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Anemia in Newly Diagnosed Pediatric Patients with Inflammatory Bowel Disease

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Abstract: Anemia is the most common extraintestinal manifestation and complication of inflammatory bowel disease (IBD). The aim of our study was to assess the prevalence of anemia in newly diagnosed pediatric patients with IBD and to analyze its association with disease type, extent, and severity. We retrospectively reviewed the medical records of all patients with IBD treated in our department in the period of November 2011 to November 2020. The final analysis included the records of 80 children with newly diagnosed IBD: 45 with ulcerative colitis (UC) and 35 with Crohn's disease (CD). The prevalence of anemia was 60.0% in the UC patients and 77.1% in the CD patients. Of the UC patients with anemia, 37.1% had pancolitis, 18.5% extensive disease, 33.3% left-sided colitis and 11.1% ulcerative proctitis. Of the CD patients with anemia, 81.5% had ileocolonic disease, 11.1% colonic disease and 7.4% ileal disease. Anemia was less common in patients with mild disease than in patients with moderate–severe disease (22.2 vs. 77.8%, $p < 0.001$ in UC and 25.9% vs. 74.1%, $p < 0.001$ in CD). Our study confirmed anemia as a frequent problem in pediatric patients with IBD. Children with more extensive and more severe disease are at higher risk to develop anemia.

Keywords: anemia; pediatric inflammatory bowel disease; pediatric ulcerative colitis; pediatric Crohn's disease; iron deficiency

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1. Introduction

Anemia is the most common extraintestinal manifestation and complication of inflammatory bowel disease (IBD) [1–3]. Its etiopathogenesis is complex and multifactorial. The main factors related to the development of anemia in IBD patients are blood loss from intestinal bleeding (acute and chronic), poor absorption of vitamins and minerals through the inflamed intestinal mucosa (such as vitamin B12, folic acid and iron) and chronic inflammation [4–7]. Other, rarer causes of anemia in IBD include the myelosuppressive effect of drugs, hemolysis and protein-losing enteropathy [7,8]. In most cases, IBD-associated anemia results from a combination of different mechanisms, mainly iron deficiency anemia and anemia of chronic disease [5,7].

It is important to highlight that anemia in IBD is more than a deviation in laboratory parameters. It is a key factor that impacts the disease severity and the quality of life in IBD patients [7,8]. Therefore, early diagnosis and appropriate treatment of IBD-associated anemia are essential to improve the disease course and for better disease prognosis [5,7].

The aim of our study was to assess the prevalence of anemia in newly diagnosed pediatric patients with IBD and to analyze its association with disease type, extent, and severity.

2. Materials and Methods

2.1. Study Design and Patients

We retrospectively reviewed the medical records of all children with an established IBD diagnosis treated in our department in the period of November 2011 to November 2020. The final analysis included the records of all patients with newly diagnosed IBD. The records of the patients with previously known disease (patients with confirmed IBD diagnosis before November 2011 or patients with confirmed IBD diagnosis and initiated treatment before being directed to our center) were excluded from the final analysis.

All study participants had been diagnosed in accordance with the Porto criteria for the diagnosis of IBD in children and adolescents [9]. Disease extent and severity had been assessed according to the Paris Classification for children and adolescents with inflammatory bowel disease and based on the clinical activity indices for children with inflammatory bowel diseases: Pediatric Crohn's Disease Activity Index and Pediatric Ulcerative Colitis Activity Index [10–12]. Anemia was defined according to the World Health Organization (WHO) criteria for anemia in children: hemoglobin levels <110 g/L in children aged 6–59 months, <115 g/L in children aged 5–11 years, <120 g/L in children aged 12–14 years, <120 g/L in non-pregnant women (15 years of age and above), <110 g/L in pregnant women and <130 g/L in men (15 years of age and above) [13]. The severity of anemia was also defined using the WHO definition of normal hemoglobin ranges (Table 1) [13].

Table 1. Normal hemoglobin by age, adapted from WHO [13].

Age	Healthy Hb, g/L	Mild Anemia Hb, g/L	Moderate Anemia Hb, g/L	Severe Anemia Hb, g/L
6–59 months	≥110	100–109	70–99	<70
5–11 years	≥115	110–114	80–109	<80
12–14 years	≥120	110–119	80–109	<80
Non-pregnant females (≥15 years)	≥120	110–119	80–109	<80
Pregnant females	≥110	100–109	70–99	<70
Males (≥15 years)	≥130	110–129	80–109	<80

2.2. Statistical Methods

Statistical analyses used in this study were of a descriptive type. Categorical variables were described using numbers (*n*) and proportions (%). Continuous variables were described using means and standard deviation if they were normal in type or using medians and interquartile ranges if normality was not respected. Data were presented in tables and graphs. The chi-square or Fisher's exact test was used to compare categorical variables. The Student's *t*-test or the Mann−Whitney U test was used to compare numerical variables between the groups. *p*-values of <0.05 were considered statistically significant.

2.3. Ethics

All analyzed data had been collected as part of routine diagnosis and treatment, which had been consistent with the current standard of care. Written informed consent had been obtained from all study participants, or their legal guardians, before all diagnostic procedures were performed. In accordance with local legislation, additional patient informed consent and ethical approval were not sought due to the study design, i.e., retrospective review of medical records.

3. Results

3.1. Characteristics of the Study Population

The records of 80 patients with newly diagnosed IBD (recently diagnosed, treatment-naive patients) were included in the final analysis. The median age at diagnosis was

15 years (range: 2–17 years). Slightly more of the study participants had ulcerative colitis. The ratio of males to females was nearly equal for both CD and UC. Most of our female patients (14 with UC and 13 with CD) were above the age of 13 years and reported that they had menarche. Demographic data and clinical characteristics of the study participants are summarized in Table 2.

Table 2. Demographic data and clinical characteristics of the study participants.

All ***n* = 80**	**Crohn's Disease** ***n* = 35**	**Ulcerative Colitis** ***n* = 45**
Gender, *n* (%)		
Male	19 (23.75)	23 (28.75)
Female	16 (20.0)	22 (27.5)
Age at diagnosis, median (range)	15 years (7–17 years)	15 years (2-17 years)
Disease duration before diagnosis, median (range)	5 months (2 weeks–180 months)	3 months (2 weeks–24 months)
Disease location, *n* (%)		
Ileal (L1)	5 (14.3)	
Colonic (L2)	4 (11.4)	
Ileocolonic (L3)	26 (74.3)	
Upper disease proximal to ligament of Treitz (L4a)	14 (40.0)	
Upper disease distal to ligament of Treitz (L4b)	3 (8.6)	
Disease behavior, *n* (%)		
Non-stricturing, non-penetrating (B1)	23 (65.7)	
Stricturing (B2)	6 (17.2)	
Penetrating (B3)	2 (5.7)	
Stricturing and penetrating (B2B3)	4 (11.4)	
Perianal disease (*p*)	6 (17.2)	
Growth, *n* (%)		
No evidence of growth delay (G0)	31 (88.6)	
Growth delay (G1)	4 (11.4)	
Disease activity at diagnosis, *n* (%)		
Mild	9 (25.7)	
Moderate to severe	26 (74.3)	
Disease extent, *n* (%)		
Ulcerative proctitis (E1)		9 (20.0)
Left-sided UC (E2)		13 (28.9)
Extensive colitis (E3)		6 (13.3)
Pancolitis (E4)		17 (37.8)
Disease severity, *n* (%)		
Never severe (S0)		30 (66.7)
Ever severe (S1)		15 (33.3)
Disease activity at diagnosis, *n* (%)		
Mild		11 (24.4)
Moderate		21 (46.7)
Severe		13 (28.9)
Anemia at diagnosis, *n* (%)		
Yes	27 (77.1)	27 (60.0)
No	8 (22.9)	18 (40.0)
Prevalence of iron deficiency in anemic patients at diagnosis, *n* (%)		
Yes	21 (77.8)	20 (74.1)
No	6 (22.2)	7 (25.9)

3.2. Prevalence of Anemia

Anemia was detected in 67.5% of the study participants. It was more frequent in CD patients than in UC patients, without being statistically significant (77.1% vs. 60.0%, $p = 0.1043$). Iron deficiency was revealed in 77.8% of anemic patients newly diagnosed with CD and in 74.1% of anemic patients newly diagnosed with UC. Of the CD patients, 59.3% had mild anemia, 37.0% had moderate anemia, and 3.7% had severe anemia. Of the UC patients, 25.9% had mild anemia, 66.7% had moderate anemia, and 7.4% had severe anemia. The corresponding mean hemoglobin concentrations (±standard deviation) are presented in Table 3.

Table 3. Mean hemoglobin concentrations (±standard deviation) in the study population.

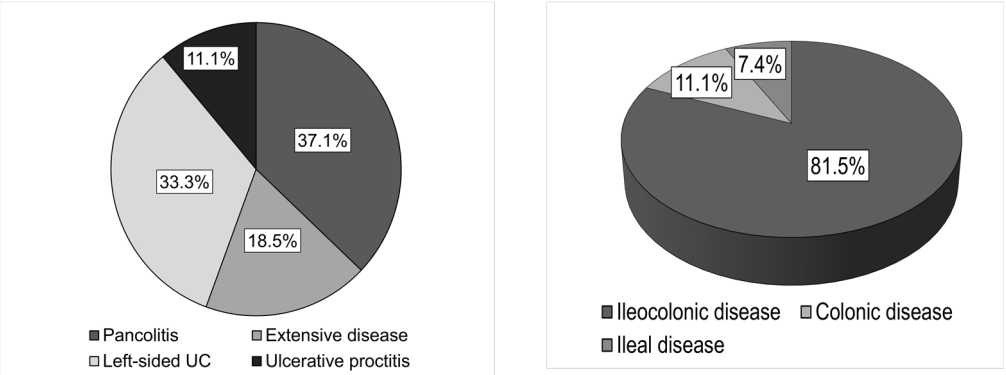
	CD Patients		UC Patients	
	***n* = 35**	**Hb g/L (±SD)**	***n* = 45**	**Hb g/L (±SD)**
With anemia, *n* (%)	27 (77.1)	110.3 (±14.6)	27 (60.0)	97.4 (±15.7)
Mild	16 (59.3)	119.2 (±5.8)	7 (25.9)	117 (±7.7)
Moderate	10 (37.0)	100.8 (±8.5)	18 (66.7)	93 (±8.7)
Severe	1 (3.7)	63.0 (NA)	2 (7.4)	68.5 (±6.3)
Without anemia, *n* (%)	8 (22.9)	133.8 (±7.3)	18 (40.0)	135.8 (±15.3)

Hb: hemoglobin, SD: standard deviation, CD: Crohn's disease, UC: ulcerative colitis.

The prevalence of anemia in boys and girls was not found to be statistically different. In our UC population, anemia was more common in female patients than in male patients, but this difference was not found to be significant (59.3% vs. 40.7%, $p = 0.088$). In CD patients, there was no difference between the prevalence of anemia in females and males (48.1% vs. 51.9%, $p = 0.59$).

3.3. Association between the Prevalence of Anemia and Disease Extent

To search for an association between the prevalence of anemia and disease extent, we found that of the UC patients with anemia 37.1% had pancolitis, 18.5% extensive disease, 33.3% left-sided colitis and 11.1% ulcerative proctitis (Figure 1a). Of the CD patients with anemia, 81.5% had ileocolonic disease, 11.1% colonic disease and 7.4% ileal disease (Figure 1b). Involvement of the upper gastrointestinal tract was observed in 51.8% of CD patients with anemia.



(**a**) (**b**)

Figure 1. Association between the prevalence of anemia and disease location in pediatric patients with IBD: (**a**) disease extent in children with UC and anemia; (**b**) disease location in children with CD and anemia.

3.4. Association between the Prevalence of Anemia and Disease Severity

As we analyzed the prevalence of anemia in children newly diagnosed with IBD, all study participants had clinically active disease. We did not find a correlation between hemoglobin levels and clinical activity scores, but anemia was generally less common in patients with mild disease than in patients with moderate to severe and severe disease (22.2 vs. 77.8%, $p < 0.001$ in UC and 25.9% vs. 74.1%, $p < 0.001$ in CD) (Figure 2).

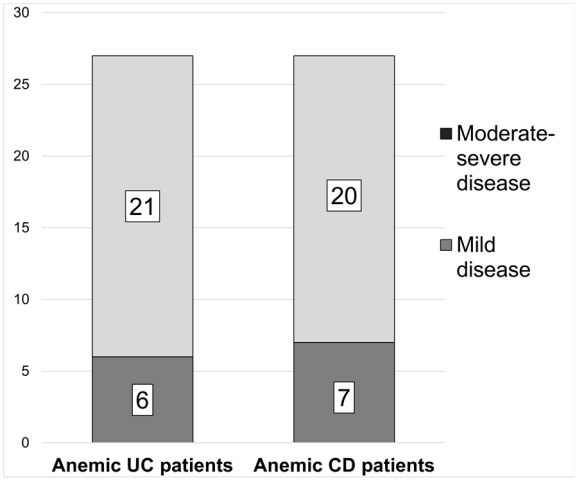


Figure 2. Association between the prevalence of anemia and disease severity in pediatric patients with IBD.

4. Discussion

Anemia is a common problem in IBD patients. Its impact on physical, emotional and cognitive functions, work or school absenteeism, hospitalization rate and health-care costs is substantial; therefore, it needs appropriate and timely diagnosis and therapy [14]. Our study demonstrates the magnitude of the prevalence of anemia in a pediatric population newly diagnosed with IBD by analyzing its association with different demographic- and disease-related variables. We show that the prevalence of anemia in children with newly diagnosed IBD is high, without a demonstrable significant association between occurrence of anemia and gender or disease type. Furthermore, we confirm the findings about the relationship between the existence of anemia and disease severity.

According to the literature, the development of anemia is more common in pediatric patients with IBD than in adults [15–19]. The reported prevalence at diagnosis ranges from 44% to 74% among various studies [7]. In our study, we found a relatively high percentage of anemic patients at presentation, 67.5%, similar to the results of Aljomah et al. [16], who established anemia in 67.31% of children with IBD at diagnosis. At the same time, the prevalence of anemia that we demonstrated was less than in other studies reported, such as the 75% observed by Wiskin et al. [17] and the 78% observed by Pels et al. [18]. It is difficult to definitively interpret the variance in findings across the different studies, as many factors contribute to the development of anemia in IBD patients. We suggest different patient cohorts, different times to diagnosis, different eating habits, etc., as factors that affect the prevalence of anemia in different studies, but all suggestions will be very speculative.

The existing research in the pediatric population provides contradictory results regarding the prevalence of anemia among the different types of IBD. Previous studies found an association between disease type and prevalence of anemia, reporting a higher frequency in patients with CD than in patients with UC [16,19,20]. A possible explanation of this difference is that, in CD patients, more pathogenic mechanisms may play a role in the development of anemia, such as systemic inflammation, which is usually more severe in CD than in UC, Vitamin B12 malabsorption due to the terminal ileum involvement, and iron malabsorption due to the proximal gastrointestinal tract involvement. In contrast, a recent study by Rempel et al. [21] demonstrated a similar prevalence of anemia in children

with CD and UC (moderate to severe anemia: CD versus UC, 40% versus 33%; mild anemia: CD versus UC, 21% versus 19%). In our study, anemia was diagnosed in proportionally more patients with CD (CD versus UC, 77.1% versus 60.0%), although the results failed to achieve statistical significance.

Analyzing the association between gender and prevalence of anemia in IBD patients, several authors reported that females had a significantly higher prevalence of anemia compared to males, suggesting the blood loss during menstruation as an additional aggravating factor [21–24]. Contrary to these findings, other authors did not find a significant difference in the prevalence of anemia in boys and girls with IBD [16]. Of course, the observed differences depend strongly on the studied population. Although in our study most of the female patients were already in puberty, we could not find a significantly higher prevalence of anemia in them compared to our male patients. We demonstrated a slightly higher frequency of anemia in girls with UC than in boys with UC, without achieving a statistical significance. In the patients with CD, we found no differences between the sexes.

Besides the multifactorial etiology of anemia in IBD, iron deficiency is the most common cause of anemia in pediatric patients with IBD, with a reported prevalence of up to 40–88% [15,25]. According to Pels et al., newly diagnosed children with IBD are more likely to have iron deficiency anemia in contrast to anemia of chronic disease [18]. This finding was confirmed by the observations of Wiskin et al. [17], who reported an extremely high prevalence of iron deficiency in newly diagnosed pediatric patients with IBD: 90% in pediatric patients with CD and 95% in pediatric patients with UC. In agreement with the literature, we detected iron deficiency in more than two-thirds of our anemic patients with newly diagnosed IBD, supporting its role as a main mechanism in the pathogenesis of IBD-associated anemia.

In a recent study, Parra et al. [24] found no association between anemia and disease location in adult patients with IBD (CD and UC). In contrast, Sjoberg et al. [19] reported extensive disease in UC and colonic CD at diagnosis as additional risk factors for anemia in pediatric patients with IBD. In our study, we revealed that only 11.1% of anemic patients with UC and CD had localized disease—ulcerative proctitis or ileal disease, respectively—suggesting that more extended disease increases the chances of developing anemia in children with IBD. Not surprisingly, we found a lower prevalence of anemia in patients with mild disease, confirming the previous observations [23].

Our study has several limitations. One of the limitations is the relatively small sample size. Despite the continuing increase in IBD incidence worldwide, IBDs are still relatively uncommon in the pediatric population. On the other hand, the nature of pediatric care in our country is such that almost all patients with chronic disease, including IBD, are cared for by pediatric specialists in corresponding referral centers, and we are the biggest referral center for the management of children with IBD in our country. Another limitation of the study is its retrospective design. By reviewing only already available data, we were not able to analyze all potential pathogenetic mechanisms for the development of anemia in our patients.

The above-mentioned limitations notwithstanding, our study is, to the best of our knowledge, the first investigation of the prevalence of anemia in the pediatric IBD population in our country. The study reveals that anemia is a common and important issue at IBD diagnosis and suggests that its early detection and timely management could be beneficial for patients. The results of the present study are an important starting point for future multicenter prospective investigations.

5. Conclusions

In conclusion, this study showed a high prevalence of anemia among newly diagnosed children with IBD in a referral center and highlighted the magnitude of the problem. In most cases, the anemia was accompanied by an iron deficiency and was associated with more extensive and severe disease. Anemia should be recognized, investigated, and treated in all pediatric patients with IBD.

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Informed Consent Statement: All analyzed data had been collected as part of routine diagnosis and treatment, which were consistent with the current standard of care. Written informed consent had been obtained from all study participants, or their legal guardian, before performing all diagnostic procedures. In accordance with local legislation, additional informed patient consent and ethical approval were not sought due to the study design, i.e., retrospective review of medical records.

Conflicts of Interest: All authors have no conflict of interest to declare.

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