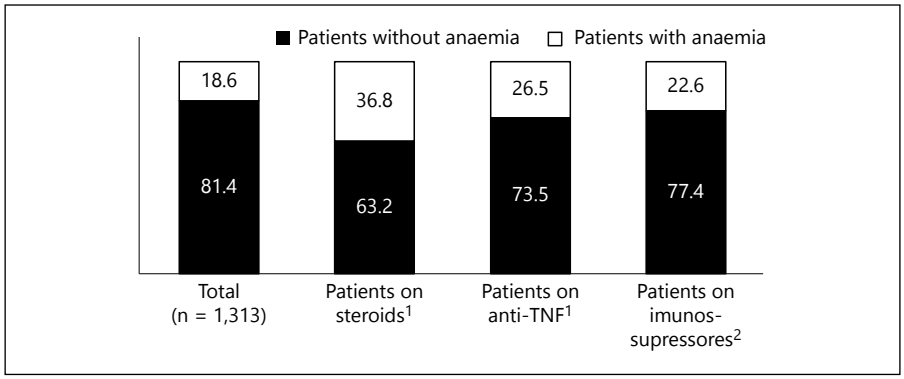

Fig. 2. Frequency of anaemia by ongoing treatment. [1] $p < 0.001$ comparing with total (n = 1,313); [2] $p < 0.007$ comparing with total (n = 1,313).

Table 2. Disease activity and treatment in CD patients with and without anaemia

	With anaemia, %	Without anaemia, %	Univariate analysis, p value	Multivariate analysis	
				OR (95% CI)	p value
Patients with CD	19.1	80.9			
Male/female	37.4/62.6	47.6/52.4	0.026	0.816 (0.534–1.247)	0.348
Active disease (HBI >4)	34.4	65.6	0.001	1.130 (1.002–1.275)	0.047
Inactive disease (n = 1,066)	17.1	82.9			
Treatment (previous)					
5-ASA	20.8	79.2	0.069	1.209 (0.736–1.986)	0.454
Corticosteroids	22.4	77.6	0.002	1.616 (0.989–2.641)	0.055
Immunomodulators	23.3	76.7	0.008	1.213 (0.753–1.953)	0.427
Anti-TNF-α	26.9	73.1	0.011	1.397 (0.795–2.455)	0.246
Treatment (ongoing)					
5-ASA	16.8	83.2	0.144	0.786 (0.495–1.248)	0.308
Corticosteroids	37.5	62.5	<0.001	2.468 (1.402–4.343)	0.002
Immunomodulators	19.4	80.6	0.862	0.946 (0.615–1.455)	0.800
Anti-TNF-α	23.5	76.5	0.036	1.342 (0.830–2.170)	0.230
Surgery	18.8	81.2	0.364		

modulators ($p < 0.001$), and anti-TNF ($p < 0.001$) were associated with higher rates of anaemia (fig. 2). Similar results were found when patients are stratified by disease type with a higher percentage of anaemia in patients treated with corticosteroids or immunomodulators including anti TNF (tables 2 and 3). The logistic regression showed that active disease (HBI >4 or SCCAI >2.5), actual treatment with corticosteroids in CD, and previous treatment with steroids or immunomodulators in UC independently correlate with the existence of anaemia (tables 2 and 3).

Only 113 (47.1%) IBD patients with anaemia were receiving specific treatment (oral, IV iron or blood transfusion), corresponding to 50% of CD patients and 40.4% of UC patients. The preferred type of treatment for anaemia was oral iron (27.5% of anaemic patients overall; 31.3% in CD, and 21.1% in UC), followed by IV iron (19.7% of anaemic patients overall; 18.4% in CD, and 20.0% in UC) and, finally, red blood cells transfusion (0.4% of anaemic patients overall).

In patients with anaemia, the subgroup without specific treatment is characterized by a higher level of Hb and a lower percentage of moderate/severe cases, but similar levels of active disease (table 4).

Discussion

The clinical characteristics of IBD Portuguese patients have been previously described [19, 20], but data concerning anaemia were lacking. In this cross-sectional study, we investigated the prevalence of anaemia in Portuguese patients with IBD.

Table 3. Disease activity and treatment in UC patients with and without anaemia

	With anaemia, %	Without anaemia, %	Univariate analysis, p value	Multivariate analysis	
				OR (95% CI)	p value
Patients with UC	17.7	82.3			
Male/female	36.7/63.3	46.3/53.7	0.097	0.629 (0.332–1.190)	0.154
Active disease (SCCAI ≤2.5)	33.1	66.9	0.001	1.359 (1.201–1.537)	<0.001
Inactive disease (n = 1,066)	12.4	87.6			
Treatment (previous)					
5-ASA	18.1	81.9	0.705	1.214 (0.556–2.651)	0.626
Corticosteroids	26.1	73.9	<0.001	2.196 (1.065–4.528)	0.033
Immunomodulators	32.1	67.9	<0.001	3.448 (1.519–7.826)	0.003
Anti-TNF-α	31.4	68.6	0.011	0.746 (0.242–2.301)	0.610
Treatment (ongoing)					
5-ASA	16.9	83.1	0.291	1.067 (0.472–2.412)	0.877
Corticosteroids	34.5	65.5	0.001	1.232 (0.524–2.898)	0.633
Immunomodulators	31.3	68.8	<0.001	0.845 (0.384–1.861)	0.677
Anti-TNF-α	33.3	66.7	<0.001	1.649 (0.725–3.749)	0.233

Table 4. Patients with anaemia

	Male/ female, %	Hb, mean	Hb <10 g/dl, %	CD/UC, %	Active/ remission, %	Actual treatment with steroids, %
Without anaemia (n = 1,069)	47.0/53.0	14.1		59.8/40.2	13.7/83.3	9.0
Anaemia and iron substitution (n = 113)	33.6/66.4	10.9	20.7	66.7/33.3	27.4/72.6	23.4
Anaemia and no iron substitution (n = 131)	40.5/59.5	11.5	6.5	58.1/41.9	32.8/67.2	22.6
Comparison among the 3 groups, p value	0.013	<0.001	<0.001	0.434	<0.001	<0.001
Comparison between anaemia and iron substitution vs. anaemia and no iron substitution, p value	0.271	<0.001	0.003	0.239	0.368	0.888

In our study, the percentage of anaemia was 18.6% (95% CI 16.6–20.9), which is contained in the interval reported in the literature (8.8–73.7%) for the prevalence of anaemia associated with IBD [5]. This wide interval can be related to several factors, namely, the definition of anaemia and the population recruited (e.g. hospitalized patients vs. outpatients, CD vs. UC, and the timepoint considered for the study). Bergamaschi et al. [21] presented a careful analysis of anaemia in patients with IBD, in which they assessed 263 out-patients and observed that almost two-thirds were anaemic at diagnosis with a slightly higher rate in CD. Høivik et al. [22] also observed that more patients with CD than UC had anaemia at diagnosis (48.4 vs. 20.2%, respectively). Our results of 19.1% in CD patients and 17.7% in UC patients are lower and much closer to the ones reported by Filmann et al. [23] (27% in CD patients and 21% in UC patients).

In our cohort, the presence of anaemia was not associated with the type of IBD, that is, patients with UC had the same probability of having anaemia as patients with CD, nor with patient's median age, or with a history of prior surgeries. On the other hand, active disease, depicted in 19.9% of the patients was correlated with anaemia (33.6 vs. 15.6% in patients in remission). The presence of anaemia had been positively associated with disease activity before, confirming that an activated immune system and disease-associated lesions of the gut are the major contributors to anaemia in IBD [21].

In our study, besides being associated with greater clinical activity, the presence of anaemia in IBD patients was also associated with the use of corticosteroids and immunomodulators, highlighting the relationship between active or more severe disease and anaemia. Other authors have also reported that patients receiving IBD-specific medication and patients with active disease were significantly more likely to have anaemia when compared with patients not receiving any IBD-specific medication or being in remission [23, 24].

The severity of anaemia in IBD varies considerably [1]. Most patients have mild to moderate anaemia (Hb >10.0 g/dl) [3, 24] as it was the scenario in our study in which a great majority of them had mild forms, irrespective of being under treatment or not for anaemia.

Only in recent years, anaemia has been highlighted as a specific therapeutic aim in patients with IBD [25]. It should not be assumed that some level of anaemia is a normal finding in IBD patients and consequently need not be treated. On the contrary, iron stores evaluation should be conducted as soon as anaemia (Hb <13 g/dl in males, and <12 g/dl in females) is detected [26]. Considering the WHO definitions we found that, in our cohort, less than half of IBD patients with anaemia were receiving treatment for the main cause of anaemia in this setting – iron deficiency. Although we only have information concerning the iron status in a small subgroup of anaemic patients (data not shown) and due to regulatory reasons, the inclusion in the protocol of further investigations (namely ferritin) was not approved for an observational study, the fact that the majority was in clinical remission makes the hypothesis of anaemia of chronic disease less likely. The comparison between these patients and the subgroup with anaemia and treatment (lower Hb and higher level of moderate or severe cases but similar percentage of active disease) suggests that Portuguese gastroenterologists are not too anxious to treat mild degrees of anaemia.

Iron tablets intake was the most used treatment for anaemia in our patients, consistent with widespread practice across Europe [27]. Although Gisbert et al. [28] and Kulnigg et al. [29] show that oral and IV iron treatment are safe and well tolerated in IBD patients with good clinical response in both formulations, other clinical trials described less tolerability of oral formulations [30, 31], and studies in animal models [32], not totally confirmed in clinical trials, suspected that oral iron formulations can increase disease activity in IBD [33]. Furthermore, a significant increase in ferritin level and a better Hb response is achieved with IV iron preparations compared to oral iron, as reported by previous studies, with an acceptable safety profile and higher rates of adherence or reduced discontinuation of intervention in patients in IV iron [30, 34, 35].

Although oral iron is a cheap and convenient treatment for anaemia, it has been shown to result in failure to control anaemia in 2 out of 3 IBD patients, probably in part due to the side effects reported by over half the number of patients [35].

In view of these data, current therapy options for IBD patients treated for anaemia in our centres should be re-evaluated, taking into account that treatment should be considered for all patients with an Hb below normal. When iron tablets are considered for patients with IBD, there should be a predetermined duration of treatment, with a pre-defined dose (some authors suggest no more than 100 mg elemental iron daily [35], a well-established target end point Hb and early review of patients with regard to adherence and adverse effects. Those with severe anaemia (Hb <10 g/dl), active disease, who fail to tolerate or do not respond adequately should consider IV iron [36].

In conclusion, the prevalence of anaemia in IBD Portuguese patients is similar to that in other cohorts that focus mainly on outpatient populations. Active disease is the parameter most consistently related to the presence of anaemia. The treatment of anaemia is still undervalued, whereas more than half the number of anaemic patients were not receiving any specific treatment, and the use of oral iron prevails contrary to the recommendations.

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Disclosure Statement

F. Portela received honoraria for lectures from AbbVie, Ferring, Merck Sharp & Dohme and Om-Pharma; P. Lago received honoraria for acting as a consultant and/or as a speaker at events sponsored by AbbVie, MSD, Ferring, and OM Pharma; P. Ministro received honoraria for lectures from Abbvie, Hospira, Ferring, MSD; P. Peixe received honoraria for lectures/consultant from AbbVie, Merck Sharp & Dohme and Om-Pharma; F. Magro received fees for lectures from Abbvie, Falk, Ferring, Lab Vitoria, MSD, Om-Pharma and Vifor. The other authors declared no conflict of interest.

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