Infantile and very early onset-inflammatory bowel disease: a multicenter study

Infantile and Very Early Onset Inflammatory Bowel Disease: A Multicenter Study

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on behalf of the Porto IBD working group of ESPGHAN

abstract

OBJECTIVES: This study described disease characteristics and long-term outcomes in patients diagnosed with very early onset inflammatory bowel disease (VEOIBD) (diagnosed before 6 years of age) and infantile-IBD (before 2 years).

METHODS: Cases from 21 centers worldwide diagnosed with VEOIBD (2008–2018), with minimum 2 years of follow-up, were retrospectively reviewed.

RESULTS: The cohort included 243 patients (52% males, median follow-up of 5.8 [range 2−18] years, including 69 [28%]) with infantile-IBD. IBD subtypes included Crohn's disease (CD), ulcerative colitis (UC), or IBD-unclassified (IBDU) in 30%, 59%, and 11%, respectively. Among patients with CD, 94% had colonic involvement, and among patients with UC/IBDU, 75% had pancolitis. Patients with infantile-IBD presented with higher rates of IBDU, lower hemoglobin and albumin levels, and higher C-reactive protein, and had lower response rates to first-induction therapy and corticosteroids therapy ($P < .05$ for all). Colectomy and diversion surgeries were performed in 11% and 4%, respectively, with no significant differences between age groups. Corticosteroid-free remission rates were 74% and 78% after 3 and 5 years, respectively, and 86% at end of follow-up. Genetic testing was performed in 96 (40%) patients. Among tested population, 15 (16%) were identified with monogenic disease. This group demonstrated lower response rates to induction therapies, higher rates of surgical intervention, and higher rates of major infections ($P < .05$ for all).

CONCLUSIONS: Patients with VEOIBD, including infantile-IBD, exhibit low rate of complications and surgical interventions at the long term. Patients with monogenic IBD are at risk for more severe disease course.

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WHAT'S KNOWN ON THIS SUBJECT: There are limited data regarding differences in characteristics and long-term course of very early onset and infantile inflammatory bowel disease (IBD).

WHAT THIS STUDY ADDS: Although patients with infantile IBD demonstrate more severe clinical features at presentation and a lower response to induction therapy, the overall long-term outcome in very early onset (including infantile) IBD is fair, with low rates of complications.

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Inflammatory bowel disease (IBD) develops during childhood in about 10% to 20% of total IBD cases, with increasing incidence worldwide.[1–3] A unique presentation of IBD occurs when intestinal inflammation manifests before the age of 6 years, defined as very early-onset IBD (VEOIBD). A diagnosis before 2 years of age is termed infantile IBD, which is characterized by a higher prevalence of monogenic etiology,[4] often requiring advanced therapies or even hematopoietic stem cell transplantation.[5]

The long-term outcome of patients with VEOIBD is unclear. There are some reports of similar,[6,7] or even favorable,[8] outcomes of children with VEOIBD compared with older children with IBD.

However, outcomes such as more extensive disease, increased requirement of immunomodulators and corticosteroid over time,[9] poor growth, and higher rates of surgical interventions in patients with VEOIBD[10] are also reported. Studies comparing infantile IBD to noninfantile VEOIBD are scarce but have reported similar outcomes in the different age groups.[11] The advance in genetic testing allows for increased recognition of monogenic etiologies among patients with VEOIBD.[12–14] Patients with monogenic diseases represent a unique subgroup of VEOIBD, regardless of age at diagnosis, and are reported with poorer outcomes including increased mortality rates.[15] Nevertheless, most patients with infantile and VEOIBD do not have an identifiable monogenic disorder, even after thorough genetic evaluation.[5,16,17]

In this large, multicenter study, we aimed to describe the clinical characteristics of infantile IBD and noninfantile VEOIBD, and compare the response to therapies and other outcomes between these 2 subpopulations.

METHODS

Study Design

We conducted a multicenter, retrospective, longitudinal study in 21 pediatric centers worldwide through members of the Porto Group and IBD Special Interest Group of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). Participating centers included 15 European centers, 4 centers from Israel, 1 center from Canada, and 1 center from the United Arab Emirates.

Data were collected using the Research Electronic Data Capture software platform, and included clinical and laboratory parameters at diagnosis and during follow-up, anthropometric measures, genetic evaluation, medication history, response to treatment, hospitalizations, and surgical interventions.

Disease activity, including remission rates, were assessed at the following time points: At diagnosis, after 1 year of follow-up, after 3 years of follow-up, after 5 years of follow-up, and at the end of follow-up for each patient. The outcomes of corticosteroid-free remission, relapse after remission, and surgical interventions were dated and analyzed continuously using Kaplan-Meier survival analysis.

Population

Inclusion criteria were: (1) patients diagnosed with IBD before the age of 6 years, (2) a minimal follow-up of 2 years from diagnosis, and (3) diagnosis from the year 2008 (when all participating centers had computerized medical records) to 2018. Exclusion criteria were the diagnosis of other noninflammatory enteropathies including: Tufting enteropathy, microvillus inclusion disease, pediatric intestinal pseudoobstruction, and short bowel syndrome.

The institutional ethical review board of each center approved the study protocol.

Parameters' Definition

Infantile IBD was defined as diagnosis of IBD before the age of 2 years, and noninfantile VEOIBD as diagnosis between the age of 2 and 6 years.[2,18] Disease classification and subtype, location, extent, and perianal involvement were all defined on the basis of the Paris classification[2] and the ESPGHAN revised Porto criteria.[19] Disease activity, remission, and response to therapeutic regimens were determined according to the Pediatric Crohn's Disease (CD) Activity Index (PCDAI)[20,21] or the Pediatric Ulcerative Colitis (UC) Activity Index (PUCAI).[22] In UC, partial response was defined as a PUCAI decrease of at least 20 points, and remission as PUCAI <10 points.[23] In CD, partial response was defined as a PCDAI decrease of at least 12.5 points, and remission as PCDAI <10 points.[21] Relapse was defined as a loss of response after achieving remission, with a rise of PUCAI or PCDAI to at least 10 points. Induction treatment was defined as medication used in the attempt to induce remission at disease presentation or at relapses. Chronic treatment beyond a course of remission induction (and over 3 months of treatment in the case of corticosteroids) was defined as maintenance therapy. The duration of induction therapy is defined by each induction agent on the basis of pediatric IBD guidelines.[23–25] The definition of extraintestinal manifestations was based on accepted criteria.[26] Underweight, stunting, and wasting were defined as z score <-2 for weight for age, height for age, and BMI for age, respectively.[27] Major infections during follow-up were defined as serious bacterial infections or atypical/opportunistic infections. C-reactive protein was expressed as mg per dL, and erythrocyte sedimentation rate as mm per hour.

Statistical Analysis

Categorical variables were described as frequencies and percentages. Continuous variables were evaluated for normal distribution using histogram, and reported as

median and interquartile range (IQR) since abnormally distributed. χ^2 and Fisher's exact tests, when appropriate, were applied to compare categorical variables, whereas Kruskal-Wallis and Mann-Whitney tests were used for continuous variables. Kaplan-Meier estimates were used to describe events during follow-up. Cox regression and log-rank test were used for univariate analysis. Multivariable Cox regression models were applied to assess the independent association between individual covariates and clinical events during follow-up. Negative binomial regression was used to study the association between number of events during follow-up period, and categorical and continuous variables. Natural logarithm of the follow-up duration was used as the regression offset.

All statistical tests were 2-tailed, and $P < .05$ was considered statistically significant. The software SPSS version 28.0 (IBM corp., Armonk, New York, United States, 2021) was used for all statistical analyses.

RESULTS

Study Population and Characteristics at Diagnosis

The cohort included 243 patients (52% males), followed over a median period of 5.8 (IQR 3.2–8.4) years. Median age at diagnosis was 3.3 (IQR 1.8–4.5) years, with 69 (28%) diagnosed before the age of 2 years. Patients' disease was classified as CD, UC, and IBD-unclassified (IBDU) in 72 (30%), 144 (59%), and 27 (11%) of the cohort, respectively. Patients' characteristics are detailed in Table 1. Colonic involvement was predominant at presentation in all disease subtypes: Among patients with UC or IBDU, 124 (73%) presented with pancolitis; among patients with CD, 41 (62%) presented with isolated colonic disease and 21 (32%) with ileo-colonic disease. Perianal involvement was reported in 13 (18%) of patients with CD, and stricturing or penetrating disease was observed in 9 (12.5%). Extraintestinal manifestations included oral aphthae in 34 patients (14%), arthritis in 14 (5.8%), sclerosing cholangitis in 12 (4.9%), erythema nodosum in 7 (2.9%), pyoderma gangrenosum in 1 patient (0.4%), and uveitis in 1 patient (0.4%). Other autoimmune diseases included: Celiac disease in 8 patients, thyroiditis in 2 patients, autoimmune hepatitis in 1 patient, and vitiligo in 1 patient.

Genetic testing was performed in 40 of 69 (58%) patients with infantile IBD, and 56 of 174 (32%) patients with noninfantile VEOIBD ($P = .001$). The genetic tests that were used included targeted gene panels in 28 (29%) patients, whole-exome sequencing in 60 (63%), and whole-genome sequencing in 8 (8%). A monogenic diagnosis was confirmed in 15 (16%) of tested cases in the total cohort, without statistically significant differences between patients with infantile IBD (9 [23%]) compared with noninfantile VEOIBD (6 [11%]), $P = .11$; however, a trend toward higher rates among patients with infantile IBD was noted. The most common monogenic diagnoses were interleukin 10 receptor mutations identified in 5 patients, followed by chronic granulomatous disease in 3 patients, and all other diagnoses were different mutations identified in single patients. The monogenic diagnoses and disease characteristics of these patients are detailed in Supplemental Table 2.

Therapies and Response to Treatment

The first induction therapeutic agents were: Corticosteroids, 5-aminosalicylic acid (5-ASA), exclusive enteral nutrition (EEN), and antitumor necrosis factor (TNF)-α monoclonal antibody therapy in 53.1%, 29.6%, 10.7%, and 2.1% of the patients, respectively. The other 4.5% were treated with different agents, mainly antibiotics. Corticosteroids were more commonly used as first induction in patients with infantile versus noninfantile VEOIBD (64% vs 49% respectively, $P = .003$). Patients with a diagnosis of CD were treated more often with EEN than patients with UC/IBDU (27.8% vs 3.5%, $P < .001$), whereas 5-ASA was used more often in patients with UC/IBDU (15.3% in CD vs 35.7% in UC/IBDU, $P = .001$).

Overall, clinical response to first induction was reported in 84.5% of the cohort as the following: 54.3% achieved clinical remission, 30.2% achieved partial response, and 15.5% were nonresponsive to first-induction therapy. Lack of response to first-induction therapy was significantly associated with infantile IBD presentation ($P < .001$), low albumin level at diagnosis ($P = .019$), impaired height (height z score <-1)[27] at diagnosis ($P = .027$), and a diagnosis of monogenic disease ($P = .05$). In multivariate regression analysis, monogenic diagnosis ($P = .044$) and low albumin ($P = .031$) remained as independent risk factors for lack of response. There were no significant associations between response rate to induction agent that was used as first therapy and sex, weight for age z score at diagnosis, duration of symptoms, inflammatory markers at diagnosis, disease classification (CD/UC/IBDU), disease location, or extent.

Repeated induction courses were common: 175 (72%) patients required a second induction (32% of them received the same medication as previously), and 122 (50.2%) patients required a third induction (47.5% of them treated with the same medication as previously). A fourth and a fifth induction course were reported in 70 (28.8%) and 43 (17.7%) patients, respectively.

Overall, the most common agents that were used for any induction treatment during follow-up were corticosteroids in 74% of patients, anti-TNF in 40%, 5-ASA in 32% (46% among patients with UC/IBDU), and EEN in 13% (44% of patients with CD). Hematopoietic stem cell transplantation (HSCT) was performed in 7 cases, among them 4 patients had monogenic diseases (3 cases with chronic granulomatous disease and 1 with interleukin 10 receptor subunit beta mutation). Three patients received

TABLE 1 Comparison of General and Disease Characteristics of Patients With Infantile Versus Noninfantile VEOIBD				
	All Cohort	**Infantile IBD**	**Noninfantile VEOIBD**	***P***
No. of patients	243	69	174	N/A
Sex, females	47.7%	46.4%	48.3%	.79
Ethnicity, white	85.4%	88.4%	84.2%	.8
Family history of IBD	26.5%	32.8%	24.0%	.16
Breastfeeding	73.4%	76.4%	72.0%	.35
Disease classification				
CD	29.6%	24.6%	31.6%	.047
UC	59.3%	56.5%	60.3%	
IBDU	11.1%	18.8%	8.0%	
Perianal disease (in patients with CD)	18.8%	31.3%	15.1%	.16
Presenting symptoms				
Weight loss or FTT	28.1%	43.8%	21.9%	.001
Vomiting	9.6%	15.9%	7.1%	.047
Diarrhea	86.6%	95.6%	82.9%	.01
Bloody stools	87.8%	94.1%	85.2%	.06
Fever	13.8%	20.6%	11.2%	.07
Extraintestinal manifestations	24.7%	23.2%	25.8%	.371
Genetic testing	39.5%	58.0%	32.2%	.001
Positive findings among tested	15.6%	22.5%	10.7%	.117
Weight for age z score at diagnosis, median [IQR]	−0.34 [−1.35 to 0.4]	−1.09 [−2.12 to −0.3]	−0.1 [−0.95 to 0.59]	<.001
Height for age z score at diagnosis, median [IQR]	−0.04 [−0.78 to 0.69]	−0.43 [−1.16 to 0.49]	0.08 [−0.69 to 0.77]	.05
Duration of symptoms (mo), median [IQR]	4 [2–8]	4 [2–8]	4 [2–8]	.718
Disease activity at diagnosis				
Mild	44.3%	34.4%	47%	.28
Moderate	40.9%	43.8%	40.2%	
Severe	14.8%	21.9%	12.8%	
Laboratory parameter at diagnosis, median [IQR]				
Hemoglobin (g per dL)	10.6 [9.2–11.5]	10 [8.6–11.2]	10.8 [9.6–11.7]	.02
Albumin (g per dL)	3.7 [3.4–4.1]	3.5 [3.1–3.9]	3.8 [3.4–4.2]	.003
ESR (mm per h)	30 [15.3–45]	35 [20.5–51.5]	28 [15–41]	.19
CRP (mg per dL)	0.7 [0.2–3.1]	1.4 [0.5–3.9]	0.6 [0.1–2.1]	.009
First induction agent				
Corticosteroids	53.1%	63.8%	48.9%	.003
5-ASA	29.6%	14.5%	35.6%	
EEN	10.7%	13.0%	9.8%	
Anti-TNF	2.1%	0.0%	2.9%	
Antibiotics	2.5%	5.8%	1.1%	
Response to first induction				
Remission	54.3%	35.30%	62.20%	<.001
Partial response	30.2%	36.80%	27.40%	
No response	15.5%	27.90%	10.40%	
Nonresponse to various agents (%)				
Nonresponse to corticosteroids	8.4%	17.5%	4.1%	.007
Nonresponse to 5-ASA	14.1%	28.6%	10.9%	.09
Nonresponse to EEN	15.6%	33.3%	8.7%	.19
Nonresponse to anti-TNF	19.4%	20.0%	19.1%	.14
Relapse rate (per person y)	0.36	0.41	0.35	.22
Hospitalization rate (per person y)	0.37	0.63	0.27	<.001
Major infection rate (per person y)	0.02	0.03	0.02	.28
Surgery (colectomy/diversion)	15.2%	14.5%	11.5%	.39

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FTT, failure to thrive. N/A, not applicable.

HSCT without a monogenic diagnosis: 1 patient with ileo-colonic CD diagnosed at 2.5 years of age that failed to achieve remission with EEN, corticosteroids, and anti-TNF; a second patient with pancolitis-IBDU diagnosis at 1.3 years of age that failed to achieve remission with EEN, corticosteroids, anti-TNF, ustekinumab, and diverting ileostomy; and a third patient with ileo-colonic CD diagnosed at 3 months of age that failed to achieve remission with repeated courses of corticosteroids and tacrolimus. All 7 patients achieved remission after HSCT and remained with sustained remission until the end of follow-up. Other rare therapies included thalidomide, tacrolimus, and immunoglobulin infusions in only a few cases. The overall remission/response/nonresponse rates to the common induction agents were: 66%/26%/8% with corticosteroids, 63%/23%/14% with 5-ASA, 53%/28%/19% with anti-TNF, and 40%/44%/16% with EEN, respectively.

The following factors were associated with lack of response to corticosteroids: Male sex ($P = .046$), diagnosis before 2 years of age ($P = .006$), and low albumin at presentation ($P = .013$). Response to corticosteroids was not associated with either disease severity at presentation ($P = .275$), disease location in CD ($P = .358$), or disease extent in UC/IBDU ($P = .423$).

5-ASA nonresponsiveness was associated with younger age ($P = .03$); however, in multivariate analysis, no single factor was found independently significant (including sex, infantile-onset, disease classification, disease location, and extent or disease severity at presentation). Response to either anti-TNF or EEN was not associated with any background characteristics.

The various medications that were used as maintenance therapy during follow-up included: Thiopurines in 144 (59.3%) patients, methotrexate in 35 (14.4%), 5-ASA in 181 (74.5%) (including 40 patients with CD), anti-TNF in 117 (48.1%), vedolizumab in 17 (7%), ustekinumab in 5 (2.1%), tacrolimus in 4 (1.6%), thalidomide in 13 (5.3%), and maintenance corticosteroids in 5 (2.1%) patients. Overall, 51.1% of the patients were treated with advanced therapy as maintenance (including biologics, tacrolimus, thalidomide, or corticosteroids), 26.7% received only immunomodulators (azathioprine or methotrexate), and 22.2% of patients were treated with nonimmunosuppressive agents (5-ASA, nutritional therapy, or antibiotics). There were no significant differences in the distribution of maintenance therapies between the 2 age groups.

Outcomes

Overall, the median time to first remission was 2.3 (IQR 1.6–6.1) months, with no significant differences between the age groups. The factors that were found to be associated with time to achieving first remission were perianal disease (longer time to remission), as well as the therapy used as first induction (shortest time to remission with corticosteroids and EEN), as demonstrated in Fig 1.

After achieving remission, 62.4% had at least 1 relapse during follow-up, with median (IQR) time to first relapse of 14.8 (3.8–48.8) months. The mean relapse rate was 0.36 relapses per person year. No significant associations were found between time to first relapse and any background variable, as demonstrated in Fig 2.

The mean hospitalization rate was 0.63 and 0.27 hospitalizations per year of follow-up in the infantile versus noninfantile VEOIBD groups, respectively ($P < .001$).

Colectomy and diversion surgery were performed in 27 (11.1%) and 10 (4.1%) cases, respectively, with no significant differences between age groups. Ileocecal resection was not performed in this cohort. Nonresponse to the first induction therapy, as well as having a monogenic diagnosis, were found to be associated with higher risk and shorter time to surgical intervention, as demonstrated in Fig 3.

Disease classification as either CD or UC/IBDU was not associated with any differences in outcomes, including time to corticosteroid-free remission ($P = .57$), time to relapse ($P = .83$), or time to surgical intervention ($P = .46$). Furthermore, the disease severity at diagnosis was not associated with later outcomes: Time to corticosteroid-free remission ($P = .35$), time to relapse ($P = .62$), or time to surgical intervention ($P = .1$). Also, disease location and extent (per Paris classification for CD and UC/IBDU) were not associated with: Time to corticosteroid-free remission ($P = .71$ and .84), time to relapse ($P = .063$ and .93), or time to surgical intervention ($P = .8$ and .96), respectively.

Corticosteroid-free remission was reported in 108 of 188 (57.4%), 91 of 123 (74%), and 68 of 87 (78.2%) patients after 1, 3, and 5 years of follow-up, respectively. At the end of follow-up, 85.8% (175 of 204) of patients were in corticosteroid-free clinical remission. Median weight for age z score and height for age z score at end of follow-up were −0.14 (IQR −0.75 to 0.7) and −0.18 (IQR −0.94 to 0.53), respectively, and no significant change was observed in the anthropometric indices during follow-up ($P = .15$ for weight for age and $P = .25$ for height for age change between diagnosis and end of follow-up). Major infections were reported in 31 (12.8%) patients, with mean infection rate of 0.02 episodes per person year. Major infection rates were significantly higher in patients with CD compared with UC/IBDU (0.04 vs 0.01 infections per person year, respectively, $P < .001$), as well as in patients with monogenic diagnosis compared with patients with negative genetic workup (0.08 vs 0.02 infections per person year, respectively, $P = .012$). The most common infections recorded were: Pneumonia (11 cases), sepsis (9 cases), *Clostridium difficile* infection (12 cases), and meningitis (3 cases). Thromboembolic events were reported in only 2 patients, both with infantile IBD (1 patient with

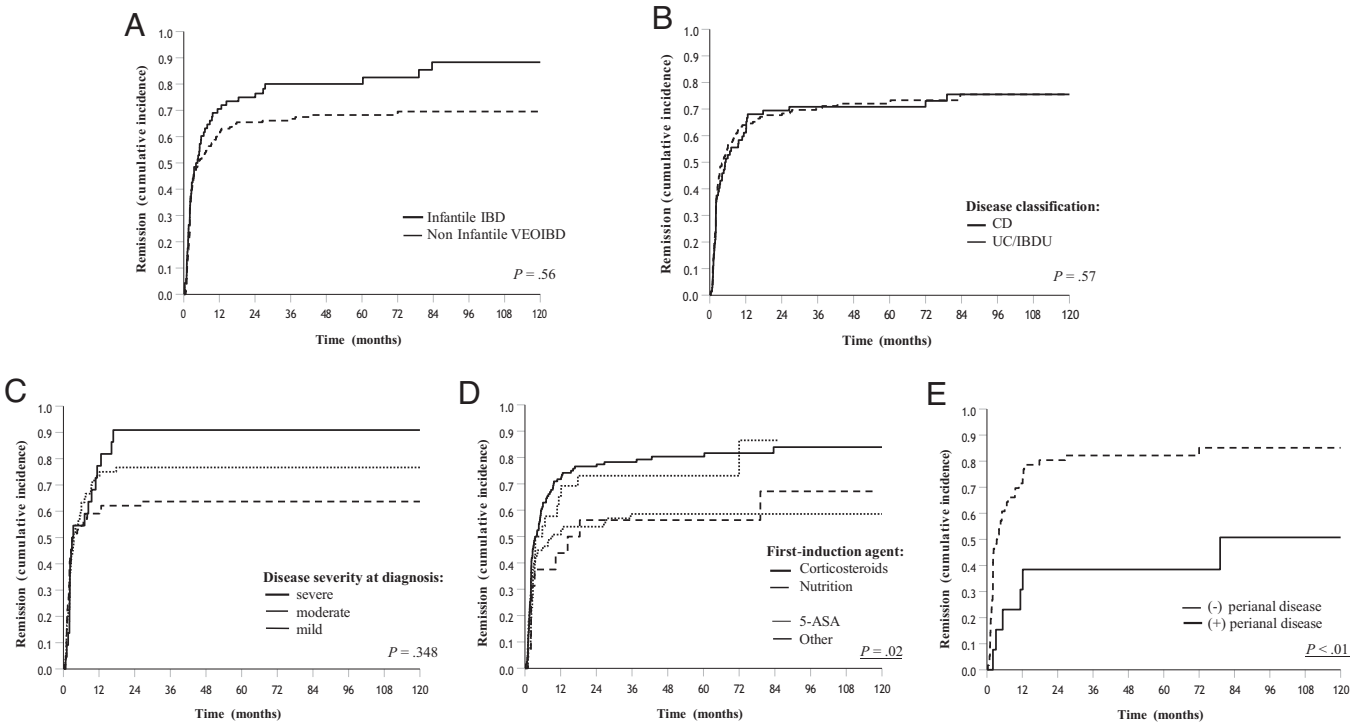

FIGURE 1

Kaplan-Meier survival curves of time to corticosteroid-free clinical remission, and the association with different variables. Time to corticosteroid-free clinical remission according to: A, infantile IBD versus noninfantile VEOIBD; B, disease classification; C, disease severity at diagnosis; D, first induction agent; E, present versus absent perianal disease.

interleukin 10 receptor subunit alpha mutation and colonic CD, and 1 patient with left-sided UC without monogenic diagnosis). The 2 events were superior vena cava syndrome, with both patients treated with parenteral nutrition at time of event, and did not receive thromboembolism prophylaxis. In both cases, the patients had active disease and were treated with infliximab before the event (1 patient achieved remission and continued infliximab as maintenance, and the other was switched to thalidomide because of partial response to infliximab).

No malignancies and no mortalities occurred in this cohort.

Infantile Versus Noninfantile VEOIBD

General and disease characteristics of patients with infantile versus noninfantile VEOIBD are detailed in Table 1. In comparison with patients diagnosed after 2 years of age, patients with infantile IBD presented with higher rates of IBDU, lower levels of hemoglobin and albumin, higher levels of C-reactive protein, and had lower weight for age at presentation. In addition, patients with infantile IBD had significantly lower rates of response to first-induction therapy and lower response to corticosteroids. However, there were no significant differences in overall clinical outcomes, including time to remission, rates of relapses during follow-up, and colectomy and ileostomy rates.

DISCUSSION

This international multicenter cohort is 1 of the largest contemporary cohorts of children diagnosed with VEOIBD, focusing in particular on infantile versus noninfantile presentation and exploring various disease and treatment-related outcomes. Overall, children with VEOIBD demonstrate fair long-term outcomes with low rates of complications as reflected from this analysis. Intriguingly, children diagnosed with infantile IBD share this favorable outcome despite more severe characteristics at presentation and lower response to first-induction therapy.

The risk of colectomy or diverting ileostomy was comparable to the study from North America by Kerur et al,[11] was similar between the 2 age groups, and was not associated with disease classification. In an earlier population-based study, Benchimol et al have demonstrated significantly lower rates of colectomy in patients with VEOIBD compared with children with later-onset IBD.[6] In addition, infantile IBD was not associated with higher rates of surgery, as reported in other studies.[11,28]

In our study, having a monogenic disease was associated with failure to respond to first-induction therapy, as well as a higher risk of surgical intervention, the latter being in contrast to the results reported by Kammermeier et al.[5] Other complications, including major infections and thromboembolic events, were uncommon in our cohort,

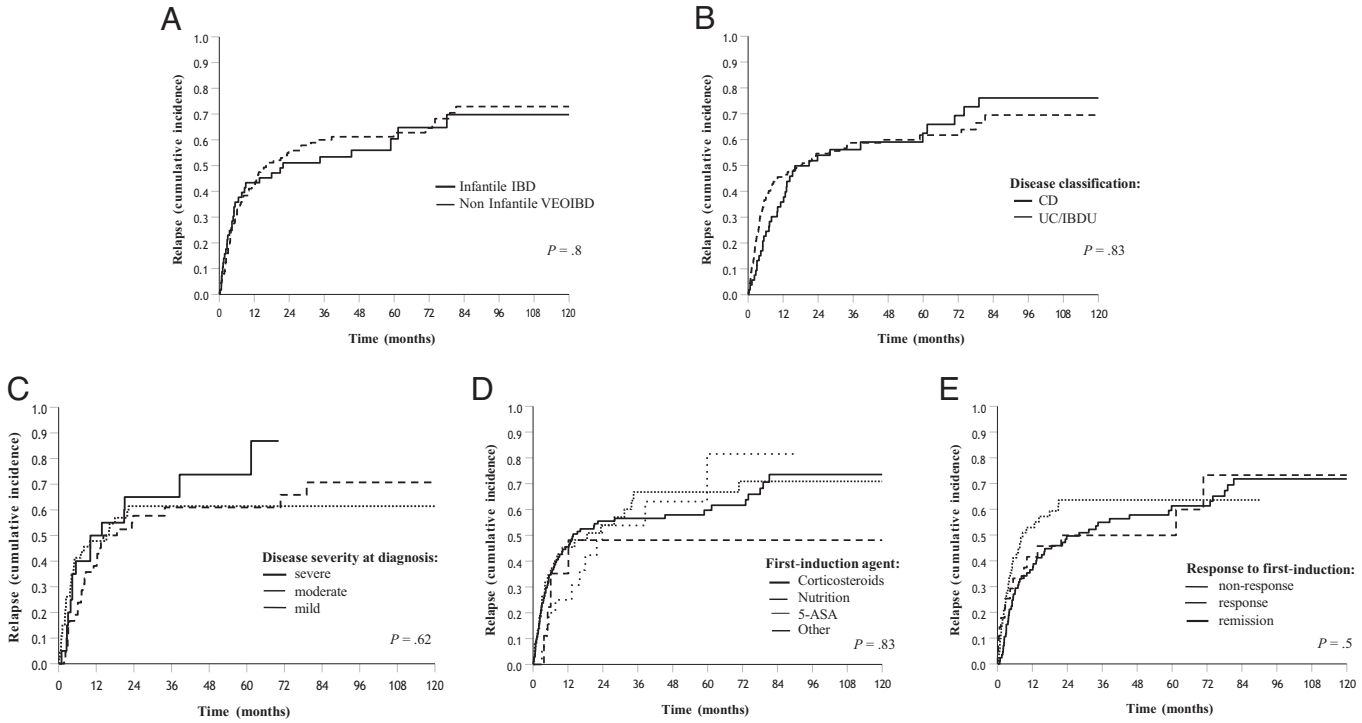

FIGURE 2

Kaplan-Meier survival curves of time to first relapse, and the association with different variables. Time to first relapse according to: A, infantile IBD versus noninfantile VEOIBD; B, disease classification; C, disease severity at diagnosis; D, first induction agent; E, response to first-induction therapy.

and no mortality was reported. In contrast to the high prevalence of linear growth failure in VEOIBD reported in earlier studies,[5,29] in this contemporary cohort, patients demonstrated near-normal height for age both at diagnosis and at the end of follow-up, perhaps indicating trends of improved care. A recent smaller cohort of patients with infantile IBD from Israel[30] reported a similar observation of normal growth trajectories, suggesting that normal growth could be preserved even in patients with very early disease presentation.

As for the distinction between infantile and noninfantile VEOIBD, it appears that the main differences are in the more severe features at presentation among patients diagnosed before the age of 2 years. This includes lower weight for age at presentation, higher rates of anemia and hypoalbuminemia, and higher inflammatory markers, as well as lower rates of response to first-induction therapy and to corticosteroids (both mainly attributed to monogenic diagnoses). However, there were no significant differences in the overall clinical outcomes, including time to remission and the rates of relapses, and no differences in disease complications in our cohort. Kerur et al[11] have divided VEOIBD by presentation before and after the age of 3 years, and demonstrated no significant differences between these age groups in disease presentation (besides chronic fever), disease behavior, and risk of colectomy. However, the defined infantile IBD was not analyzed separately. A smaller cohort from Japan[28] reported pediatric patients with IBD before the age of 8 years, and identified some differences in children with infantile IBD that included higher rates of perianal disease and lower height for age at diagnosis. The use of biologic treatments and the rates of colectomy were similar between the age groups.

In contrast to the limited differences by age groups, it appears from our results that characterizing monogenic versus nonmonogenic VEOIBD could be more valuable. Patients diagnosed with monogenic diseases demonstrated higher rates of lack of response to induction therapies, required bone marrow transplantation in several cases, had higher rates of major infections, and required more surgical intervention in a shorter period of time.

Among the genetically tested patients in our cohort, 16% were diagnosed with monogenic disease (and >22% of patients with infantile IBD); however, these are real-life data in a heterogenous, multicenter, international population without universal screening. Nevertheless, considering the inherent selection bias, our finding probably represents the higher end of the scale. In a recent single-center cohort from Boston, United States, offering whole-exome sequencing to all patients with VEOIBD,[15] detection rate of monogenic mutations was 8%. Similarly, the detection rate reported by the

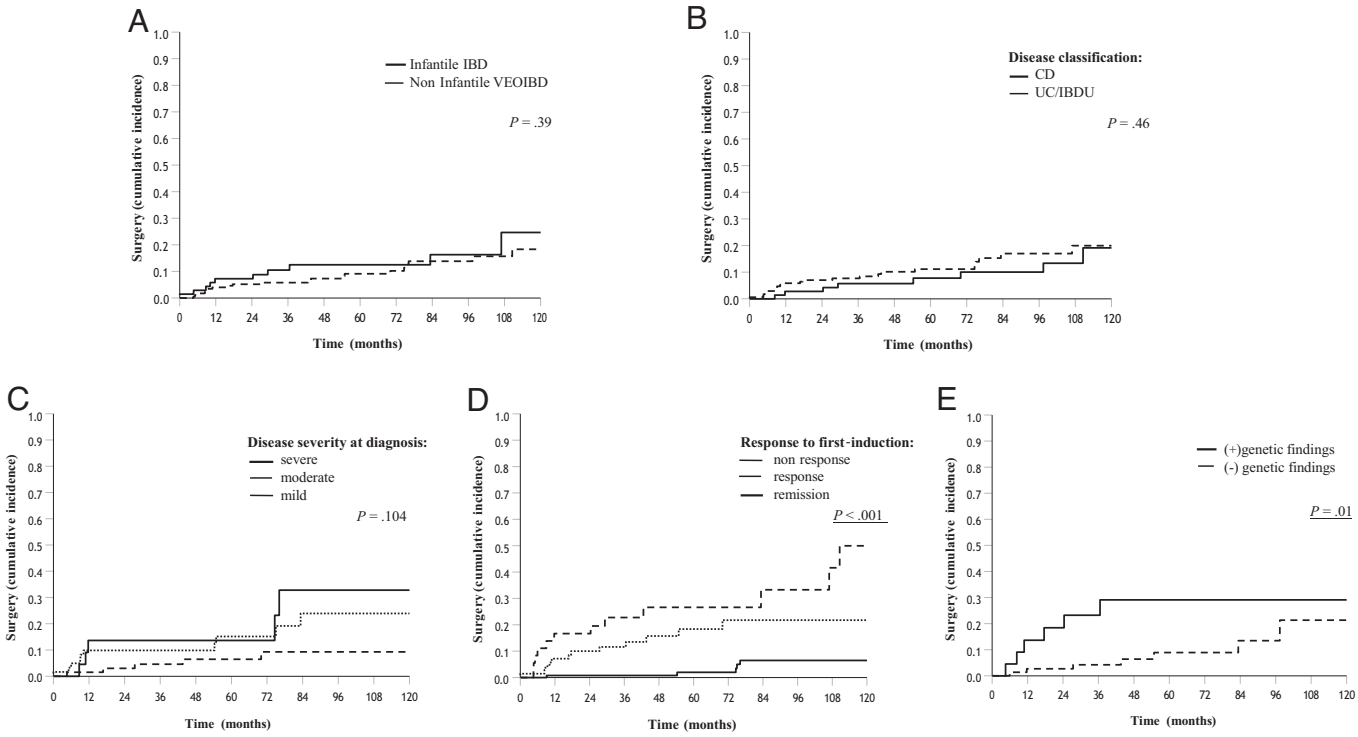

FIGURE 3

Kaplan-Meier survival curves of time to surgery, and the association with different variables. Time to surgery according to: A, infantile IBD versus noninfantile VEOIBD; B, disease classification; C, disease severity at diagnosis; D, response to first induction; E, positive versus negative genetic findings.

Children's Hospital of Philadelphia was 6.3%.[31] Another study from Italy, where different genetic testing methods were used, reported 13% prevalence of monogenic diseases among patients with infantile IBD and early-onset IBD with severe/atypical phenotypes.[32] On the contrary, a study from Pakistan reported 50% detection rate of monogenic diagnoses in VEOIBD (with a mortality rate of >50%), highlighting the potential differences between different ethnic populations, together with variability in consanguinity prevalence. In a large study among unselected population of >1000 pediatric patients with IBD,[16] the detection rate of monogenic disease in patients with VEOIBD was 7.8%, whereas described risk factors included onset before 2 years, as well as extraintestinal manifestations. The pediatric IBD Porto Group of ESPGHAN has recommended in their position article published in 2021[33] to perform genetic screening for monogenic IBD in all patients with infantile IBD, and to consider testing in patients with VEOIBD, particularly in cases with additional red flag features (including comorbidities, extraintestinal manifestations, and/or relevant family history). These recommendations are also supported by the British Society of Pediatric Gastroenterology, Hepatology, and Nutrition.[14] Although some patients in this cohort with monogenic diagnosis demonstrated extraintestinal features, comorbidities, and family history of IBD (as detailed in Supplemental Table 2), many did not have any red flags pointed in the position article.[33] However, because a more severe or refractory course was demonstrated in our cohort among these patients (including high rates of nonresponsiveness to first induction and higher rates of disease complications), we suggest that genetic evaluation should be considered in all cases of infantile IBD and in cases of noninfantile VEOIBD characterized by the described red flags, but also by refractory disease or early complications, regardless of the existence of red flags.

This study has several limitations that should be acknowledged. As a multicenter study conducted in 21 medical centers from different countries, no routine protocols were used for different therapies, endoscopic examinations during follow-up, and genetic evaluation. The clinical scores used to assess disease activity and severity rely in part on subjective measures that could be influenced by patients' young age and physicians' assessment rather than more objective measures as mucosal healing. Moreover, because of the retrospective nature of the study, some data are missing, including indications for hospitalization, indications for therapy escalation, therapeutic drug monitoring, and complete immunologic evaluation. Nonetheless, this large-scaled study provides real life data from a wide range of expert centers in pediatric IBD, over a long period of follow-up. The comprehensive analysis of various aspects of disease presentation and course, together

with the comparisons between different disease subgroups, adds valuable knowledge to the scarce literature on this unique population of patients. However, because our study focused on VEOIBD, comparison of outcomes with later-onset pediatric IBD is beyond the scope of this analysis.

In conclusion, patients with VEOIBD demonstrate fair long-term outcomes, with low rates of complications and surgical interventions. Although patients with infantile IBD have more severe clinical features at presentation and a lower response to induction therapies, no significant differences in long-term disease outcomes are observed in this age group. Identifying monogenic diseases is important in patients with VEOIBD, because these patients are at risk for more severe disease course and may require advanced interventions.

ABBREVIATIONS

5-ASA: 5-aminosalicylic acid
CD: Crohn's disease
EEN: exclusive enteral nutrition
ESPGHAN: European Society for Pediatric Gastroenterology Hepatology and Nutrition
HSCT: hematopoietic stem cell transplantation
IBD: inflammatory bowel disease
IBDU: inflammatory bowel disease-unclassified
IQR: interquartile range
PCDAI: Pediatric Crohn's Disease Activity Index
PUCAI: Pediatric Ulcerative Colitis Activity Index
TNF: tumor necrosis factor
UC: ulcerative colitis
VEOIBD: very early-onset inflammatory bowel disease

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