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Original article

Beyond the Gut: Extraintestinal Manifestations of Inflammatory Bowel Disease in Children and Adolescents

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Abstract

Background: Extraintestinal manifestations (EIM) are common in children and adults and their presence is associated with a higher severity of inflammatory bowel disease (IBD). In pediatrics, studies are scarce in Latin America and do not exist in Colombia. **Objective:** To describe the prevalence of EIM in children with IBD and the associated demographic, clinical, and biochemical characteristics. **Methodology:** Retrospective study of patients diagnosed with pediatric-onset IBD between 2007 and 2022 treated at an institution in Bogotá. A descriptive analysis was performed and in the groups with and without EIM clinical and biochemical variables were compared using Fisher's exact test, Student's T, and Mann-Whitney's U. **Results:** Of 71 confirmed cases, 45% had typical ulcerative colitis, 27% Crohn's disease, 7% atypical ulcerative colitis, 1.4% colonic Crohn's, and 20% unclassifiable IBD. Thirteen patients (18%) had at least one EIM, and mucocutaneous was the most frequent (58%). The time from symptoms onset to diagnosis was higher in the EIM group (13.2 years vs. 10.2 years; p = 0.02). Nocturnal diarrhea, hyporexia, and weight loss were more frequent in children with EIM. The EIM group showed lower hemoglobin levels, and higher globular sedimentation rate, and received biologics more frequently (38% vs. 23%, p = 0.2). **Conclusions:** The frequency of MEI in this series is similar to that reported in the literature; its presence is associated with higher disease severity, higher frequency of biological use, and longer time IBD diagnosis.

Keywords

Inflammatory bowel disease, arthritis, uveitis, erythema nodosum, hepatitis, pyoderma, pediatrics.

INTRODUCTION

Inflammatory bowel disease (IBD) is a condition of unknown etiology that includes Crohn's disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBDU) in adults. In children, it also encompasses atypical ulcerative colitis (AUC) and colonic Crohn's disease (CCD)[1,2]. IBD can manifest at any age, and its incidence is rising across all age groups[3,4]. The pathogenesis involves polygenic and epigenetic factors and is characterized by chronic inflammation of the gastrointestinal tract[2,5].

The presentation, progression, behavior, and prognosis of pediatric-onset inflammatory bowel disease (PIBD) differ

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significantly from adult-onset IBD. The reclassification by the Porto Group since 2011 has established criteria that are highly informative for understanding PIBD. These criteria aim to guide classification for accurate diagnosis in children and adolescents by defining phenotypes based on clinical, endoscopic, histopathological, and radiological differences. The result is the PIBD-classes, which divides PIBD into five phenotypes: typical ulcerative colitis (TUC), atypical ulcerative colitis (AUC), Crohn's disease (CD), colonic Crohn's disease (CCD), and inflammatory bowel disease unclassified (IBDU)[1,2].

Although the intestine is the primary target, other organs can be affected. In adults, 50% develop at least one extra-intestinal manifestation (EIM) during the course of the disease, and EIMs can precede intestinal symptoms in 16% to 25% of cases[6-9]. In Colombia, a prevalence of 23.3% has been reported in adults, with joint involvement being the most frequent, as noted in other series[6,10]. Most EIMs occur in parallel with bowel disease activity and are more common in CD, especially in CCD patients[11,12].

Patients with PIBD experience significantly more EIMs both at diagnosis and during follow-up[13,14]. In pediatrics, the prevalence of EIMs at diagnosis ranges from 6% to 29%[15]. In a cohort of 1649 patients, the cumulative incidence was 9% at one year, 19% at five years, and 29% at fifteen years post-diagnosis[16]. EIMs usually present in children older than six years and, like in adults, are more frequently associated with CD (61%) than with UC (29%) [12,16,17], with 4% to 25% possibly preceding intestinal involvement[11,12,15].

When PIBD is accompanied by EIMs, it follows a more aggressive clinical course in terms of progression and extent, necessitating increased use of corticosteroids, immunosuppressants, biological therapies[14], and surgery, particularly in UC[13]. Increased EIM activity is associated with a higher relapse rate in CD[15].

The pathophysiology of EIMs is not fully understood. Possible contributing factors include genetic predisposition, changes in the intestinal microbiome, and alterations in the immune response from the intestine to other organs, affecting leukocyte circulation[12,18]. Based on these factors, EIMs can be classified as *classic* when the inflammatory process occurs in distant sites (musculoskeletal, mucocutaneous, ocular, and hepatobiliary), *associated* when they occur with other immunologically mediated diseases (multiple sclerosis, myocarditis, psoriasis, systemic lupus erythematosus), and as *complications* in the case of anemia and malnutrition, as manifestations of systemic inflammation[18-21].

Classic EIMs most frequently affect the joints, skin, and eyes but can also involve other organs such as the liver, lungs, and pancreas[18]. A common misconception is that successful therapy of intestinal inflammation is sufficient to satisfactorily treat EIMs[22]; generally, peripheral spondyloarthropathy, oral ulcers, episcleritis, and erythema nodosum may improve with standard treatment of intestinal inflammation, but uveitis, ankylosing spondylitis, and primary sclerosing cholangitis (PSC) progress independently of disease flares[12].

In children, EIMs primarily affect the joints and skin[13,14], and less frequently the eyes and liver, significantly impacting and worsening quality of life[15]. Although their improvement or resolution is part of the general management of PIBD, their presence should always be considered when deciding on therapy for managing intestinal inflammation[8,12].

In this context, it is essential to understand the clinical, evolutionary, and prognostic characteristics of EIMs in the pediatric population, as well as their prevalence, to estimate their impact and thus offer a comprehensive approach in the therapy and follow-up of patients with PIBD.

MATERIALS AND METHODS

Study Type

A descriptive cross-sectional study was conducted through a retrospective review of medical records from 2007 to 2022. The manuscript was prepared according to the STROBE guidelines[23].

Study Population

The study population consisted of pediatric patients with a confirmed diagnosis of IBD treated at the Fundación Hospital Pediátrico La Misericordia (HOMI), a high-complexity hospital and national referral center for pediatric gastrointestinal diseases located in Bogotá, Colombia (**Figure 1**).

Sample Selection and Size

Sampling was carried out using a non-probabilistic, sequential method. Due to the descriptive nature of the study, no formal sample size calculation was performed. All patients who met the inclusion criteria during the study period were included.

Diagnostic Criteria

The diagnosis of PIBD was made according to the recommendations of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) established in 2014 through the Porto criteria and PIBD-classes. These criteria integrate the majority of evidence on recommended diagnostic methods and provide an initial

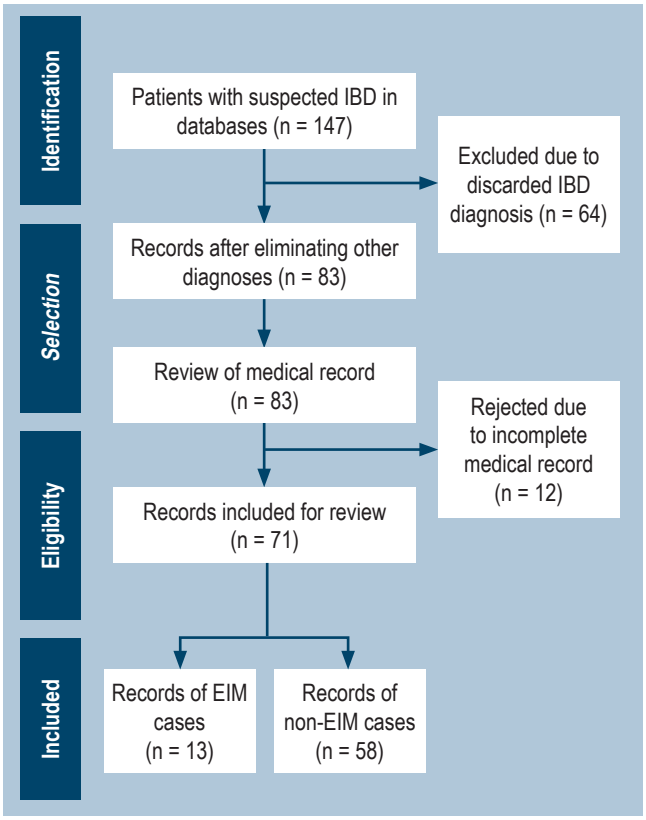


Figure 1. Flowchart of Record Eligibility. IBD: inflammatory bowel disease; EIM: extraintestinal manifestations. Author's file.

approach for the practical classification of the five disease phenotypes[1]. This classification allows for a more precise diagnosis, appropriate therapeutic decisions, and prediction of disease progression and prognosis.

The diagnosis of EIMs was based on the medical evaluation by the pediatric gastroenterology team through physical examination and interdisciplinary clinical criteria recorded in the medical record. The classic EIMs analyzed included spondyloarthropathies (peripheral and axial), uveitis, pyoderma gangrenosum, erythema nodosum, aphthous stomatitis, skin tags (anal folds), psoriasis, and sclerosing cholangitis.

Anemia, malnutrition, and growth failure were considered complications and therefore were not included. Nutritional diagnosis was conducted using the current criteria of the World Health Organization (WHO), endorsed by the Ministry of Health and Social Protection of Colombia[24]. Anemia was defined according to WHO criteria (hemoglobin < 11 g/dL for children)[18].

EIMs affecting the musculoskeletal system, particularly the joints, were grouped under the term *spondyloarthropathies*, using the diagnostic criteria developed by the Assessment in SpondyloArthritis International Society (ASAS), which distinguish between peripheral and axial manifestations; both can occur in PIBD patients, with special considerations for application to the pediatric population[25,26].

Mucocutaneous involvement was classified into four groups:

- Reactive: when they share the immunopathogenic mechanism but not the histopathological characteristics (erythema nodosum, pyoderma gangrenosum, Sweet syndrome, oral lesions).
- Specific: when the histopathological characteristics are similar but present outside the gastrointestinal tract, as in metastatic Crohn's disease[27].
- Treatment-associated: psoriasiform lesions, skin infections, and eczema are manifestations secondary to treatment complications, adverse or paradoxical reactions to medications used: thiopurines, sulfasalazine, methotrexate, and especially anti-tumor necrosis factor (anti-TNF)[28].
- Nonspecific: these lesions can be diverse, and their diagnosis is based on clinical characteristics and the exclusion of other dermatological disorders[18,29].

All EIMs were diagnosed by the corresponding expert pediatricians in dermatology, rheumatology, ophthalmology, and hepatology.

To control for potential information and recall biases when retrospectively applying the PIBD-classes criteria in reclassifying PIBD, the following strategies were employed:

- Integration into REDCap of the "IBD Classes (Catherine McEwasan Foundation)" application.
- Verification and clarification of inconsistent data.
- Review of data entry values for variables.
- Simple imputation of missing data when required.
- Confirmation of the appropriate phenotypic classification of patients by one of the investigators, who had prior training in its application.

Data Collection

Medical records of patients who met the diagnostic criteria for PIBD and EIM at the time of disease diagnosis were reviewed. Data collection was carried out through retrospective review of medical records, with variables recorded using a data collection form created in REDCap®, which was later exported to the statistical software STATA 18.0®.

Statistical Analysis

Descriptive statistics determined the frequency and percentages of categorical variables. For continuous variables, central tendency measures were determined according to

their distribution (mean with standard deviation [SD], median with interquartile range [IQR]). The association between EIMs and demographic, clinical, and biochemical characteristics was evaluated using Fisher's F for qualitative variables; for quantitative variables, the Mann-Whitney U test and Student's T test were used according to the nature of the data distribution. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the ethics committee of Fundación Hospital Pediátrico La Misericordia (HOMI). Data were extracted from medical records, so there was no interaction with participants, and informed consent was not required.

Data were collected using an MS Excel format. No individual data or information that could identify any patient or their family were disclosed, in accordance with the Statutory Law on Data Protection.

RESULTS

Demographic Features

Over a 15-year period, 71 cases of PIBD were confirmed, of which 18% (13/71) presented EIMs during the course of the disease. Among these, 62% (8/13) were male. The median age at diagnosis for the entire group was 11.4 years (IQR = 7.4-17.6). **Table 1** summarizes the demographic characteristics of patients in the EIM and non-EIM groups.

Clinical Features

The time from the onset of symptoms to diagnosis was longer in the group with EIMs (13.2 years versus 10.2 years; $p = 0.02$). Four patients had a personal history of autoimmune disease (two with arthritis and two with autoimmune hepatitis), while another four reported a history of psychiatric illness; among the latter, three had depression and one had attention deficit hyperactivity disorder. Regarding family history, four patients had a first-degree relative with IBD, and none belonged to the group with EIMs. **Table 2** shows the most frequently reported symptoms and signs in the group with EIMs.

Nutritional Status

Of the 71 patients, 42% (28) exhibited short stature or were at risk of short stature, 43% (29) were malnourished, and 10% (6) were overweight or obese. No significant differences were found between the groups analyzed with or without EIM.

Table 1. Demographic Characteristics of Patients with PIBD

	Does Patient Have EIM?		Total	*p*-Value
	With EIM	Without EIM		
Time in years	n =13 (18%)	n = 58 (82%)	n = 71 (100%)	
- Age at symptom onset	9.9 (SD: 6.1)	9.07 (SD: 4.8)	10.2 (IQR: 4.7-9.25)	0.4
- Age at PIBD diagnosis	13.2 (SD: 3.5)	10.2 (SD: 4.4)	11.4 (IQR: 7.4-17.6)	**0.02***
Sex			Total: 71 (100%)	
- Female	5 (38%)	27 (47%)	32 (45%)	0.4+
- Male	8 (62%)	31 (53%)	39 (55%)	
Origin			Total: 58 (100%)	
- Urban	8 (80%)	43 (89%)	51 (88%)	0.3
- Rural	2 (20%)	5 (10%)	7 (12%)	
Affiliation regime			Total: 71 (100%)	
- Contribution-based	11 (85%)	40 (69%)	51 (72%)	0.6
- Subsidized	2 (15%)	13 (22%)	15 (21%)	
- Private	0	5 (9%)	5 (7%)	

+Fisher's exact test. * Mann-Whitney U test. Author's own research.

Table 2. Clinical Characteristics at Diagnosis

	Does Patient Have EIM?		Total = 71 (100%)	*p*-Value
	Yeas = 13 (18%)	No = 58 (82%)		
Symptom				
- Rectal bleeding	10 (77%)	48 (83%)	58 (82%)	0.4
- Diarrhea	12 (92%)	41 (71%)	53 (75%)	0.9
- Abdominal pain	6 (46%)	36 (62%)	42 (59%)	0.2
- Weight loss	9 (69%)	19 (33%)	28 (39%)	**0.02**⁺
- Disruption of activities	6 (46%)	11 (19%)	17 (24%)	0.05
- Hyporexia	6 (46%)	8 (14%)	14 (20%)	**0.02**⁺
- Nocturnal diarrhea	7 (54%)	5 (9%)	12 (17%)	**0.001**⁺
- Vomiting	1 (8%)	4 (7%)	5 (7%)	0.6
- Fever in the last three days	1 (8%)	4 (7%)	5 (7%)	0.6
Physical Exam				
- Pallor	8 (62%)	13 (22%)	21 (30%)	**0.009**⁺
- Perianal fissures	4 (31%)	1 (2%)	5 (7%)	**0.003**⁺
- Fistulas	2 (15%)	1 (2%)	3 (4%)	0.08
- Perianal abscess	1 (8%)	1 (2%)	2 (3%)	0.3
- Jaundice	1 (8%)	0	1 (1.4%)	0.2
Time to Diagnosis				
- Average time between symptom onset and diagnosis	3.2 (SD: 3.4)	1.1 (SD: 1.4)	1.5 (SD: 2.1)	**0.02***

⁺Fisher's exact test. * Mann-Whitney U test. Author's own research.

Extraintestinal Manifestations

Among the 13 patients with EIMs, 54% (7/13) had one manifestation and 46% had two or more. These were more frequent in women (p = 0.08) (**Table 3**) and predominantly mucocutaneous, followed by musculoskeletal involvement. The frequency distribution of EIMs in the entire sample is presented in **Figure 2**.

Table 4 shows the distribution of EIMs according to phenotype.

Paraclinical Tests

Among the 71 patients, half were anemic. The hemoglobin levels were significantly lower in the group with EIMs (9.8 [SD: 2.7] vs. 12.3 [SD: 2.8] g/dL; p = 0.004). Albumin levels were also lower in this group, and they exhibited higher erythrocyte sedimentation rates (ESR: 36.4 [SD: 12.3] vs. 22 [SD: 17.3] mm/h, p = 0.02) and higher platelet counts (**Figure 3**). Calprotectin levels were reported in 21 patients, with 17 of them showing positive results (> 250 µg/g).

Treatment

Induction treatment with biological therapy was more common in the EIM group compared to the non-EIM group (38% vs. 23%). Four of the 71 patients required surgical intervention as part of their treatment, including two colectomies with ileostomy, one drainage of an intra-abdominal abscess, and one exploratory laparotomy. None of these four patients were in the EIM group.

DISCUSSION

This study examined the prevalence of EIMs in the largest cohort of patients with PIBD over a 15-year period in Colombia. The findings reveal that EIMs are common, with

Table 3. Types of EIMs

Type	Frequency
Articular (spondyloarthropathy)	8 (33%)
- Axial (ankylosing spondylitis)	1 (4%)
- Peripheral	7 (29%)
Mucocutaneous	14 (58%)
- Aphthous stomatitis	3 (12.5%)
- Erythema nodosum	4 (16.6%)
- Pyoderma gangrenosum	3 (12.5%)
- Psoriasis	1 (4%)
- Skin-tag	4 (16.6%)
Hepatic	1 (4%)
- Sclerosing cholangitis	1
Ophthalmologic	1 (4%)
- Uveitis	1

Author's own research.

Table 4. Distribution of EIMs According to PIBD Phenotype

Type of EIM	TUC (n = 10)	AUC (n = 0)	IBDU (n = 3)	CCD (n = 0)	CD (n = 12)
Articular					
- Axial: sacroiliitis	1	0	0	0	0
- Peripheral	4	0	1	0	2
Cutaneous					
- Aphthous stomatitis	1	0	0	0	2
- Erythema nodosum	0	0	1	0	3
- Pyoderma gangrenosum	1	0	0	0	2
- Psoriasis	1	0	0	0	0
- Skin-tag	1	0	1	0	2
Hepatic					
- Sclerosing cholangitis	1	0	0	0	0
Ophthalmologic					
- Uveitis	0	0	0	0	1

Author's own research.

a prevalence of 18% at the time of diagnosis, which aligns with previously reported figures in the literature ranging from 6% to 29%[15]. Additionally, it has been reported that between 4% and 25% of EIMs could precede intestinal involvement[11,12]. Furthermore, the presence of MEIs is associated with greater clinical and paraclinical severity of PIBD.

The prevalence of EIMs in PIBD varies significantly across published studies, likely due to the lack of unified criteria for defining them in pediatrics, as current guidelines are primarily based on adult data[11]. This variability is reflected in studies reporting prevalences as high as 80%, likely an overestimation due to the inclusion of osteopenia and growth retardation, which are now considered complications of PIBD[18]. While the prevalence at diagnosis found in this study is similar to the reports by Jansson and colleagues (14.1%) and Duricova and colleagues (8.9%) [13,15], it is notable that it is slightly higher in the present cohort, possibly due to the interdisciplinary approach.

This study also found that the time between the onset of symptoms and the age at diagnosis of PIBD was significantly longer in cases with EIMs. This delay in definitive diagnosis may suggest that the initial evaluation was directed at other organs or systems rather than the digestive system[7].

EIMs often involve more than one organ or system. In this study, nearly half (6/13) of the patients with EIMs had involvement in multiple organs or systems. In fact, the likelihood of developing an EIM increases as the disease progresses and with the prior presence of an EIM[11]. Over the course of the disease, up to 50% of adult patients with IBD will develop at least one EIM, and this involvement can be a significant source of morbidity and even a risk factor for mortality, especially in cases such as primary sclerosing cholangitis or venous thromboembolic events[18].

In the present cohort, mucocutaneous manifestations were the most common, occurring in 58% of cases. Mucocutaneous involvement has been described in 15%-20% of patients and is often determined by the shared underlying immunopathogenic mechanisms of PIBD[18,29]. In the pediatric population, reports of mucocutaneous involvement are scarce, but this study suggests a higher association with CD, which aligns with existing literature[27]. These manifestations are strongly linked to intestinal inflammatory activity and, in up to 50% of cases, appear simultaneously with the initial gastrointestinal symptoms[29]. Diagnosis is based on clinical characteristics and the exclusion of other dermatological disorders. Given the heterogeneity of lesions, diagnosing these manifestations can pose a challenge for pediatric gastroenterologists, emphasizing the importance of interdisciplinary evalua-

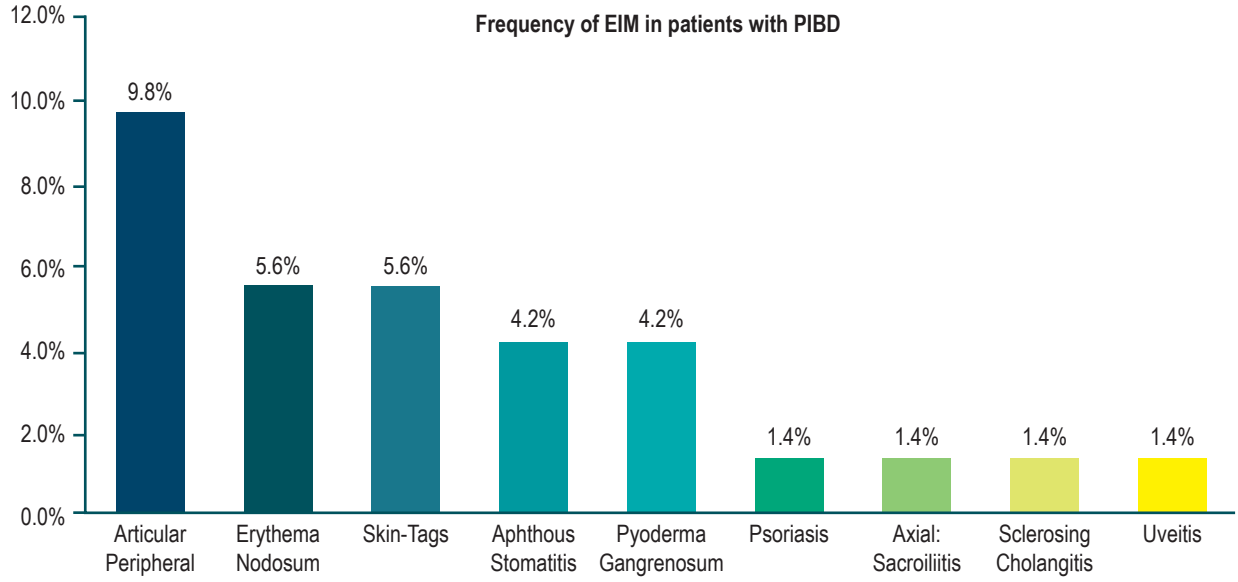


Figure 2. Frequency of EIMs in patients with PIBD. Author's file.

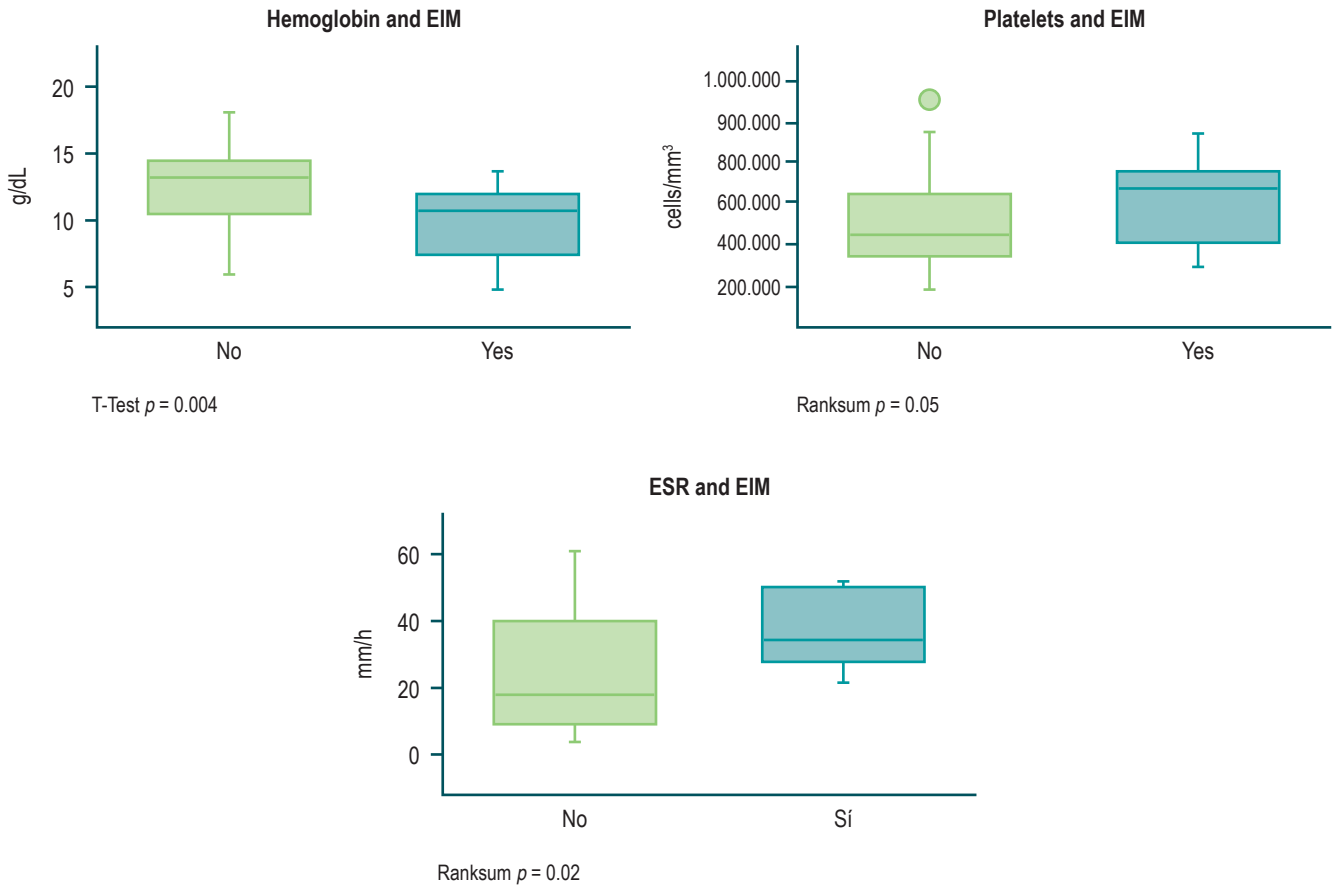


Figure 3. Paraclinical Tests at the Time of Diagnosis in PIBD. Author's file.

tion, including dermatology, and considering the psychological implications and impact on quality of life[18,27].

Musculoskeletal involvement (spondyloarthropathies) was the second most frequent EIM in this cohort. The association between IBD and axial or peripheral spondyloarthropathy indicates a common inflammatory pathway; genomic studies have identified shared loci that increase the risk of these diseases, involving the interleukin (IL)-12/23 signaling pathways[18]. Recent systematic reviews in adults have described peripheral joint involvement as the most frequent manifestation, with a prevalence of 13%, similar to data reported in adults in Colombia[6,30]. In this study, the prevalence is 33%, which is consistent with other reports, although the prevalence reported in pediatrics varies between 2% and 35%, highlighting a lack of standardized definitions and criteria[31].

The most frequently reported signs and symptoms in these 13 patients were nocturnal diarrhea, weight loss, and pallor. Additionally, these patients exhibited significantly lower levels of hemoglobin and albumin, along with elevated ESR. These findings are considered indicators of higher disease activity and greater systemic involvement. This is consistent with multiple studies indicating a more aggressive clinical course in terms of progression and extension when PIBD is associated with EIMs[19], with a higher likelihood of corticosteroid use, immunosuppressive therapy[14], biological therapy, and surgical management, especially in UC[13]. In CD, EIMs are associated with a higher relapse rate[15].

The prevalence of anemia in all PIBD cases was 50%. Although anemia was not considered an EIM, the most recent guidelines from the European Crohn's and Colitis Organisation (ECCO) define it as a complication of the disease[18]. Thus, it is a fundamental aspect to evaluate and treat in patients with IBD, given its negative influence on disease progression[32]. Reports of anemia in adults are highly variable, ranging from 6% to 74%, likely due to the heterogeneity of the patients included in studies[18]. In children, the prevalence of anemia at the time of diagnosis has been described as high as 90%[21,33]. In this cohort, the high prevalence of anemia is particularly relevant due to the potential consequences in children during critical phases of growth and development[32]. Calprotectin levels do not appear to be related to EIMs, and there is no evidence to support its routine use for their identification, as it is a nonspecific marker of inflammation[34].

Among the study's limitations is the risk of information bias due to its retrospective design. Data taken only at the time of diagnosis may lead to an underestimation of cases. Over the 15-year study period, scientific advances may have led to lower initial diagnosis rates.

Regarding the COVID-19 pandemic, which occurred during the study period and caused significant global changes in life and health, its occurrence could not have been anticipated in the study design.

This study's strength lies in being the first in Colombia to describe the frequency of EIMs in PIBD, with an interdisciplinary approach that enabled comprehensive management of these patients at a high-experience center.

CONCLUSIONS

EIMs are common in PIBD and their presence is associated with greater disease severity and progression. This study corroborates this association through the presence of symptoms and certain biochemical markers. However, these findings need to be confirmed in prospective investigations.

The diagnosis of PIBD in patients with EIMs tends to occur at older ages, possibly due to a clinical focus on systems other than the digestive system, representing an opportunity to improve early diagnosis.

In the pediatric context, it is essential to provide an interdisciplinary approach in specialized centers that comprehensively address all aspects related to the diagnosis, treatment, and follow-up of patients with PIBD associated with EIMs, to not overlook the potential impact on disease course, pharmacological treatment decisions, quality of life, and emotional well-being of patients.

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