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Short Communication

Outcome of Very Early Onset Pediatric Inflammatory Bowel Diseases Compared to Later-Onset Pediatric IBD: The 15-Year Single-Center Experience of a Referral Pediatric IBD Unit

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Abstract

Background: In last years, research interest increased for very early onset (VEO) inflammatory bowel disease (IBD), defined by age at diagnosis < 6 years. Previous works reported more severe disease course of VEO-IBD, compared with later-onset pediatric IBD, mainly attributed to a greater role of genetics in this age group. Otherwise, some studies questioned these results and reported comparable outcomes. Our study aimed to verify the effective role of age as a predictive factor of severity in the disease course. **Methods:** In this referral IBD single-center retrospective observational study**,** VEO-IBD was compared with IBD diagnosed between 6 and 17 years of age (ped-IBD). Patients with monogenic-IBD or IBD-like disease were excluded. We chose a minimum follow up period of 18 months since the diagnosis or any period in patients with Ulcerative Colitis (UC) who underwent surgery. The two cohorts were homogeneous for extension of disease and clinical severity at diagnosis and were compared for different clinical outcomes. Primary outcomes were the cumulative incidence of biological therapy use and the cumulative incidence of major surgery, as severity disease' indices. Secondary outcomes were the cumulative incidence of clinical remission, steroid-dependence and the relapse free survival at the last follow up. **Results:** 29 VEO-IBD cases were compared with 52 ped-IBDs. Median follow up time was 4,9 years. UC were most represented in both groups (83% of VEO-IBD, 81% of ped-IBD). At the end of follow up, the surgical rate was significantly higher for VEO-UC group compared with ped-UC (p 0.018). No difference in biologic therapy use was detected (45,6% VEO-IBD *vs* 43,5% ped-IBD; p 0.72). Cumulative incidences of relapse free survival, steroid-dependence, use of immunosuppressive therapy and clinical remission at the end of follow up were comparable. **Discussion:** Our data question the evidence of a worse outcome of VEO-UC, in comparison with ped-UC. Notably, we demonstrate a higher need for surgery in VEO-UC.

Keywords: Very early onset inflammatory bowel disease (VEO-IBD); pediatric IBD; Crohn's disease; ulcerative colitis; VEO-IBD outcome.

Introduction

The incidence of inflammatory bowel diseases (IBD) had shown an increasing trend in children and adolescent population [1-4]. The rate of incidence of pediatric IBD in Italy in the last decade seems to have stabilized, while it has doubled compared to previous Italian reports, confirming other studies conducted worldwide [5,6]. The onset of IBD is frequently observed in pediatric age and up to 25% of IBDs are diagnosed before 20 years of age [1,7]. Research interest has increased for IBD diagnosed during the first years of life, that are classified as very early onset (VEO-IBD), defined by age at diagnosis < 6 years, and early onset IBD, diagnosed between 6 and 10 years of age, according with Paris classification [8,9]. Worldwide, VEO-IBD represent 6 to 15% of the pediatric IBD [10,11] and recent Italian data confirmed a proportion of 9,8% [5]. In this peculiar category of patients, previous works reported a more severe disease course [10,12,13] associated with a distinctive phenotype with major disease extent at diagnosis and more frequent colonic location, making it harder to distinguish Ulcerative Colitis (UC) from colonic Crohn's disease (CD) [1,3,14]. The worse disease course, together with the earlier age at onset and a frequent IBD family history, has been attributed to a greater role of genetics in the pathogenesis of VEO-IBD compared to later onset-IBD [15,16].

Monogenic anomalies have been demonstrated in up to 20% of VEO-IBD, many of them involving genes associated to primary immunodeficiency's and enteral barrier abnormalities [10]. Otherwise, some studies questioned these results and reported comparable outcomes [17]. Several retrospective studies compared pediatric IBD outcome at different ages of onset. Disparities have been described regarding responsiveness to medical therapies, need for surgery, relapse rate and impact on linear growth [3,14,17-24]. These findings have led to consider VEO-IBD as worse diseases than later onset IBD [23]. These studies are limited by the wide variability in extent, location, behavior and clinical severity at the onset of IBD between the enrolled groups of patients, questioning the effective role of age in determine IBD outcome. The present work evaluates the outcome of VEO-IBDs in comparison with later onset pediatric IBDs diagnosed between 6 and 17 years of age (ped-IBDs), homogeneous in extent, location, behavior and clinical severity at diagnosis.

Methods

Patients selection

We conducted a single-center retrospective observational study of patients affected by pediatric-onset-IBD diagnosed between 2005 and 2018 in the Pediatric Gastroenterology Unit of Maggiore Hospital in Bologna, a reference Italian center for pediatric IBD. Eligible subjects were patients affected by IBD diagnosed before the age of 18 years. The last follow-up update was at February 2022, with a minimum follow up period of 18 months since the diagnosis or any period in patients with UC who have undergone surgery. Patients with monogenic-IBD or IBD-like disease were excluded. Eligible subjects were divided in two cohorts: 1) VEO-IBD, defined as patients diagnosed with IBD before the age of 6 years, and 2) ped -IBD, defined as patients diagnosed with IBD from 6 to 17 years of age. Patients in the ped-IBD cohort also need to have the same extent (for UC and IBD-unclassified), location and behavior (for CD), according to the Paris classification, and clinical severity at onset, according to the international clinical score for pediatric ulcerative colitis (PUCAI) and for pediatric Crohn disease (PCDAI) [22,23]. We also reported the UC/CD ratio for each IBD groups.

Population characteristics

We collected data about past medical and family history. Clinical manifestations (including extra-intestinal manifestations), laboratory datas, radiologic features and endoscopic findings at the diagnosis were also reported. IBD diagnosis was defined according to ESPGHAN revised Porto criteria [25]. The two cohorts were homogeneous for extension of disease, according to Paris classification [7], and clinical severity, according to the international clinical score for pediatric ulcerative colitis (PUCAI) and for pediatric Crohn disease (PCDAI) [22,23].

The time between symptom onset and diagnosis was also reported and considered a diagnostic delay if longer than 6 months in CD and 4 months in CU [5]. Endoscopic severity was determined by Simple Endoscopic Score (SES) for CD and Mayo Score for UC [28,29].

Outcomes

We compared VEO-IBD with ped-IBD for different clinical outcomes. When appropriate, analysis was also performed comparing VEO-UC with ped-UC and VEO-CD with ped-CD subgroups. Primary outcomes were the cumulative incidence of biologic therapy and the cumulative incidence of major surgery. Biologic therapies included all approved medical treatments for pediatric IBD [30-32]. Small bowel resection, ileocecal resection, partial or subtotal colectomy, stricture-plasty, ileostomy and colostomy were considered as major surgeries.

Secondary outcomes were the cumulative incidence of clinical remission, steroid-dependence and relapse-free survival at the last follow up. The use of immune-suppressive treatments (methotrexate and thiopurines), severe relapses, changes in CD behavior and the impact on patient's growth were also analyzed.

Clinical remission was defined by a PUCAI < 10 or a PCDAI ≤ 10 [27,31]. Steroid-dependence was defined by failure to discontinue steroid therapy because of symptoms recurrence during 3 months of weaning attempts, or disease relapse within 3 months after steroid discontinuation [31]. Relapse was identified by clinical or endoscopic flare-up requiring systemic corticosteroids, immunomodulators, biologic therapy initiating or optimization, or surgery [27,32]. Changes in CD's behavior were defined by penetrating, structuring, or perianal disease, according to Paris Classification [8]. Impact on growth was measured by body mass index (BMI) Z-scores, calculated through the WHO (patients ≤2 years) and CDC (patients > 2 years) at diagnosis and at the end of follow up.

Statistical Analysis

Continuous variables were summarized and displayed as the mean ± SD. Categorical data were expressed as frequencies and percentages. Chi-square test, associated with Fisher's correction in the case of small samples, was used to evaluate differences for categorical variables. Student's t-test was adopted to compare the mean of continuous variables. Relapse free survival considered time interval from diagnosis to the first relapse or the date of the last follow-up. The probability of relapse was calculated with Kaplan-Meier method, and the log-rank test was used for their comparison. Cumulative Incidence (CI) was calculated from diagnosis to the date the occurrence of the outcome event, or date of last follow-up. The CI curves were outlined according to the method of Kalbfleisch and Prentice and compared with Gray's test. A p-value of 0,05 or less was considered statistically significant. STATA 7.0 (StataCorp. Stata Statistical Software: Release 7.0. College Station; 2000) and the NCSS 2020 package (NCSS, LLC. NCSS 2020 Statistical Software [Internet]. Kaysville; 2020) were used to perform all statistical analyses.

Ethical Considerations

This study was approved by the Independent Ethics Committee of "Area Vasta Emilia Centro" on April 23rd, 2020 (354-2020-OSS-AUSLBO). Signed parental and patient informed consent and signed youth assent, when appropriate, were required from all patients enrolled.

Results

Patients characteristics at diagnosis

A total of 81 subjects were enrolled, including 29 children with VEO-IBD and 52 with ped-IBD. The median age at diagnosis was 4,1 years in the VEO-IBD group (interquartile range [IQR] 2,8-5,5) and 12,3 years in the ped-IBD group (IQR 10,0-13,8). Median follow up time was 4,9 years (range 1,5-17). No significant differences between the two groups were observed regarding demographic, clinical and laboratory characteristics at diagnosis, as shown in Table 1. In our patients, extraintestinal manifestations (EIMs), including those present at diagnosis and those emerged during follow up, were: erythema nodosum (n=1), pyoderma gangrenosum (n=1), pyostomatitis vegetans (n=1), peripheral arthritis (n=6), spondyloartritis (n=2), sclerosing cholangitis (n=3), episcleritis (n=1). A diagnostic delay occurred in 17 patients (21%), with no significant differences between the two groups (p 0.83).

	VEO-IBD	**ped-IBD**	**Total (IBDs)**	**p**
	n= 29	n= 52	n= 81	
Males, N (%)	12 (41)	28 (54)	40 (49)	0.28
Age at diagnosis (years), median (IQR)	4.3 (2.8, 5.5)	12,3 (10, 13.8)	9,1 (5.1, 13)	
Follow up (years), median (IQR)	5.5 (2.5-8)	4.8 (2.7-7.6)	4.9 (2.7-8)	0.46
Family history of IBD, N (%)	6 (20.7)	8 (15.4)	14 (17.3)	0.55
Diagnostic delay, N (%)	5 (17.2)	8 (15.4)	13 (16)	0.83
Clinical manifestations at IBD onset				
Diarrhea, N (%)	27 (93.1)	47 (90.4)	74 (91.4)	0.67
Bloody stool, N (%)	25 (86.2)	44(84.6)	69 (85.2)	0.84
Abdominal pain, N (%)	9 (31.0)	34 (65.4)	43 (53.1)	**0.003**
Vomit, N (%)	3 (10.3)	1 (1.9)	4 (4.9)	0.09
Fever, N (%)	6 (20.7)	7 (13.5)	13 (16)	0.39

Growth failure or stunting, N (%)	7 (24.1)	18 (34.6)	25 (30.9)	0.33
ASCA, N (%)	8 (27.6)	8 (15.4)	16 (19.8)	0.18
pANCA N (%)	10 (34.5)	12 (23.1)	22 (27.2)	0.27
EIMs	6 (20.6)	9 (17.3)	15 (18.5)	0.08

Table 1: Baseline characteristics of patients. VEO-IBD: Very early onset-inflammatory bowel diseases; ped-IBD: later-onset pediatric IBD; IQR: Interquartile range; SD: Standard deviation; IBD-U: IBD-unclassified; EIMs: extraintestinal manifestations;

ASCA positivity were found in 16 patients (19.5%) and p-ANCAs positivity in 22 (27.2%), with no differences between the two cohorts. UC resulted to be the most represented diagnosis in both groups, 24/29 (83%) of VEO-IBD (ratio UC/CD 4,8) and 42/52 (81%) of ped-IBD (ratio UC/CD 3,8), with a major prevalence of pancolitis (47/66, 71,2%). A diagnosis of CD was made in 15 patients, 5 (17%) with VEO-CD and 10 (19%) with ped-CD, 11 (73.3%) of them with an ileo-colonic location (L3 according to Paris Classification). No patient was affected by penetrating, structuring, or perianal disease. Specific data about CD and UC groups are shown in Supplementary material (Supplementary Tables 1 and 2).

Primary outcomes

Primary outcomes are described in (Figure 1) (Supplementary Table 3)

Major surgery

Considering the overall study population, 13/81 (19,8%) patients underwent major surgery. At the end of follow up, the surgical rate was significantly higher for VEO-IBD group compared to ped-IBD group (33.6% *vs* 11.6% respectively, p 0.04). Considering UC subgroups, VEO-UC group has a surgical rate significantly higher than the ped-UC group (p 0.018). On a multivariate analysis, age at diagnosis >6 years was protective against surgery for IBD with an odd ratio of 0,015±0,028 (p 0,03). UC surgery was performed for severe refractory disease. Details are shown in (Supplementary Table 4)

Biologic therapy

The CI of biologic therapy was 45,6% VEO-IBD vs 43,5% ped-IBD (p 0.72). No difference in biologic therapy use was detected also considering the subgroups analysis: 60% VEO-CD vs 77.8% ped-CD (p 0.82); 37.5% VEO-UC vs 32.6% ped-UC (p 0.64). Specifically, biologic therapy was adopted at diagnosis in 15% of patients with VEO-IBD and in the 85% of cases as an approach to severe relapse. Among ped-IBD subjects, 40% needed biologic therapy at diagnosis while 60% because of no response to 1st and 2nd line therapy.

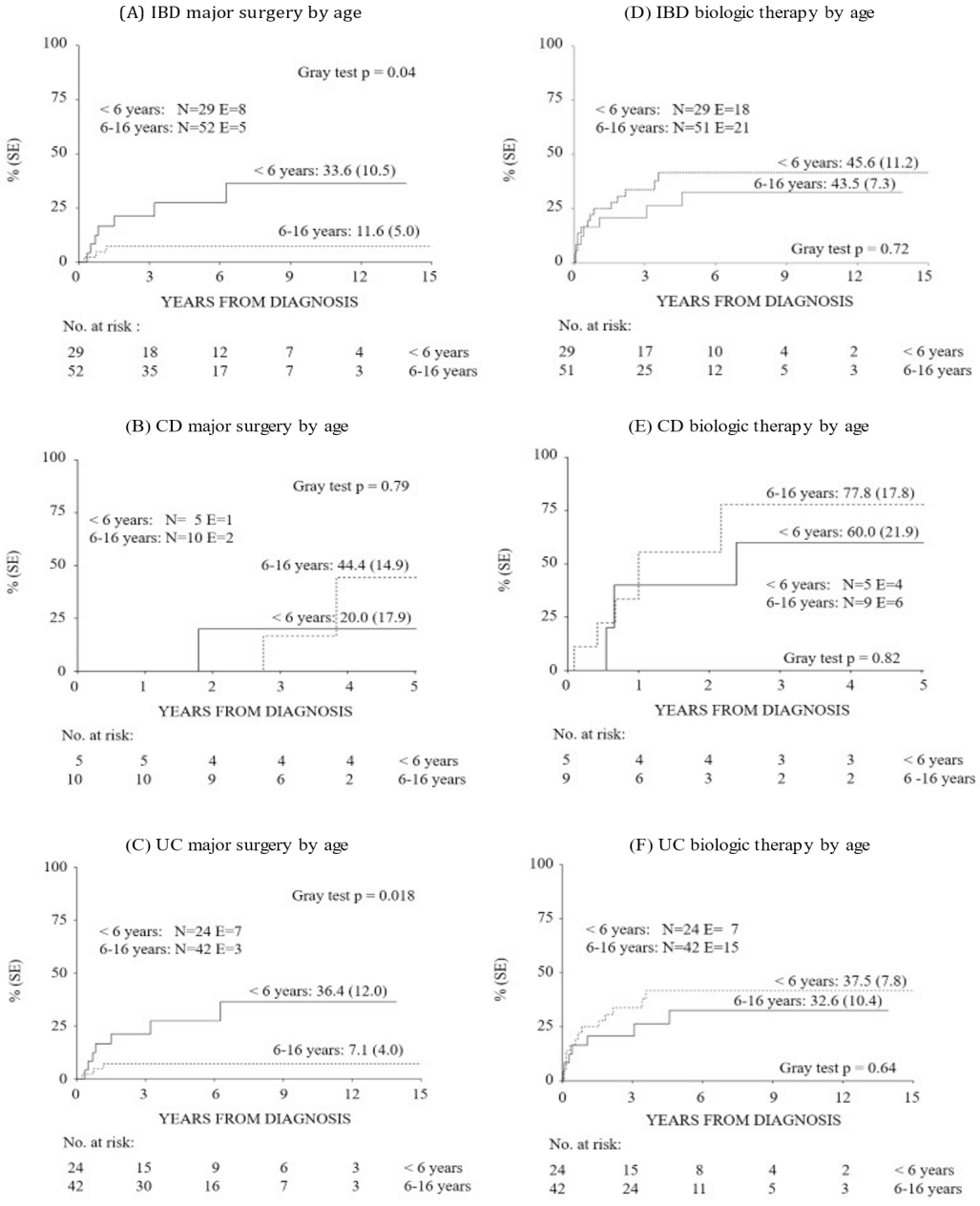

Figure 1: Cumulative incidence of major surgery in VEO vs EO-IBD (1A), CD (1B) and UC (1C). Cumulative incidence of biologic therapy in VEO vs EO-IBD (1D), CD (1E) and UC (1F).

Secondary outcomes

Secondary outcomes are described in Figure 2 (Supplementary Table 3).

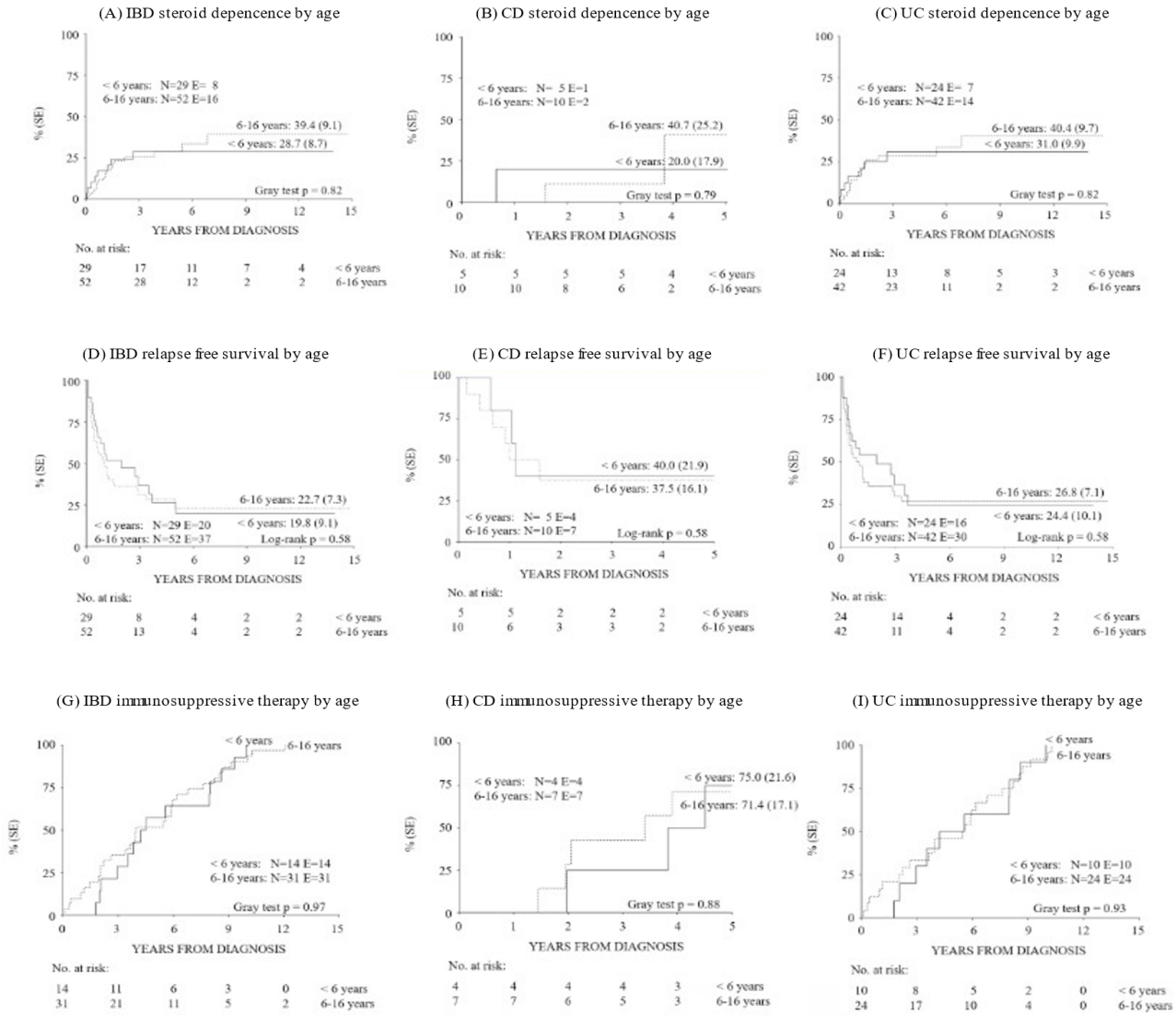

Figure 2: Cumulative incidence of steroid dependance in VEO vs EO IBD (2A), CD (2B) and UC (2C). Relapse-free survival in VEO vs EO IBD (2D), CD (2E) and UC (2F). Cumulative incidence of immunosuppressive therapy in VEO vs EO IBD (2G), CD (2H) and UC (2I).

Clinical Remission

At last follow up, according to PUCAI or PCDAI, 98,3% of patients showed clinical remission, with similar rates in both groups: 100% of patients with VEO-IBD vs 96.6% of those with ped-IBD (p 0.61). No patient was experiencing a severe disease activity at the last follow up visit.

Steroid-dependent disease

The 28.7% of VEO-IBD and 39.4% of ped-IBD showed a steroid-dependent disease at the end of follow up. The difference did not result statistically significant (p 0,82), even in the subgroup analysis (VEO-CD 20% *vs* ped-CD 40.7%, p 0.79; VEO-UC 31% *vs* ped-UC 40.4%, p 0.82).

Relapse free-survival and relapse-rate

Relapse-free survival (e.g. survival without experiencing of any relapse) at the end of follow up was achieved with similar rates in the two groups (19.8% in VEO-IBD *vs* 22.7% in ped-IBD; p 0.58)**.** The same result was obtained considering separately patients with VEO-UC and ped-UC (24,4% *vs* 26,8% respectively; p 0.58) and those with VEO-CD and ped-CD (40% *vs* 37.5% respectively; p 0.58). At the end of follow up, the CI of severe relapses was 64.3%, with similar rates in both groups: 43.9% VEO-IBD *vs* 73.7% ped-IBD (p 0.37)**.** Considering CD and UC subgroups separately, CI of severe relapses was 33.6% VEO-CD *vs* 100% ped-CD (p 0.40) and 43,3% VEO-UC *vs* 62.3% ped-UC (p 0.65).

Immune suppressive treatments

No significant differences in the rate of treatment with thiopurines (58,6% in VEO-IBD and 50% in ped-IBD; p 0.45) and methotrexate (13.8% in VEO-IBD and 5.8% in ped-IBD; p 0.22) during follow up were detected.

Crohn's disease behavior

All the patients affected by CD had non stricturing-non penetrating phenotype at diagnosis. At the end of follow-up, we detected a change in CD's behavior in 4/15 (26.7%) patients: 3 patients of VEO-IBD group developed terminal ileum strictures, which requires ileocecectomy in two, and 1 patient with ped-IBD developed a penetrating disease, which resolved with pharmacological therapy alone. During follow up no patients with CD developed complex perianal disease.

Growth

At diagnosis, the mean BMI Z-score was similar in both group: -0,2 ± 0,3 for patients with VEO-IBD *vs* -0,2 ± 0,2 for those with ped-IBD (p 0.44). This finding was confirmed at last follow up visit, with a mean BMI Z-score of 0,1 ± 0,3 for patients with VEO-IBD *vs* -0,2 ± 0,2 for those with ped-IBD (p 0.5).

Discussion

Pediatric IBD attracted scientific interest in recent years. Several studies compared VEO-IBD and later onset pediatric IBD with various results in term of severity disease' indices; previous findings prompted to consider IBD diagnosed before the age of 6 years to be associated with a more aggressive course [3,9]. However, a limit of prior works is the lack of homogeneity between the cohorts evaluated, resulting in a high risk of confounding variables affecting the outcome beside the key role of age.

The aim of our study was to verify the effective role of age as a predictive factor of disease severity course. We indeed compared two cohorts, VEO-IBDs and ped-IBDs, homogenous in extent, location, behaviour and clinical severity at diagnosis. Disease progression was evaluated for a proper follow-up time (4 years and 11 months, median).

Our main result was a significant higher risk of major surgery in acute VEO-UCs in comparison with ped-UCs. Previous works are not concordant about the occurrence of surgery in VEO-IBD. In particular, Kelsen et al performed a retrospective single-center study of 971 subjects, collecting datas from 2008 to 2016, comparing 229 VEO-IBD patients with 742 older-onset IBD (6-17y) and stating that the former have a more severe disease course with increased surgical interventions and poor growth [23]. On the other hand a retrospective cohort study of 269 VEO-IBD patients diagnosed between 2008 and 2013 by Kerur et al, reported a cumulative risk of bowel surgery of 14-15% by 5 years [24], which is similar, according with literature, to the surgical risk of later onset pediatric IBD [19].

One explanation of these discrepant reports could be related to different regard to monogenic etiologies [33]. Interestingly, patients with these conditions were not excluded from the VEO-IBD group in the aforementioned study by Kelsen et al, questioning the role of underlying disease on disease severity. We excluded monogenic diseases from our analysis in order to reduce the variability of patients, but larger studies specifically exploring this topic are certainly needed.

Considering the other primary outcome (CI of biologic therapy), VEO-IBDs did not require a therapy escalation to biologics with higher rate than ped-IBDs, also when UC and CD groups were considered separately. This finding is consistent with that showed by Kelsen et al who reported similar exposure to biologics in both VEO-IBD (58,1%) and ped-IBD (69,5%) [23].

Moving to the secondary outcomes, VEO-UC and VEO-CD showed a comparable cumulative incidence of relapse free survival, steroid-dependence, use of immunosuppressive therapy and clinical remission at the end of follow up when compared with ped-UC and ped-CD, respectively. Previous studies reported

a general worse outcome in VEO-IBDs compared to later onset diseases, particularly regarding to medical therapy refractory. Even though, results of different works are conflicting and therapeutic interventions have resulted efficacious in these younger patients, including immunomodulators and biologics [33]. Interestingly, in our cohort, the percentage of patients who needed biological therapy at diagnosis was higher in ped-IBD (40%) compared to VEO-IBD (15%) further questioning the possible worse clinical onset of IBD in younger children.

However, it is conceivable that increased attention to reducing corticosteroid use, because of their inhibitory effect on linear growth and bone density and their plethora of side effects that can be physically and emotionally disruptive in adolescence, could be an indication for biologic therapy and may lead to greater utilization of anti-TNF therapies in this cohort [34-35].

The results did not confirm the major severity of VEO-IBDs in the other outcomes, even when the VEO-UCs with severe phenotype at diagnosis has been censured by the curves, because no longer properly evaluable after curative surgery.

Lastly we found an overall predominance of UC over CD (ratio 4,4), with 83% UC in the VEO-IBD and 81% in the ped-IBD. This predominance is slightly higher when compared to the national Italian recent data. In fact UC was the most prevalent IBD in all age-related groups, especially in children aged < 6 years (62.2% UC *vs.* 18.6% CD, UC/CD ratio 3.3) [5].

Our study has several limitations. Firstly, the small number of patients, particularly with CD, enrolled in our cohort. Secondary the large extent of enrolment time of our study necessarily determined a variability in IBD management during these years. On the contrary, the monocentric design of the study supports a uniform approach in these patients.

Our data question the evidence of a worse outcome of VEO-UCs, in comparison with later onset diseases. Notably, we only demonstrate that the need of surgery has been significantly higher in VEO-UC compared to ped-UC, without other significant findings. Larger studies are necessary to straighten the effective role of age as negative prognostic factor in paediatric IBD.

Conflict of Interest

No funding was received for this work. Authors have no financial disclosures and conflicts of interest to declare for this study.

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	VEO-CD	**ped-CD**	**Total (CD)**	**p**
Crohn's disease, N (%)	5	10		
Crohn's disease location, N (%)				
L1 (distal 1/3 ileum ± limited cecal disease)	1 (20)	3 (30)	4 (26.7)	0,89
L3 (ileocolonic)	4 (80)	7 (70)	11 (73.3)	
Crohn's disease behavior, N (%)				
B1 (nonstricturing – nonpenetrating)	5 (100)	10 (100)	15 (100)	0.82
PCDAI, N (%)				
11-30 (mild disease activity)	3 (60)	8 (80)	11 (73.3)	0.41
>30 (moderate-severe disease activity)	2 (40)	2 (20)	4 (26.7)	
Crohn's disease endoscopic activity (*SES*), mean ± SD (median)	1.4 ± 0.5 (1)	1.8 ± 1 (2)	1.7 ± 0.9 (2)	0,4
Mild, N (%)	3 (60)	4 (40)	7 (46.7)	
Moderate, N (%)	2 (40)	3 (30)	5 (33.3)	
Severe, N (%)	0	3 (30)	3 (20)	

Supplementary Table 1: Baseline characteristics of patients with CD; VEO: Very early onset; SD: Standard deviation; PCDAI: Pediatric Crohn's Disease Activity Index; SES: Simple Endoscopic Score.

	VEO-UC	**ped-UC**	**Total (UC)**	**p**
Ulcerative colitis, N (%)	24	42		
Ulcerative colitis extent, N (%)	VEO-UC	ped-UC	Total UC	
E1 (proctitis)	5 (20.8)	9 (21.4)	14 (21.2	0.75
E2 (left-sided)	1 (4.2)	5 (11.9)	6 (9.0)	
E4 (pancolitis)	14 (58.3)	33 (78.5)	47 (71.2)	
PUCAI, N (%)				
10-34 (mild disease activity)	11 (45.8)	21 (50)	32 (49.5)	0.55
35-64 (moderate disease activity)	9 (37.5)	22 (52.3)	31 (346.9)	
≥65 (severe disease activity)	0 (0)	3 (7.1)	3 (4.5)	
Ulcerative colitis endoscopic activity (*Mayo score*) mean ± SD (median)	1.5 ± 0.7 (1)	1.7 ± 0.7 (2)	1.7 ± 0.7 (2)	0.52
Mild, N (%)	13 (54.2)	17 (40.5)	30 (45.5)	
Moderate, N (%)	9 (37.5)	19 (45.2)	28 (42.4)	
Severe, N (%)	2 (8.3)	6 (14.3)	8 (12.1)	

Supplementary Table 2: Baseline characteristics of patients with UC; VEO: Very early onset; SD: Standard deviation; PUCAI: Pediatric Ulcerative Colitis Activity Index; CI: cumulative incidence.

	VEO-IBD n= 29		**ped-IBD** n= 52		**Total (IBD)** n= 81	**p**	
	CD n=5	**UC** n=24	**CD** n=10	**UC** n=42		**Tot (IBD)**	
						CD	**UC**
Relapse free survival, CI %	19.8		22,7		21.5	0.58	
	40	24,4	37.5	26,8		0.58	0.58
Severe relapse, CI %	43.9		73.7		64.3	0.37	
	33.6	43.3	100	62.3		0.40	0.65
Clinical remission at the end of follow up, CI %	100		96.6		98.3	0.61	
Steroid-dependent disease, CI %	28,7		39,4		34,7	0,82	
	20	31	40,7	40,4		0,79	0,82
Thiopurines, N (%)	17 (58.6)		26 (50)		43 (53.1)	0.45	
Methotrexate, N (%)	4 (13.8)		3 (5.8)		7 (8.6)	0.22	
Biologics, CI %	45,6		43,5		33 (40.7)	0.72	
	60	37,5	77,8	32,6		0,82	0,64
Surgery, CI %	33.6		11.6		19.8	**0.04**	
	20	36.4	44.4	7.1		0.79	**0.018**
Change in Crohn's disease behavior, N (%)	5		10		15		
B2 (structuring)	2 (40)		1 (10)		3 (20)	0.07	
B3 (penetrating)	1 (20)		0		1 (6.6)		
Growth, (Z score) at diagnosis	-0,2 ± 0,3		-0,2 ± 0,2			0.44	
at the end of follow-up	0,1 ± 0,3		-0,2 ± 0,2			0.52	

Supplementary Table 3: Outcomes of VEO-IBD *vs* ped-IBD; VEO: Very early onset; UC: ulcerative colitis; CD: Crohn Disease; CI: cumulative incidence.

	VEO-IBD n= 29		**ped-IBD** n= 52		**LL IBD** n= 81		**p value**	
	CD n=5	**UC** n=24	**CD** n=10	**UC** n=42			**CD**	**UC**
Surgery, CI % (N)	33.6 (8)		11.6 (5)		19.8 (13)		**0.04**	
	20 (1)	36.4 (7)	44.4 (2)	7.1 (3)			0.79	**0.018**
Total colectomy, N	0	7	2	3	12			
Ileocecectomies, N	1	0	0	0	1			

Supplementary Table 4: cumulative incidence of surgery and major surgery procedures.