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Original article

Very early onset versus pediatric onset inflammatory bowel disease: a prospective cohort analysis

Background: *Inflammatory bowel disease (IBD) in the pediatric age group is divided into two categories: very early onset IBD (VEO-IBD) and pediatric IBD (PIBD). The goal of this study was to determine the difference between the two entities concerning disease presentation, severity and treatment response.* ***Methods:*** *We conducted an observational prospective study that involved 70 newly diagnosed children with IBD, diagnosed using modified Porto criteria and followed up over a period of one year (35 VEO-IBD and 35 PIBD). It was conducted at the Pediatric Gastroenterology and Endoscopy Unit at Ain Shams University. Recruited cases were subjected to clinical assessment, laboratory investigations including stool tests, full blood counts, inflammatory markers in addition to ileo-colonoscopy and esophagogastroduodenoscopy. They were assessed initially and at follow-up for a total duration of one year for disease activity and treatment response and disease relapse.* ***Results:*** *Gender distribution was similar among both VEO-IBD and PIBD groups. Rural residence (p=0.048), positive family history (p= 0.010), oral ulcers (p=0.022) and perianal skin tags (p=0.066) were more frequent among patients with VEO-IBD. Colonoscopy showed deeper ulcers in VEO-IBD (25.7%) than in PIBD (2.9%). Regression analysis showed that younger age (p=0.032) and high disease severity scores (p=0.011) were the main determinants of steroid non-responsiveness.* ***Conclusion:*** *Young age and severity score were the most predictive risk factors for steroid unresponsiveness in pediatric IBD*

Keywords: Pediatric Onset Inflammatory Bowel Disease; Very Early Onset Inflammatory Bowel Disease; ulcerative colitis.

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INTRODUCTION

The way in which inflammatory bowel disease (IBD) manifests itself clinically in children varies greatly. In contrast to Crohn's disease (CD), which is more likely to present with fever, weight loss, nonspecific stomach discomfort, diarrhea, unexplained anemia, or growth retardation, ulcerative colitis (UC) patients most commonly present with bloody diarrhea. Only 25% of CD patients had the traditional "triad" of diarrhea, weight loss, and abdominal discomfort. Six to 23% of children may have extra intestinal symptoms at diagnosis, with a greater prevalence in those older than six years.[1] Based on clinical signs and symptoms, endoscopy, histology, and radiological findings, the Porto diagnostic criteria offer a tool for the diagnosis of pediatric inflammatory bowel disease (IBD).[2]

Treatment of IBD require two phases; initially is induction of remission by 5-Aminosalycilic acid (5-

ASA) in mild to moderate disease and by systemic steroids and immunosuppressants (i.e. Thiopurines and Methotrexate) in moderate to severe diseases, Monoclonal antibodies are used to induce remission in patients with moderate-to-severe disease who didn't respond to conventional therapy. Then maintaining the remission by 5-ASA, Thiopurines, and monoclonal antibodies in patients who achieved remission with anti-TNF agents .[3]

VEO-IBD which occurs in children less than 6 years of age is often characterized by higher severity, aggressive progression, and poorer response to conventional therapy.[4] Finding the clinical and pathologic determinants of treatment response in a group of children with VEO-IBD compared to a group with pediatric-onset IBD is the primary objective of this work, while the secondary aim is to propose the ideal regimen of treatment for each patient based on clinic-pathologic predictors.

METHODS

Study design

A prospective observational study was conducted in the Pediatric Gastroenterology and Endoscopy Unit at Children's Hospital, Ain Shams University, Egypt, where 70 pediatric patients with IBD who presented between June 2020 and June 2022 were included.

Study population and randomization

We recruited patients who presented with symptoms suggestive of inflammatory bowel disease and met the modified Porto criteria,[2] based on clinical characteristics, laboratory, radiographic, and pathological results. We recruited patients in 2 groups according to the age of disease onset: VEO-IBD (n=35) with age of disease onset less than 6 years or PIBD (n=35), with age of onset more than 6 years. Exclusion criteria included patients with documented cow milk protein allergy, eosinophilic gastrointestinal disorders, known humoral or cell-mediated immunodeficiency, or those with primary gastrointestinal tract infections.

Study methods

A longitudinal study was carried out, in which patients were assessed at enrollment, then every month for the first 3 months to determine their response to corticosteroid treatment, then they were followed-up at 3-monthly interval till the end of the year to determine their relapse rate. Details of assessment were as follows.

Evaluation at enrolment:

The medical history of each patient was taken, including the presenting complaint, any related gastrointestinal (GI) symptoms, systemic signs, and family history (FH) of a related disease. Anthropometry, abdominal examination, and perianal area check were all part of the comprehensive clinical examination. Stool analysis, full blood counts, immunological evaluation, and inflammatory marker measurements were among the laboratory tests conducted. Ileo-colonoscopy was carried out for all patients and multiple biopsies were taken from each segment, and esophagogastroduodenoscopy (EGD) was carried out for all patients who had upper gastrointestinal symptoms, very early onset IBD, or suspicion of CD.[5] During colonoscopy, the degree of colitis was assessed using Mayo score.[6] The extent of inflammation was recorded according to Paris classification.[1] Confirmed cases of IBD were included in the study.

Application of Treatment and evaluation of treatment response according to ESPGHAN guidelines of IBD:[3]

The Pediatric Ulcerative Colitis Activity Index (PUCAI) or the Pediatric Crohn's Disease Activity Index (PCDAI) were used to measure disease activity at the time of diagnosis, and therapy was initiated accordingly.[7] Treatment was provided, and patients were followed-up monthly for the first 3 months to assess treatment response.

Induction of remission: Treatment protocols were applied according to the guideline from European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology and Nutrition.[8] Corticosteroids were used for mild to moderate disease not responding to salicylate [9] or moderate to severe disease,[10] at a dose of 1mg/kg/day (maximum 40 mg per day) of oral prednisolone/prednisone once daily for 2 to 3 weeks followed by a tapering period of up to 8 to 10 weeks.[11] Biological therapy was used for patients with steroid resistance not responding to induction[12] or fistulizing CD or penetrating disease, including infliximab, adalimumab or golimumab.[10] Clinical remission was defined as activity index less than 10 points according PUCAI and PCDAI.[7] Patients were evaluated by the end of the first 3 months of study for clinical and laboratory status to determine their response to initial corticosteroid therapy and accordingly were classified to steroid responsive and steroid irresponsive/dependant. Patients whose disease activity was severe necessitating starting

biological therapy from the start were excluded from the analysis.

Follow-up at 3 monthly intervals till the end of the first year

Patients were evaluated regularly every 12 weeks and accordingly were put on maintenance or treatment escalation regimens based on their clinical and laboratory status. Salicylates were used for UC patients and thiopurines for CD patients or patients with UC with steroid dependency,[8]at a dose of 2 to 2.5 mg/kg,[8] with follow up blood counts and liver enzymes.[8] Biological therapy were continued or changed for patients who needed biological for induction or steroid dependant patients.[13] Patients were assessed for the frequency of relapses. At the end of the follow-up period patients were assessed on clinical, laboratory and endoscopic bases to confirm their disease activity status.

Ethical considerations

The study was approved by The Research Ethics Committee of Ain Shams University's Faculty of Medicine before being carried out with approval number FWA 000017585; FMASU: MD 95/2020. Written informed consent was obtained from parents/caregivers or patients after explanation of the study and with preserving patients' anonymity.

Sample size calculation: The study's sample size was determined using the PASS 11 program. Assuming that children with VEO-IBD have a 50% remission rate and those with PIBD have an 80% remission rate, a sample size of 35 patients per group was determined to detect the difference between the two groups with a power of 80% and an x-error of 0.05.

Statistical analysis

Version 23 of the Statistical Package for Social Science was used to enter, edit, and review the data. When the quantitative data were determined to be non-parametric, they were given as the median and inter-quartile range (IQR), and when they were parametric, they were described as mean, standard deviation and range. Qualitative variables were expressed as percentages and numbers. The comparison between two groups with quantitative data and parametric distribution was done by using independent t-test while the comparison between two groups with quantitative data and non-parametric distribution was done by using Mann-Whitney test. The chi-square test was used for categorical data. Univariate and multivariate logistic regression analysis was done to assess predictors of non-responders with its odds ratio (OR) and 95% confidence interval (CI) and also to assess the predictors of patients needing biological therapy with OR and 95% CI using Backward method.

RESULTS

Throughout the study, 70 children were included with the diagnosis of IBD, including 35 patients with VEO-IBD and 35 patients with PIBD based on the age of disease onset. The gender distribution was comparable across both groups, with 14 males and 21 females in each.

Concerning clinic demographic data, children with VEO-IBD were more likely to live in rural areas (48.6%), have a family history of a comparable condition (17%; 3 with UC, 1 with CD, and 2 with IBD-U) and experiencing a stillbirth (11.4%) (Table 1). Chronic diarrhea (85.7%), rectal bleeding (82.9%), recurrent fever (42.9%), and the requirement for a blood transfusion (63.3%) were the most common clinical manifestations in children with VEO-IBD. These rates did not differ substantially from PIBD (68.6%, 74.3%, 43.3, 31.3%, and 80%, respectively) (Table 2). Growth faltering at presentation was comparable among both groups including underweight (42.9% and 34.3%) and stunting (14.3% and 17.1%). Oral ulcers were much more common in children with VEO-IBD (25.7%) than in those with PIBD (5.7%). Perianal disease was present in 17.1% of children with VEO-IBD and 14.3% of PIBD, with PIBD having a significantly greater frequency of skin tags.

Among children with VEO-IBD, 91.4% had anemia, 68.6% leukocytosis, 91.6% neutrophilia, 71.4% thrombocytosis, and 37.1% had hypoalbuminemia. These frequencies did not differ significantly from PIBD (71.4%, 48.5%, 76.4%, 62.8, and 31.4%, respectively) (Table 3) Both groups had comparable levels of CRP and fecal calprotectin while ESR was higher among patients with PIBD (Table 4).

Regarding colonoscopy findings, most children with VEO-IBD had extensive distribution of inflammation (66%) compared to 68% in PIBD and moderate to severe colitis (76%) compared to 79% in PIBD. The terminal ileum was successfully cannulated in 34.3% of children with VEO-IBD and 77.1% of children with PIBD and abnormalities were found among only 2 children with VEO-IBD **.**

Diagnostic delay was significantly higher in VEO-IBD than in PIBD (p= 0.045). The median diagnostic delay in VEO-IBD and PIBD were 6 months (IQR, 2 - 12 months) and 2 months (IQR, 1 – 6 months), respectively.

Among the children with VEO-IBD, the diagnosis of IBD-Undifferentiated was the most common (45.7%), although a significant number of patients were diagnosed with ulcerative colitis (34.3%) (table 5).

After 3 months from starting the treatment (induction of remission), patients were classified according to their response to initial theroid therapy into corticosteroid responsive (n=30) or corticosteroid dependent/unresponsive (n=31) (Table 6). Nine children who started biological therapy for induction of remission from the start as they have fistulizing CD or penetrating disease were excluded from these comparisons as they didn't receive corticosteroids. Out of the remaining 61 children, 30 children (49.2%) responded well to steroids in comparison to 31 children (50.8%) who didn't respond to steroids during induction of remission. Clinical remission was defined as activity index (PCDAI or PUCAI) less than 10 points. Relapse rate over the study period was higher in the steroid unresponsive group with average rate (1.8/ year) compared to steroid responsive group (0.8/year), p= 0.013.

Steroids responsive patients has initial IBD score that was either mild (33.3%), moderate (50%) or severe (16.7%) in comparison to patient with steroids unresponsiveness (0.0%, 51.6% and 48.4%, respectively). Using Logistic regression analysis for predictors of response to steroids during induction of remission the younger the age at time of diagnosis and the more severe the clinical score were found to be predictors of steroids dependency/unresponsiveness (table 7).

Table 1. Comparisons of the distribution of sociodemographic data among VEO-IBD and PIBD

		IBD	**VEO-IBD**	**PIBD**	P-value
		No.=70	No. = 35	No. = 35	
Sex	Female	28 (40%)	14 (40.0%)	14 (40.0%)	1.000
	Male	42 (60 %)	21 (60.0%)	21 (60.0%)	
Residence	Rural	26 (37 %)	17 (48.6%)	9 (25.7%)	**0.048**
	Urban	44(62.9%)	18 (51.4%)	26 (74.3%)	
Parents consanguinity		20(28.6%)	11 (31.4%)	9 (25.7%)	0.597
Positive family history of IBD		6(8.6%)	6 (17.1%)	0 (0.0%)	**0.010**
History of Sibling deaths		4 (5.7%)	4 (11.4%)	0 (0.0%)	0.039

Table 2. Comparisons of the distribution of clinical presentations among VEO-IBD and PIBD

	IBD	**VEO**	**PIBD**	P-value
	No.=70	**No. = 35**	**No. = 35**	
Fever	26(37.2%)	15 (42.9%)	11 (31.4%)	0.322
Diarrhea	54(77.2%)	30 (85.7%)	24 (68.6%)	0.088
BPR	55(78.6%)	29 (82.9%)	26 (74.3%)	0.382
Vomiting	10(14.3%)	4 (11.4%)	6 (17.1%)	0.495
Abdominal pain	14(20%)	3 (8.6%)	11 (31.4%)	**0.017**
Weight loss	40(57.1%)	20 (57.1%)	20 (57.1%)	1.000
GIT obstruction	3(4.3%)	0 (0.0%)	3 (8.6%)	0.077
Perianal disease	11(15.7.%)	6 (17.1%)	5 (14.3%)	0.743
Skin manifestation	2(2.8%)	2 (5.7%)	0 (0.0%)	0.151
Oral ulcers	11(15.7%)	9 (25.7%)	2 (5.7%)	**0.022**
Joint affection	3(4.3%)	1 (2.9%)	2 (5.7%)	0.555

Table 3. Comparisons of the results of initial laboratory investigations among children with VEO-IBD and PIBD

		IBD	**VEO**	**PIBD**	**Test value**	**P-value**
		No=70	**No. = 35**	**No. = 35**		
*TLC(x1000/mm3)	Mean ± SD	–	14.23 ± 5.62	12.86 ± 5.72	1.010•	0.316
	Range	–	3.3 – 27.5	4.1 – 27		
TLC	Leukocytosis	41(58.6%)	24 (68.6%)	17 (48.6%)	4.481*	0.106
	Leukopenia	1(1.4%)	1 (2.9%)	0 (0.0%)		
*HGB (gm/dl)	Mean ± SD	–	8.74 ± 1.94	9.44 ± 1.86	-1.546•	0.127
	Range	–	4 – 13	6 – 13		
Anemia		57(81.4%)	32 (91.4%)	25 (71.4%)	**4.629***	**0.031**
*PLT (x1000/mm3)	Mean ± SD	–	546.60 ± 187.32	507.37 ± 201.80	0.843•	0.402
	Range	–	260 – 1026	123 – 900		
Thrombocytosis		47 (67.1%)	25 (71.4%)	22 (62.9%)	0.583*	0.445
Albumin	Mean ± SD	–	3.33 ± 0.55	3.31 ± 0.47	0.186•	0.853
	Range	–	2.5 – 4.5	2.2 – 4		
Hypoalbuminemia		24 (34.3%0	13 (37.1%)	11 (31.4%)	0.254*	0.615

HGB: hemoglobin; PLT: platelets; TLC: total leukocyte count
*Chi-square test; ● Independent t-test

Table 4. Comparisons of the results of inflammatory markers among children with VEO-IBD and PIBD

Markers of inflammation		**VEO-IBD**	**PIBD**	Test value	P-value
		No. = 35	**No. = 35**		
CRP (mg/l)	Median (IQR)	30 (15 – 78)	40 (24 – 55)	-0.288‡	0.773
	Range	4 – 160	1 – 150		
ESR (mm/hr) 1st hr	**Mean ± SD**	**41.29 ± 21.67**	**55.43 ± 24.17**	**-2.578•**	**0.012**
	Range	**5 – 80**	**12 – 113**		
Fecal calprotectin	Median (IQR)	750 (450 – 950)	650 (550 – 750)	-1.489‡	0.137
	Range	35 – 1500	40 – 1000		

Table 5. Comparisons of the types of IBD among children with VEO-IBD and PIBD

		VEO	**PIBD**	Test value	P-value
		No. = 35	No. = 35		
Classification	Ulcerative colitis	12 (34.3%)	23 (65.7%)	22.471*	0.000
	Crohn's disease	6 (17.1%)	10 (28.5%)		
	Atypical Ulcerative colitis	1 (2.9%)	1(2.9%)		
	IBD unclassified	16 (45.7%)	1 (2.9%)		

*Chi-square test

Table 6. Comparison between steroids responsive and steroids dependent/unresponsive children in terms of demographic data and initial clinical and endoscopic data

		Steroids responsive	Steroids dependent/ unresponsive	Test-value	P-value
		No.=30	No.=31		
Age (years)	Median (IQR)	10.5 (6 - 13)	7 (4 - 12)	-1.164‡	0.244
	Range	0.18 – 15	0.75 – 15		
Age of onset (months)	Median (IQR)	108 (36 - 144)	60 (12 - 120)	-1.937‡	0.053
	Range	4 – 180	1 – 168		
Sex	Female	11 (36.7%)	12 (38.7%)	0.027*	0.869
	Male	19 (63.3%)	19 (61.3%)		
Age of diagnosis (months)	Median (IQR)	123 (48 - 147)	61 (20 - 132)	-2.114‡	0.034
	Range	10 – 181	3 – 170		
Time lag (months)	Median (IQR)	4.5 (2 - 12)	3 (2 - 6)	-1.443‡	0.149
	Range	1 – 24	1 – 16		
Endoscopic scoring	Normal	1 (3.3%)	1 (3.2%)	2.675	0.445
	Mild	7 (23.3%)	7 (22.6%)		
	Moderate	13 (43.3%)	8 (25.8%)		
	Severe	9 (30.0%)	15 (48.4%)		
Histopathological scoring	Normal	0 (0.0%)	0 (0.0%)	0.317	0.853
	Mild	2 (6.7%)	2 (6.5%)		
	Moderate	27 (90.0%)	27 (87.1%)		
	Severe	1 (3.3%)	2 (6.5%)		
Classification	Ulcerative colitis	18 (60.0%)	17 (54.8%)	1.423	0.700
	Crohn's disease	6 (20.0%)	7 (22.6%)		
	Atypical UC	1 (3.3%)	0 (0.0%)		
	IBD unclassified	5 (16.7%)	7 (22.6%)		
IBD clinical score	Mild	10 (33.3%)	0 (0.0%)	15.02	0.001
	Moderate	15 (50.0%)	16 (51.6%)		
	Severe	5 (16.7%)	15 (48.4%)		
Relapse rate/12 months		0.8 (0.3)	1.8 (0.5)	3.12	0.013

*:Chi-square test; ‡: Mann Whitney test

Table 7. Logistic regression analysis for predictors of steroid dependency/unresponsiveness among studied pediatric patients with IBD

	Uni-variate regression				Multi-variate regression			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Age at diagnosis	**0.032**	3.140	1.104	8.933	0.078	2.686	0.896	8.048
Severe IBD score	**0.011**	4.687	1.425	15.421	**0.023**	4.118	1.213	13.975

DISCUSSION

In this current study, children with IBD showed a male predominance (60%) that was comparable between VEO-IBD and PIBD groups. This finding is similar to that of **Lee et al**[14] who found that IBD is more common in males (75.8%).

For children with VEO-IBD, the odds of living in a rural region (48.6%), experiencing a stillbirth (11.4%), and having a similar condition (17%) were significantly higher. These results corroborate those of **Al-Hussaini et al.,**[15] who discovered that families of children with VEO-IBD (29%) exhibited higher levels of familial aggregation than those with PIBD (4%). These results imply that compared to PIBD, VEO-IBD has a stronger genetic heritage. From another perspective, **Roma et al.**[16] noted that children with familial IBD exhibited an earlier beginning of the disease in comparison to those with sporadic IBD, based on a retrospective analysis involving 411 children with IBD.

Children with VEO-IBD and PIBD had comparable clinical presentations, which included chronic diarrhea, rectal hemorrhage, growth failure, recurrent fever, and the requirement for blood transfusion. Children with VEO IBD have a significantly higher frequency of oral ulcers (25.7%) and a lower frequency of abdominal pain (8.6%) than children with PIBD (5.7% and 31.4%, respectively). These findings are consistent with those of **Ledder et al.,**[17] who reported that most clinical features at first presentation were similar among younger and older children with IBD, with the exception of abdominal pain, which was significantly less common in the younger age group.

Growth faltering at presentation was comparable among VEO-IBD and PIBD including underweight (42.9% and 34.3%) and stunting (14.3% and 17.1%). This is in line with the findings of **Ledder et al.,**[17] who discovered that there was no significant difference in the age-adjusted weight and height z scores between younger and older IBD children at presentation. On the other hand**, Al-Hussaini et al.**[15] found that growth parameters were significantly lower among VEO-IBD compared to PIBD.

Compared to children with PIBD, who have an increased prevalence of skin tags, children with VEO-IBD have a comparable frequency of perianal lesions. According to **Kelsen et al.,**[18] there were no significant differences in the two age groups' prevalence of perianal lesions. According to **Ye et al.,**[19] perianal lesions might present as perianal abscess, rectovaginal fistula, anal fistula, perianal rash and ulcers, or anal skin tags in those with VEO-IBD.

Laboratory tests on children with VEO-IBD showed that 91.4% of patients had anemia, 68.6% had leukocytosis, 71.4% had thrombocytosis, and 37.1% had hypoalbuminemia. These rates did not differ significantly from PIBD (71.4%, 48.5%, 76.4%, 62.8 and 31.4%, respectively). Inflammatory markers such as fecal calprotectin, ESR, and CRP were considerably high in both groups. This is consistent with Al-Hussaini et al.[9] who found no differences in the two groups' laboratory results.

In comparison to PIBD, VEO-IBD had a significantly greater diagnostic delay (p= 0.045). This is consistent with **Kammermeier et al.**[20] findings, which showed that 44% [25/57] of his patients had a diagnostic delay of more than six months. He linked the larger time lag in VEO-IBD diagnosis to patients being diagnosed with different diseases instead of VEO-IBD. Among them were various multi-system illnesses with sporadic non-bloody diarrhea [n = 5], chronic idiopathic constipation [n = 2], and allergic GI disease [n = 12]. However, this finding contradicts that of **Banerjee et al.,**[21] who found that VEO¬IBD had a considerably smaller diagnostic delay (>6 months) than PIBD. They linked the earlier referral in VEO-IBD to a more severe illness at presentation, which resulted in a shorter delay. Another reason would be that babies wear diapers, which makes it simpler to observe their feces. We attribute the diagnosis delay in our study to a broad range of differential diagnoses, such as infections and allergies to cow's milk protein, that might coincide with VEO-IBD.

After dividing all the patients again into steroid responsive and steroid nonresponsive groups, we found that both age of diagnosis and IBD severity score are the most important predictors for steroids response in pediatric IBD. This is consistent with research by **Kammermeier et al.,**[20] who found that IBD is often resistant to therapy and cannot be differentiated from Crohn's disease or ulcerative colitis in children whose illness begins before the age of two years. In order to assess steroid responsiveness in patients with ulcerative colitis ranging from mild to severe, **Cakir et al.**[22]conducted a single center's study and noticed that, over a prolonged period of time, over half of the pediatric patients totally reacted to steroid therapy.

In our study the initial severity score on multivariate analysis proved to be the most significant predictor for steroid unresponsiveness. Therefore, we can suggest starting by steroids therapy (step up policy) in patients with mild IBD scores (UC and Crohn’s), while patients with initial severe scores and possibly the moderate ones are suggested to start in a step-down pattern (biological therapy from the start). Further long-term wide scale follow-up studies are needed to support our suggestion. According to the **PROTECT research,**[23] there is little probability that UC patients who do not reach a clinical remission after one month and who have poor hemoglobin, a high PUCAI, or a high Mayo score would have a remission free of corticosteroids after a year. It follows that in these individuals, rapid escalation to biologic treatment should be seriously contemplated. In another multi-center prospective pediatric cohort study was carried out by **Dhaliwal et al.**[24] to observe the consequences of acute severe colitis at the time of initial presentation. The following clinical factors were associated with

starting infliximab: male sex, higher age, increased PUCAI, and hypoalbuminemia.

In conclusion, children with VEO-IBD have clinical presentations similar to classic PIBD with higher frequencies of family history of similar condition and still birth. This might reflect the higher frequency of monogenic pattern of inheritance among this group. From the data analysis, it is clear that both age of diagnosis and IBD severity score are the most important predictors for outcome represented by steroids responsiveness. Moreover, the severity score on multivariate analysis proved to be the most significant predictor for the disease course. Hence, we suggest starting steroids therapy (step up) policy in patients with mild IBD scores, while biological therapy is better to be started with in patients with severe IBD activity scores and possibly the moderate ones. Our study had several points of limitation, including the relatively small sample size, the lack of genetic testing and the non-inclusion of adequate numbers of patients on different biological therapies. We recommended focusing on the family history in younger children in suspecting the diagnosis of VEO-IBD, considering the assessment for possible associated immunodeficiency/ autoinflammatory disorder with VEO-IBD, and consider the value of initial severity scoring in decision making for the management plan.

AUTHORS CONTRIBUTION:

All the authors participated in conceiving and designing the study. All the authors made substantial intellectual contributions to the work. **RMA**: collected and analyzed the data. **OHN:** performed the histopathological examination of the intestinal biopsies. **AMH:** interpreted the clinical, endoscopic and laboratory results. **DAN:** wrote the manuscript. **MAE:** revised the manuscript for publication. All authors approved the manuscript.

CONFLICTS Of INTEREST

The authors declare no conflict of interest.

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