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Systemic Inflammation and Anemia in Inflammatory Bowel Disease: Frequency and Co-occurrence

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Abstract

Background

Systemic inflammation and anemia are the laboratory abnormalities most frequently encountered in inflammatory bowel disease (IBD), but data from Morocco, and particularly from its eastern region, are scarce. This descriptive, exploratory study primarily aimed to estimate the frequency of biological inflammation and of anemia at the first laboratory panel in patients followed for IBD at a Moroccan university hospital. Secondary objectives were to describe the distribution of IBD subtypes, the severity and morphology of anemia, the co-occurrence of the two abnormalities, and their distribution in Crohn's disease (CD) and ulcerative colitis (UC). The study was not designed to test causal relationships.

Methods

This retrospective, single-center, descriptive study was conducted at the Laboratory of Biochemistry of Mohammed VI University Hospital, Oujda, Morocco, from July 2021 to August 2023. All consecutive patients of any age followed for IBD who had at least one C-reactive protein (CRP) measurement and/or complete blood count (CBC) were included through exhaustive non-probability sampling. Biological inflammation was defined as CRP >5 mg/L, and anemia and its severity were defined according to World Health Organization (WHO) age- and sex-specific criteria. The primary analysis was based on the first laboratory panel of each patient; analyses of all panels were descriptive only. CD and UC were compared using the Mann-Whitney U test for quantitative variables and Pearson's chi-squared (χ^2) test or Fisher's exact test for categorical variables; $p<0.05$ was considered significant.

Results

A total of 155 patients were included (median age 36 years, interquartile range (IQR) 28-46; women 85/155, 54.8%), of whom 102/155 (65.8%) had CD, 36/155 (23.2%) UC, and 17/155 (11.0%) unclassified IBD. Biological inflammation was found in 73/146 patients (50.0%; 95% confidence interval (CI) 42.0-58.0), and CRP exceeded 10 mg/L in 44/146 (30.1%). Anemia affected 56/151 patients (37.1%; 95% CI 29.8-45.0); it was mild in 34/56 (60.7%), moderate in 16/56 (28.6%), severe in 6/56 (10.7%), and microcytic in 20/56 (35.7%). Among the 142 patients with both CRP and hemoglobin (Hb), 28/142 (19.7%) had both abnormalities and 95/142 (66.9%) had at least one. No statistically significant difference was found between CD and UC in the frequency of inflammation (51/96, 53.1% vs 17/35, 48.6%; $\chi^2(1)=0.21$; $p=0.64$) or of anemia (35/100, 35.0% vs 15/34, 44.1%; $\chi^2(1)=0.90$; $p=0.34$), although the confidence intervals were wide. Patients with UC were older than those with CD (median 44.5 vs 34 years; Mann-Whitney $U=1272$; $z=-2.74$; $p=0.006$).

Conclusions

In this hospital-based cohort, half of the patients with IBD showed biological inflammation and more than one-third were anemic, with no statistically significant difference between CD and UC, a comparison that was underpowered to exclude moderate differences. Because the two abnormalities were often dissociated, CRP and Hb appear to convey complementary rather than interchangeable information, which is consistent with guideline recommendations to monitor both. Whether combined testing improves clinical outcomes was not assessed and warrants prospective evaluation.

Categories: Medical Education, Internal Medicine, Gastroenterology
Keywords: anemia, c-reactive protein, crohn's disease, inflammatory bowel disease, morocco, prevalence, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD), ulcerative colitis (UC), and unclassified IBD, and is characterized by chronic, relapsing inflammation of the gastrointestinal tract. Over

the past decades, its epidemiology has shifted: incidence has reached a plateau in Western countries, whereas it continues to rise in newly industrialized regions of Asia, South America, Africa, and the Middle East [1]. The Middle East and North Africa (MENA) region illustrates this transition. An analysis of the Global Burden of Disease 2019 database estimated that 282,534 people were living with IBD in the region in 2019, with incidence and prevalence rising steadily since 1990; Morocco had the lowest estimated incidence in the region (1.6 per 100,000), a value that probably reflects, at least in part, limited case ascertainment and the scarcity of local registries [2]. More recently, the multinational tertiary-care MIRAGE registry, which included 10,340 patients from seven MENA countries, confirmed that IBD is no longer a rare condition in the region and that it predominantly affects young adults, with a mean age of 34.6 years in CD and 39.8 years in UC [3]. Despite this growing burden, data describing the biological profile of patients with IBD in North Africa remain sparse.

Disease monitoring in IBD relies on a combination of clinical, endoscopic, radiological, and biological assessments. Because endoscopy is invasive, costly, and not always readily accessible, and because fecal biomarkers are not routinely available in many centers in low- and middle-income countries, simple blood tests continue to play a central role in everyday follow-up. C-reactive protein (CRP) is the most widely used serum marker of systemic inflammation in IBD. It is an acute-phase protein produced by hepatocytes in response to interleukin-6, and its short half-life of about 19 hours allows it to rise and fall rapidly with changes in inflammatory activity [4]. The CRP response is, however, heterogeneous. In the population-based Norwegian IBSEN cohort, patients with CD had a markedly stronger CRP response than those with UC [5], and in the Mayo Clinic series of Solem et al., CRP correlated with clinical, endoscopic, histological, and radiographic activity in CD, whereas the association was weaker in UC and largely confined to extensive or severe disease [6]. This difference is classically attributed to the transmural nature of inflammation in CD, as opposed to the more superficial mucosal involvement of UC. A meta-analysis of symptomatic patients further showed that CRP has high specificity but limited sensitivity for endoscopic activity, so that a normal value does not rule out mucosal inflammation [7]. CRP nevertheless remains clinically relevant, and its normalization is retained as an intermediate treatment target in the STRIDE-II treat-to-target recommendations [8].

Anemia is the most common systemic complication and extraintestinal manifestation of IBD. Its pathogenesis is typically multifactorial, combining chronic blood loss from the inflamed mucosa, impaired duodenal iron absorption, reduced dietary intake, vitamin B12 or folate deficiency, drug-induced myelotoxicity, and anemia of chronic disease [9,10]. In the latter, inflammatory cytokines, particularly interleukin-6, induce hepatic hepcidin, which blocks intestinal iron absorption and traps iron within macrophages, while also blunting erythropoietin production and the bone marrow response [11,12]. Iron deficiency and anemia of chronic disease therefore frequently coexist in the same patient. Anemia is far from a benign laboratory finding: it impairs quality of life, cognitive function, and work capacity; persistent or recurrent anemia has been associated with a more severe and disabling disease course, with more hospitalizations and surgery [13]; and in a large Italian multicenter study, increasing severity of anemia was associated with greater fatigue and poorer quality of life [14].

The reported prevalence of anemia in IBD varies considerably, from 8.8% to 73.7% depending on the population studied [15]. Recent figures include 13.6% among 5,416 Italian outpatients [14], 18.6% in a Portuguese nationwide cross-sectional study [16], 19% in Scandinavian outpatients [17], and 24% in a European individual-patient data meta-analysis [18]. Prevalence was 21% in Brazilian outpatients [19], between 36% and 42% in a Korean hospital cohort [20], and 39.5% in an Italian tertiary cohort [21]. Such heterogeneity reflects differences in recruitment setting, case mix, timing of assessment, diagnostic thresholds, and access to iron supplementation. Timing is particularly important, since anemia is most frequent around diagnosis: in the IBSEN cohort, it affected 48.8% of patients with CD at diagnosis [22]. Based on this evidence, European guidelines recommend regular screening of hemoglobin (Hb) and iron status in all patients with IBD [9], every 3 months in patients with active disease and every 6 to 12 months in those in remission [23]. Despite these recommendations, anemia remains underdiagnosed and undertreated; in the Italian multicenter study, only 68.9% of anemic patients with iron deficiency received appropriate supplementation [14].

Inflammation and anemia are linked through two partly independent pathways. On the one hand, active inflammation drives interleukin-6-mediated hepcidin synthesis, which restricts iron absorption and iron release from macrophages and produces a functional iron deficiency; this component of anemia should, in principle, parallel CRP [11,12]. On the other hand, absolute iron deficiency caused by chronic mucosal blood loss and malabsorption, together with vitamin B12 or folate deficiency and drug-induced myelotoxicity, can persist after inflammation has subsided or develop with little systemic acute-phase response, notably in mucosal disease or in isolated small-bowel involvement [9,10]. Conversely, transmural or extraintestinal inflammation can raise CRP without causing anemia when iron stores are preserved. The two abnormalities may therefore be dissociated in individual patients. Although inflammation and anemia are closely linked pathophysiologically, the extent to which they overlap in routine practice is uncertain. If anemia were mainly inflammatory, CRP alone might suffice to identify patients at risk; if, conversely, the two abnormalities were largely dissociated, both tests would be needed. Quantifying their co-occurrence therefore has direct practical implications for laboratory monitoring, particularly in settings where resources must be used efficiently.

In Morocco, published laboratory data on patients with IBD remain limited and originate mainly from a single tertiary center in Marrakech [24]. To our knowledge, no series from the eastern region of the country has been reported. We therefore conducted a descriptive, exploratory study of patients followed for IBD at Mohammed VI University Hospital in Oujda. The primary objective was to estimate the frequency of biological inflammation and of anemia at the first laboratory panel of each patient. Secondary objectives were to describe (i) the distribution of IBD subtypes; (ii) the severity and morphological type of anemia; (iii) the co-occurrence of biological inflammation and anemia; and (iv) the distribution of these abnormalities in CD and UC. The study was not designed to test causal relationships between systemic inflammation and anemia.

Materials And Methods

Study design, setting, and duration

We conducted a retrospective, observational, single-center descriptive and exploratory study, complemented by an analytical comparison between IBD subtypes. The study took place at the Laboratory of Biochemistry of Mohammed VI University Hospital, Oujda, Morocco, a tertiary referral center for the eastern region of the country, and covered a 26-month period from July 2021 to August 2023.

Sampling technique and eligibility criteria

Sampling was exhaustive and non-probabilistic, and all consecutive patients who met the eligibility criteria during the study period were included. Patients of any age were eligible if they had a diagnosis of IBD documented in the hospital medical record and at least one laboratory panel, consisting of a CRP measurement and/or a complete blood count (CBC), performed in our laboratory during the study period. Exclusion criteria were an IBD diagnosis that could not be confirmed in the medical record, the absence of both CRP and CBC results, and identification data insufficient to reliably link repeated panels from the same patient. The diagnosis and subtype of IBD (CD or UC) were taken from the diagnosis recorded by the treating gastroenterologist in the hospital medical file; they were not re-adjudicated by the investigators on the basis of endoscopic or histological reports. Patients recorded as having colitis without a definite subtype were classified as having unclassified IBD. Figure *1* summarizes the patients included and the data available for each analysis; the number of records screened and the exclusions by criterion could not be retrieved retrospectively from the laboratory information system.

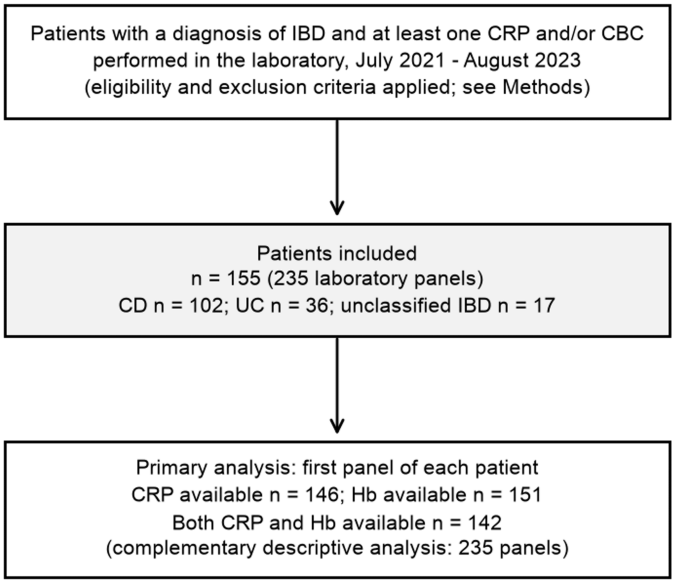


FIGURE 1: Flowchart of patient selection

IBD: inflammatory bowel disease; CRP: C-reactive protein; CBC: complete blood count; CD: Crohn's disease; UC: ulcerative colitis; Hb: hemoglobin

Unit of analysis

Because some patients underwent several laboratory panels during the study period, the primary analysis was restricted to the first panel of each patient, so that each of the 155 patients contributed a single

observation. The first panel was defined as the earliest panel recorded in our laboratory during the study period; it did not necessarily correspond to the time of diagnosis. Because exact sampling dates were not available in the laboratory extract, CRP and CBC were considered paired when they belonged to the same first panel, and the co-occurrence analysis was restricted to patients with both measurements at that panel. A complementary analysis of all 235 panels was performed to describe the abnormalities observed at any time during follow-up. Because repeated panels from the same patient are not independent, this analysis was purely descriptive, and no inferential test was applied to it. No clinical, endoscopic, or histological activity index was available.

Laboratory methods

Serum CRP was measured with a particle-enhanced immunoturbidimetric assay on an ARCHITECT c-series analyzer (Abbott Laboratories, Abbott Park, IL, USA) and expressed in milligrams per liter (mg/L). The CBC, including Hb in grams per deciliter (g/dL) and mean corpuscular volume (MCV) in femtoliters (fL), was performed on a Sysmex hematology analyzer (Sysmex Corporation, Kobe, Japan). Internal quality control and external quality assessment were carried out according to the routine procedures of the laboratory.

Operational definitions

Biological inflammation was defined as a CRP value above the upper reference limit of our laboratory (>5 mg/L). CRP values were also grouped into four strata: ⩽5, >5-10, >10-50, and >50 mg/L. Anemia was defined according to WHO 2011 age- and sex-specific criteria [25]: Hb <11.0 g/dL in children aged 6-59 months, <11.5 g/dL in children aged 5-11 years, <12.0 g/dL in children aged 12-14 years, and, from 15 years of age, <12.0 g/dL in non-pregnant women and <13.0 g/dL in men. Severity was graded using the corresponding WHO age- and sex-specific cut-offs; for patients aged 15 years or older, anemia was mild (Hb ⩾11 g/dL and below the sex-specific threshold), moderate (Hb 8-10.9 g/dL), or severe (Hb <8 g/dL) [25]. Pregnancy status is not systematically recorded in the laboratory information system; no pregnant patient was identified in the medical records, and non-pregnant thresholds were therefore applied to all women. Anemia was considered microcytic when MCV was <80 fL.

Variables and potential confounders

The variables collected were age, sex, IBD subtype, CRP, Hb, and MCV. Age, sex, and IBD subtype were regarded as potential confounders of the relationship between inflammation and anemia; the frequencies of inflammation and anemia are reported by sex and by subtype, and age was compared between subtypes. No multivariable adjustment was performed because of the limited number of anemic patients and the absence of data on disease activity, extent, and treatment. Information on disease duration, disease extent or behavior, current treatment (corticosteroids, immunosuppressants, biologics, salicylates), iron or vitamin supplementation, surgical history, intercurrent infections, and comorbidities was not recorded in the laboratory information system; these unmeasured confounders are acknowledged as a limitation.

Sample size

No a priori sample size calculation was performed, as this descriptive study relied on the exhaustive recruitment of all eligible patients over a fixed 26-month period. With 151 patients with available Hb, the half-width of the 95% confidence interval around an observed prevalence of 37% is approximately ±7.7 percentage points, which was considered acceptable for a descriptive objective. The comparison between CD (n=100 with available Hb) and UC (n=34) had approximately 80% power to detect an absolute difference of about 27 percentage points in anemia prevalence (for example, 35% vs 62%); smaller but potentially clinically meaningful differences therefore could not be excluded.

Statistical analysis

After graphical assessment of their distribution, quantitative variables were summarized as median and interquartile range (IQR), and categorical variables as counts and percentages (n/N, %), using as denominator the number of patients with available data for each variable. Ninety-five percent CIs for proportions were calculated with the Wilson score method, and CIs for differences in proportions with the Newcombe hybrid score method. CD and UC were compared with the Mann-Whitney U test for quantitative variables (reporting U, z, and p) and with Pearson's χ^2 test for categorical variables (reporting χ^2, degrees of freedom, and p); Fisher's exact test was used when an expected cell count was below five. The trend in anemia prevalence across the four CRP strata was assessed with the Cochran-Armitage test for trend, and the association between CRP and Hb was quantified with Spearman's rank correlation coefficient (ρ). Because individual-level data for the four patients younger than 18 years could not be re-extracted, their influence on the main estimates was assessed with a bounding sensitivity analysis, in which each proportion was recalculated after their exclusion under the most extreme assumptions regarding their data availability and laboratory status. Patients with unclassified IBD were included in the overall estimates but excluded from the CD versus UC comparisons. Missing data were not imputed, and analyses were performed on available cases. Inferential tests were applied only to the first-panel (patient-level) data; panel-level results are presented descriptively. All tests were two-sided, and $p<0.05$ was considered statistically significant. Analyses were performed with IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

Ethical considerations and data management

The study protocol was reviewed and approved by the Mohammed VI University Hospital, Oujda. The study was conducted in accordance with the Declaration of Helsinki. Data were extracted from the laboratory information system and de-identified before analysis by replacing personal identifiers with a study code; the correspondence key was kept separately by one investigator. The analysis dataset was stored on a password-protected institutional computer accessible only to the investigators, and no identifying information is reported in this article.

Results

Patient characteristics

Over the 26-month study period, 155 patients met the eligibility criteria (Figure *1*); they contributed a total of 235 laboratory panels. The median number of panels per patient was one (range 1-5), and 102/155 patients (65.8%) had a single panel, indicating that most patients were tested only once in our laboratory. The median age was 36 years (IQR 28-46; range 4-74). Four patients (4/155, 2.6%) were younger than 18 years, 86/155 (55.5%) were aged 18-39 years, 55/155 (35.5%) were aged 40-59 years, and 10/155 (6.5%) were aged 60 years or older; young adults thus accounted for nearly three-fifths of the cohort. There were 85 women (85/155, 54.8%) and 70 men (70/155, 45.2%). CD was the predominant subtype (102/155, 65.8%), followed by UC (36/155, 23.2%) and unclassified IBD (17/155, 11.0%). Demographic and laboratory characteristics at the first panel, overall and by subtype, are presented in Table *1*.

Variable	All patients (n=155)	CD (n=102)	UC (n=36)	Test statistic (CD vs UC)	P
Age, years, median (IQR)	36 (28-46)	34 (28-43)	44.5 (31.8-55.3)	U=1272; z=-2.74	0.006
Women, n/N (%)	85/155 (54.8)	54/102 (52.9)	21/36 (58.3)	$\chi^2(1)=0.31$	0.58
CRP, mg/L, median (IQR)	4.93 (1.71-14.66); n=146	5.44 (1.92-16.07); n=96	4.67 (1.75-10.78); n=35	U=1594; z=0.45	0.65
Inflammation (CRP >5 mg/L), n/N (%)	73/146 (50.0)	51/96 (53.1)	17/35 (48.6)	$\chi^2(1)=0.21$	0.64
CRP >10 mg/L, n/N (%)	44/146 (30.1)	30/96 (31.3)	10/35 (28.6)	$\chi^2(1)=0.09$	0.77
Hb, g/dL, median (IQR)	12.7 (11.8-14.3); n=151	12.7 (11.8-14.4); n=100	12.7 (10.7-13.6); n=34	U=1435.5; z=1.35	0.18
Anemia (WHO criteria), n/N (%)	56/151 (37.1)	35/100 (35.0)	15/34 (44.1)	$\chi^2(1)=0.90$	0.34

TABLE 1: Demographic characteristics and laboratory findings at the first laboratory panel, overall and according to the inflammatory bowel disease subtype

Units: age in years; C-reactive protein (CRP) in milligrams per liter (mg/L); hemoglobin (Hb) in grams per deciliter (g/dL). Quantitative variables were compared with the Mann-Whitney U test (reporting U and z) and categorical variables with Pearson's chi-squared (χ^2) test with one degree of freedom; $p<0.05$ was considered statistically significant. The "All patients" column includes 17 patients with unclassified inflammatory bowel disease (IBD), who were excluded from the comparison between Crohn's disease (CD) and ulcerative colitis (UC). n denotes the number of patients with available data.

IQR: interquartile range; WHO: World Health Organization

As shown in Table *1*, age was the only characteristic that differed significantly between subtypes. Patients with UC were about ten years older than those with CD (median 44.5 vs 34 years; Mann-Whitney U=1272; z=-2.74; p=0.006) and showed a wider age distribution (IQR 31.8-55.3 vs 28-43). No statistically significant difference between subtypes was observed for sex distribution, median CRP, median Hb, or the proportions of patients with inflammation or anemia (all $p \geq 0.18$); given the small UC group, these results do not demonstrate that the two subtypes are equivalent. In the whole cohort, median CRP (4.93 mg/L) lay just below the 5 mg/L threshold, so that this cut-off divided the cohort almost exactly in half; likewise, median Hb (12.7 g/dL) was close to the WHO anemia thresholds, meaning that small shifts in Hb resulted in substantial changes in the proportion of patients classified as anemic.

Biological inflammation

In the first panel, CRP was available for 146/155 patients (94.2%), with a median value of 4.93 mg/L (IQR 1.71-14.66). Exactly half of these patients had biological inflammation (73/146, 50.0%; 95% CI 42.0-58.0). By stratum, CRP was ≤5 mg/L in 73/146 (50.0%), >5-10 mg/L in 29/146 (19.9%), >10-50 mg/L in 34/146 (23.3%),

and >50 mg/L in 10/146 (6.8%). Among patients with raised CRP, most (44/73, 60.3%) had values above 10 mg/L, and 1 in 7 (10/73, 13.7%) had values above 50 mg/L, a level generally associated with marked systemic inflammation or an intercurrent infectious or suppurative complication. The frequency of inflammation did not differ significantly between CD and UC (51/96, 53.1% vs 17/35, 48.6%; difference 4.6 percentage points, 95% CI -14.1 to 22.9; Pearson's $\chi^2(1)=0.21$; p=0.64) or between women and men (37/79, 46.8% vs 36/67, 53.7%; Pearson's $\chi^2(1)=0.69$; p=0.41); the width of these intervals means that moderate differences between subgroups cannot be excluded.

Anemia

Hb was available for 151/155 patients (97.4%). Anemia was present in 56/151 patients (37.1%; 95% CI 29.8-45.0), affecting 33/82 women (40.2%) and 23/69 men (33.3%); this difference was not statistically significant (Pearson's $\chi^2(1)=0.77$; p=0.38). The prevalence of anemia was 35/100 (35.0%) in CD and 15/34 (44.1%) in UC (difference -9.1 percentage points, 95% CI -27.6 to 8.9; Pearson's $\chi^2(1)=0.90$; p=0.34). The severity and morphological type of anemia are detailed in Table 2.

Characteristic	n	% of anemic patients (N=56)	% of all patients with available hemoglobin (N=151)
Mild anemia(adults ≥15 years: Hb ≥11 g/dL and below the sex-specific threshold)	34	60.7	22.5
Moderate anemia (adults ≥15 years: Hb 8-10.9 g/dL)	16	28.6	10.6
Severe anemia (adults ≥15 years: Hb <8 g/dL)	6	10.7	4.0
Microcytic anemia (MCV <80 fL)	20	35.7	13.2

TABLE 2: Severity grade and morphological type of anemia at the first laboratory panel

Units: hemoglobin (Hb) in grams per deciliter (g/dL); mean corpuscular volume (MCV) in femtoliters (fL). Severity was graded according to World Health Organization age- and sex-specific criteria; cut-offs shown are those for patients aged 15 years or older. Severity categories are mutually exclusive and sum to 56; microcytic anemia is a morphological subgroup that overlaps with the severity categories. No statistical test was applied to this descriptive distribution.

Anemia was mostly of limited severity (Table 2): 6 in 10 anemic patients had mild anemia, and almost 9 in 10 had mild or moderate anemia. Severe anemia nevertheless affected 6/56 anemic patients (10.7%), corresponding to 6/151 (4.0%) of the whole cohort, a group in which prompt clinical evaluation is warranted. Microcytosis, which points toward iron deficiency, was observed in only about one-third of anemic patients (20/56, 35.7%), indicating that most anemic patients had normocytic red cell indices; in the absence of iron studies, the mechanism of anemia could not be determined.

Sensitivity analysis: Because individual-level data for the 4 patients younger than 18 years could not be re-extracted, a bounding analysis was performed. Whatever the data availability and laboratory status of these four patients, their exclusion would yield a prevalence of biological inflammation between 48.6% (69/142) and 51.4% (73/142), compared with 50.0% in the whole cohort, and a prevalence of anemia between 35.4% (52/147) and 38.1% (56/147), compared with 37.1%. Likewise, no category of the joint distribution of inflammation and anemia (Table 3) could change by more than 2.4 percentage points. The main estimates are therefore robust to the inclusion of pediatric patients and to the choice of age-specific anemia thresholds.

Laboratory profile	N	%
Neither inflammation nor anemia	47	33.1
Inflammation only	43	30.3
Anemia only	24	16.9
Both inflammation and anemia	28	19.7
Total	142	100

TABLE 3: Joint distribution of biological inflammation and anemia at the first laboratory panel (N=142 patients with both measurements available)

Biological inflammation was defined as C-reactive protein >5 mg/L. Anemia was defined according to the World Health Organization age- and sex-specific criteria described in the Methods. Categories are mutually exclusive. This table is descriptive; the corresponding statistical comparison is reported in Table 4.

CRP stratum (mg/L)	Patients, n	Anemic patients, n (%)
≤5	71	24 (33.8)
>5-10	29	9 (31.0)
>10-50	33	14 (42.4)
>50	9	5 (55.6)
Total	142	52 (36.6)

TABLE 4: Prevalence of anemia according to the C-reactive protein stratum at the first laboratory panel

Units: C-reactive protein (CRP) in milligrams per liter (mg/L). Anemia was defined according to World Health Organization age- and sex-specific criteria. The trend across strata was tested with the Cochran-Armitage test for trend (z=1.30; p=0.19); the association between CRP and hemoglobin was assessed with Spearman's rank correlation (ρ=-0.14; p=0.09). p<0.05 was considered statistically significant.

Co-occurrence of biological inflammation and anemia

Both CRP and Hb were available for 142/155 patients (91.6%), and their joint distribution is shown in Table *3*. Two-thirds of these patients (95/142, 66.9%) had at least 1 abnormality, whereas only one-third (47/142, 33.1%) had normal values for both markers. Isolated abnormalities were much more frequent than their combination: 43/142 patients (30.3%) had inflammation without anemia, and 24/142 (16.9%) had anemia without inflammation, while both abnormalities coexisted in only 28/142 (19.7%). Consequently, almost half of the 52 anemic patients in this subgroup (24/52, 46.2%) had a normal CRP, and their anemia would not have been flagged had CRP been relied on alone.

Table *4* details the relationship between the intensity of inflammation and the occurrence of anemia. Anemia was present in 28/71 patients with inflammation (39.4%) and in 24/71 patients without inflammation (33.8%), a difference of 5.6 percentage points (95% CI -10.0 to 20.9) that was not statistically significant (Pearson's $\chi^2(1)=0.49$; p=0.49). Across the four CRP strata, the prevalence of anemia increased from 33.8% for CRP ⩽5 mg/L to 55.6% for CRP >50 mg/L; however, this gradient was not monotonic, with the lowest prevalence observed in the >5-10 mg/L stratum, and it did not reach statistical significance (Cochran-Armitage test for trend, z=1.30; p=0.19), the highest stratum including only 9 patients. In line with these findings, CRP and Hb were only weakly and non-significantly correlated (Spearman's ρ=-0.14; n=142; p=0.09), indicating a weak monotonic association at most.

Complementary analysis of all laboratory panels

This analysis is descriptive only, because repeated panels from the same patient are not independent observations. When all 235 panels were considered, biological inflammation was found in 107/225 panels (47.6%) and anemia in 78/231 panels (33.8%). These figures were close to those of the first-panel analysis, suggesting that the primary analysis did not systematically over- or underestimate these abnormalities. At

the panel level, the proportions of panels with inflammation (CD 47.8% vs UC 50.0%) and with anemia (CD 32.7% vs UC 36.7%) were similar in the two subtypes, and the Spearman correlation coefficient between CRP and Hb was -0.14 (n=221 panels), identical to that of the first-panel analysis. Over the entire follow-up period, 77/148 patients (52.0%) had at least one CRP value >5 mg/L and 60/153 patients (39.2%) had at least one episode of anemia, slightly more than at the first panel alone.

Discussion

This study provides the first description of the biological profile of patients with IBD in eastern Morocco. Among 155 patients, CD accounted for two-thirds of cases, half of the patients had biological inflammation, and more than one-third were anemic, with no statistically significant difference between CD and UC. The most clinically relevant finding is that the two abnormalities were frequently dissociated: nearly half of the anemic patients had a normal CRP, and CRP and Hb were only weakly and non-significantly correlated. Because the study was descriptive and exploratory, these observations describe co-occurrence and do not establish causal relationships.

Subtype distribution and demographic profile

The predominance of CD in our cohort (102/155, 65.8%) differs from the pattern reported elsewhere in the MENA region. The MIRAGE registry found 52% UC, 45% CD, and 3% unclassified IBD among 10,340 patients from tertiary centers [3], and an earlier hospital-based Lebanese series likewise reported more UC than CD (142 vs 100 patients) [26]. In contrast, our distribution is close to that of the Moroccan tertiary-center series from Marrakech (55% CD, 40% UC) [24] and to hospital-based European series from Portugal (59% CD) [16] and Spain (53% CD) [27], suggesting that CD predominance may be a feature of Moroccan referral centers rather than an isolated finding. Two mechanisms may explain this pattern. First, patients with CD more often require intensive biological monitoring, immunosuppressive or biologic therapy, and surveillance for stricturing or penetrating complications, which increases their representation in a hospital laboratory database compared with a clinical registry. Second, recruitment through the laboratory rather than the gastroenterology department amplifies this referral bias, because patients with mild UC managed with salicylates are tested less often. The proportion of unclassified IBD in our series (17/155, 11.0%) was considerably higher than the 3% reported in MIRAGE [3]. This most likely reflects incomplete transmission of endoscopic and histological diagnoses to the laboratory record rather than a true excess of indeterminate colitis, and underlines the need for better integration of clinical and laboratory information systems.

The 10-year age difference between UC and CD (median 44.5 vs 34 years; p=0.006) closely mirrors the MIRAGE data, in which the mean age was 39.8 years in UC and 34.6 years in CD (p<0.0001) [3], and the Korean cohort of Lee et al., in which the mean age at diagnosis was 39.8 years in CD and 53.3 years in UC [20]. This consistency across very different populations supports the classical observation that UC tends to occur later in life than CD [1]. The slight female predominance in our cohort (85/155, 54.8%) was less marked than in the Marrakech series (68.3%) [24] but identical to that of the Portuguese nationwide study (54.8%) [16]. Sex ratios are, however, unstable in small single-center samples and should not be over-interpreted.

Biological inflammation

Half of our patients had CRP >5 mg/L, and almost one-third had CRP >10 mg/L. This proportion is very close to the 53.3% of patients with elevated CRP reported in the Marrakech cohort [24], which may reflect similar case mix and referral patterns in two Moroccan tertiary centers located more than 600 km apart. These findings suggest that a substantial proportion of patients were not in biological remission at the time of testing. Nevertheless, in the absence of clinical or endoscopic activity indices, an elevated CRP cannot be equated with active IBD, since intercurrent infections, abscesses, and other comorbidities also increase CRP; the 6.8% of patients with CRP >50 mg/L are particularly likely to include such complications. Conversely, because CRP has limited sensitivity for endoscopic activity [7], some patients with a normal CRP probably had ongoing mucosal inflammation, so the true proportion of patients with active disease may be underestimated. In a treat-to-target perspective, in which CRP normalization is an intermediate objective [8], these results are compatible with incomplete biological control in part of our population, although treatment data were not available to assess this directly.

Unlike most published series, we found no statistically significant difference in CRP between CD and UC; this should not be interpreted as evidence of an equivalent inflammatory burden, as the 95% CI of the difference in the proportion of patients with inflammation ranged from -14.1 to 22.9 percentage points. The literature consistently describes a stronger acute-phase response in CD, attributed to its transmural and often granulomatous inflammation and to a greater interleukin-6 drive [4]. This difference has been demonstrated prospectively in the population-based IBSEN cohort [5] and in the Mayo Clinic series, where CRP correlated with clinical, endoscopic, and histological activity in CD but only with extensive and severe disease in UC [6]. Two factors may explain our discordant result. First, our UC group was small (n=35 with available CRP) and, as shown by the power calculation, could only detect large differences. Second, information on disease extent, the main determinant of the CRP response in UC, was not available; a higher proportion of extensive colitis among our UC patients, consistent with their referral to a tertiary center, would attenuate the expected difference.

Anemia

The prevalence of anemia in our cohort (56/151, 37.1%) sits at the upper end of published estimates and should be interpreted according to the recruitment setting. It was clearly higher than in European outpatient and population-based studies: 24% overall (27% in CD and 21% in UC) in the individual patient data meta-analysis of Filmann et al. [18], 18.6% in the Portuguese nationwide study of 1,313 patients [16], 19% in Scandinavian outpatients [17], and 13.6% in the recent Italian IG-IBD multicenter study of 5,416 outpatients [14]. It was also higher than the 21% reported in Brazilian outpatients [19], a middle-income setting. In contrast, our figure was close to those of hospital-based cohorts, namely, approximately 30% in the Spanish series of de la Morena and Gisbert [27] and in the Marrakech cohort [24], 39.5% (104/263) in the Italian cohort of Bergamaschi et al. [21], and 36.3% in UC and 41.6% in CD in a Korean cohort [20]. It was virtually identical to the 37.1% recorded in 2009 in the United States tertiary-center cohort of Koutroubakis et al., where prevalence subsequently declined to 33.2% in 2013 [13].

Four factors plausibly account for this gradient between settings. The first is the recruitment setting since tertiary laboratories concentrate patients with more active or complicated disease, a selection bias that probably inflates our estimates relative to the overall IBD population. The second is the timing of assessment: anemia is most frequent around diagnosis, reaching 65% at diagnosis in the series of Bergamaschi et al. [21] and 48.8% in CD in the IBSEN cohort [22], and our laboratory-based recruitment probably captured a substantial number of newly diagnosed or flaring patients. The third is the definition used, since studies applying treatment-oriented rather than WHO thresholds report lower figures. The fourth is differential access to iron supplementation, including intravenous iron, which may be more limited in our context than in European cohorts; treatment and supplementation data were not available to verify this. The decline observed in the American cohort over time [13] and the low prevalence in the recent Italian study [14] suggest that systematic screening and treatment can reduce the burden of anemia. Taken together, these comparisons indicate that anemia is at least as frequent among Moroccan patients with IBD followed in a tertiary setting as in high-income tertiary cohorts and considerably more frequent than in European outpatient and community-based populations, which supports attention to its detection and work-up in our setting.

The severity profile of anemia in our cohort was reassuring and consistent with published data: 50/56 anemic patients (89.3%) had mild or moderate anemia, compared with 90% in the Portuguese nationwide study, in which anemia was also more frequent in patients with active disease and in those receiving corticosteroids [16]. Nevertheless, 6/151 patients (4.0%) had severe anemia requiring prompt management, a proportion that is far from negligible in a laboratory serving a large catchment area. We found no statistically significant difference in anemia prevalence between CD and UC (35.0% vs 44.1%; p=0.34), in agreement with the Portuguese study (19.1% vs 17.7%) [16]. Most other series, however, reported a higher frequency in CD, including the European meta-analysis (27% vs 21%) [18], the Scandinavian study (p=0.01) [17], the IBSEN cohort at diagnosis (48.8% vs 20.2%) [22], and the Korean cohort (41.6% vs 36.3%) [20]. This excess in CD is usually explained by small-bowel involvement, which impairs duodenal iron absorption, and by a stronger inflammatory drive. The discordance with our data is most likely related to limited statistical power, as our study could exclude only differences greater than about 27 percentage points (95% CI of the observed difference, -27.6 to 8.9 percentage points); the numerically higher prevalence in UC may also reflect bleeding from extensive colitis in a referral population. Similarly, the higher prevalence in women than in men (40.2% vs 33.3%; p=0.38) is in line with larger series: in the Italian IG-IBD study, women were more often anemic (odds ratio 1.5) and had more severe anemia [14], and a female excess was also observed among Korean patients with both CD and UC [20]. Menstrual blood loss adds to disease-related losses, although our sample was underpowered to confirm this difference.

Only 20/56 anemic patients (35.7%) had microcytosis, well below the prevalence of iron deficiency reported among anemic patients with IBD, which was 57% in the European meta-analysis [18] and 62.5% in the Italian IG-IBD study [14], with comparable proportions in the Spanish series [27]. This apparent discrepancy is expected rather than contradictory. MCV is an insensitive marker of iron deficiency, and when iron deficiency coexists with anemia of chronic inflammation, or with drug-induced macrocytosis such as that caused by thiopurines, red cell indices frequently remain normocytic [9,10]. In agreement with our findings, normocytic normochromic anemia was the most common morphological type in the Korean cohort, accounting for 64% to 79% of anemic patients [20], and Bergamaschi et al. showed that anemia of chronic disease predominated at diagnosis, whereas iron deficiency and mixed forms became more frequent during follow-up [21]. Microcytosis should therefore be regarded as a specific but insensitive sign of iron deficiency. Because ferritin, transferrin saturation, vitamin B12, and folate were not available, the mechanism of anemia in our patients could not be established. The diagnosis requires iron studies, primarily serum ferritin and transferrin saturation interpreted in the light of CRP, as recommended by the European Crohn's and Colitis Organisation, which proposes a ferritin threshold of 30 µg/L in the absence of inflammation and of 100 µg/L in its presence [9]; newer markers, such as soluble transferrin receptor, reticulocyte hemoglobin content, and hepcidin, may help distinguish iron deficiency from anemia of chronic disease when ferritin is uninterpretable [28]. The finding that 60/153 patients (39.2%) had at least one anemic episode during the study period is also relevant. In a longitudinal Scandinavian study, more than half of IBD outpatients were anemic at some point during a two-year follow-up [29], and persistent or recurrent anemia has been linked to a more severe and disabling disease course, with more hospitalizations and surgery [13]. A single normal

Hb value should therefore not be considered reassuring over the long term.

Relationship between inflammation and anemia

The weak inverse correlation between CRP and Hb (ρ=-0.14; p=0.09) indicates, at most, a weak monotonic association between systemic inflammation and Hb in our patients. The observation that 24/71 patients without inflammation (33.8%) were nevertheless anemic is consistent with the multifactorial nature of anemia in IBD, which combines chronic blood loss, iron, vitamin B12, and folate deficiencies, drug toxicity, and hepcidin-mediated iron restriction [9-12]. The Italian IG-IBD study provides a plausible explanation for this pattern: iron deficiency, alone or combined with other mechanisms, accounted for 62.5% of anemia cases, whereas pure anemia of inflammation accounted for only 8.3% [14]. When most anemia is driven by iron loss rather than by inflammation itself, a weak correlation between CRP and Hb is precisely what would be expected; however, because iron studies were not performed, this explanation could not be tested in our cohort. In addition, intercurrent infections and other inflammatory conditions may have raised CRP independently of IBD activity, and treatments such as corticosteroids, biologics, immunomodulators, and iron supplementation, which were not recorded, may have modified both markers. At the same time, the increase in anemia prevalence from 33.8% at CRP ⩽5 mg/L to 55.6% above 50 mg/L, although not statistically significant in our sample (p=0.19), is directionally consistent with the inflammatory component of anemia of chronic disease [11,12] and with the higher frequency of anemia reported in patients with active disease [16,21]; this gradient deserves confirmation in a larger series.

Clinical implications

Within the limits of a descriptive design, these findings may inform the biological follow-up of patients with IBD in our setting; they are consistent with, rather than additional evidence for, existing guideline recommendations. First, our data suggest that CRP and CBC provide complementary information; relying on CRP alone would not have flagged almost half of the anemic patients, while relying on Hb alone would not have identified the 30.3% of patients with isolated inflammation. Second, the frequency of anemia observed supports adherence to the systematic screening recommended by current guidelines, every three months in patients with active disease and every six to 12 months in those in remission [9,23]. Third, in line with these guidelines, an etiological work-up of anemia including ferritin, transferrin saturation, and, when indicated, vitamin B12 and folate appears warranted regardless of MCV, since most anemic patients in our cohort were normocytic. Finally, a persistently elevated CRP may justify clinical and endoscopic reassessment, in keeping with treat-to-target strategies [8], after exclusion of intercurrent infection. Clinical laboratories could contribute to this process, for instance through reflex iron testing when anemia is detected in a patient with IBD. This study did not assess whether combined CRP and Hb monitoring, or any of these measures, improves disease control or patient outcomes.

Strengths and limitations

The main strengths of this study are its exhaustive recruitment of consecutive patients over 26 months, the use of standardized analytical methods with quality control in a single laboratory, the use of internationally accepted definitions of inflammation and anemia, and the analysis of the first panel per patient, which avoids overrepresentation of frequently tested individuals, complemented by a descriptive all-panel analysis that yielded consistent results.

Several limitations should also be acknowledged. First, the retrospective, single-center, laboratory-based design limits the generalizability of our estimates to the overall IBD population of eastern Morocco; in particular, recruitment through a tertiary laboratory introduces a selection bias toward patients requiring more intensive monitoring, so that the frequencies of inflammation and anemia are probably overestimated relative to the overall IBD population. Second, clinical and endoscopic activity indices were not available, so an elevated CRP could not be attributed to active IBD rather than to another cause. Third, ferritin, transferrin saturation, vitamin B12, and folate were not measured, and anemia could be characterized only by WHO severity grade and MCV; its mechanisms could not be distinguished. Fourth, treatment information, including corticosteroids, biologics, immunomodulators, and iron supplementation, was not available, and no adjustment for these factors, or for disease location, extent, and behavior, was possible. Fifth, intercurrent infections and other inflammatory conditions, which were not recorded, may have raised CRP independently of IBD activity. Sixth, repeated panels from the same patient are not independent; the all-panel analysis was therefore restricted to descriptive statistics, and the primary conclusions rely only on the first panel of each patient. Seventh, the UC subgroup was small (n=36), so subgroup estimates were imprecise, as shown by the wide confidence intervals, and the comparisons between CD and UC were underpowered to exclude moderate but clinically meaningful differences; no multivariable adjustment was attempted because of the limited number of anemic patients. Other limitations include the derivation of the IBD diagnosis and subtype from the medical record without independent adjudication; the absence of exact sampling dates, so that CRP and CBC were paired by panel rather than by date; the absence of systematic recording of pregnancy; the impossibility of retrieving retrospectively the number of records screened and excluded; the lack of re-extractable individual data for the four pediatric patients, which allowed only a bounding sensitivity analysis; missing laboratory values, with denominators ranging from 142 to 155; and, given the short half-life of CRP, the possibility that a single measurement misclassifies inflammatory status. Despite these limitations, this study provides the first laboratory description of inflammation and anemia in

patients with IBD from eastern Morocco and a baseline for future prospective work.

Conclusions

In this descriptive cohort study of 155 patients followed for IBD at Mohammed VI University Hospital in Oujda, CD was the predominant subtype (65.8%), and patients with UC were significantly older than those with CD. Half of the patients had biological inflammation (50.0%) and more than one-third were anemic (37.1%), with no statistically significant difference between CD and UC for either abnormality in this sample, although the study was underpowered to exclude moderate differences. Anemia was mostly mild or moderate, but 4.0% of patients had severe anemia, and only about one-third of anemic patients had microcytic indices. Because CRP and Hb were only weakly correlated and nearly half of the anemic patients had a normal CRP, the two tests provided complementary information, which is consistent with guideline recommendations for their combined use in the routine biological monitoring of patients with IBD. Clinical outcomes were not assessed, and this study does not show that combined testing improves disease control or patient outcomes. Prospective studies incorporating disease activity indices, treatment data, and complete iron status are needed to clarify the mechanisms and clinical consequences of these abnormalities in the Moroccan population.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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