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Research Article

Incidence, Disease Course, and Medical Treatment of a Danish Population-Based Cohort of Very Early-Onset Inflammatory Bowel Disease

Giaan Ninh,[1] **Thomas Kallemose**,[2] **Vibeke Wewer**,[1] **and Christian Jakobsen**[1]

[1]*The Paediatric Department, Copenhagen University Hospital, Hvidovre, Denmark*
[2]*Department of Clinical Research, Copenhagen University Hospital, Denmark*

Correspondence should be addressed to Giaan Ninh; giaanninh@gmail.com

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Background and Aims. In very early-onset IBD patients (VEO-IBD), studies have shown an incidence ranging from 0.4 to 2.1/100,000, extensive disease location, and a corresponding difficult and debatable treatment. We therefore aimed to investigate the incidence and medical and surgical treatment of VEO-IBD in a well-defined Danish population-based cohort. *Methods*. All VEO-IBD patients, defined as an IBD diagnosis before 6 years of age, were included from the Capital Region and the Zealand Region in 2015-2020. Demographic and clinical data including medical and surgical treatment were systematically extracted from the patient files. *Results*. Forty VEO-IBD patients were identified, 11 diagnosed with CD, 23 UC, and 6 IBD-U. The incidence rate of VEO-IBD was 2.0/100,000 (95% CI 0.8-5.9). All VEO-IBD patients except one had extensive colonic involvement or pancolitis. A total of 34 (85.0%) and 23 (57.5%) of the VEO-IBD patients received immunomodulators and/or biologicals, respectively. The cumulative risks of receiving immunomodulators and/or biologicals after 1/3/5 years was 55.3%/86.8%/90.1% and 36.8%/45.9%/57.0%, respectively. During follow-up, six VEO-IBD patients (15.0%) were treated with vedolizumab—although off-label for this age group—as second-line biological therapy. Four patients (17.4%) with UC had a colectomy. Two colectomised patients were treated with vedolizumab. *Conclusion*. Our population-based study showed an incidence of VEO-IBD comparable with the incidence in other countries. The population were treated intensively with immunomodulators and biologicals—including off-label vedolizumab—and compared to other studies had the same risk of undergoing IBD-related surgeries.

1. Introduction

Inflammatory bowel disease (IBD) present in children <6 years of age is known as very early-onset IBD (VEO-IBD) [1]. The incidence of VEO-IBD in Denmark is currently unknown as no studies have been performed until now. There are few population-based studies from other countries regarding the incidence rate of VEO-IBD. The few existing studies have shown incidence rates ranging from 0.4 to 2.1/100,000, and approximately 3-15% of pediatric IBD presents before the age of six years [2–4]. A Canadian study reported VEO-IBD to be the fastest growing subgroup of all IBD patients with an increasing incidence of 7.2% per year [3].

Studies of the disease course in children with VEO-IBD are scarce with contradicting results. Some nonpopulation-based studies reported that children with VEO-IBD are at higher risk of surgery compared with children with older onset of pediatric IBD, while others have reported similar or even lower surgery risk [5–8]. Compared to children with later onset of IBD, children with VEO-IBD respond less well to conventional therapy and are less likely to reach remission one year after starting immunomodulatory and biological therapy [5]. At present, there are no international guidelines for the treatment of VEO-IBD [9]. As previous studies regarding VEO-IBD mainly originate from referral centers, where the most severe cases are followed, the true clinical spectrum of VEO-IBD is unclear. Thus, population-based

studies are needed to understand the long-term outcomes and provide guidance to medical and surgical decisions. The aim of our study is to investigate the incidence and disease course of VEO-IBD in a population-based cohort from two Danish regions in the period 2015-2020.

2. Methods

2.1. Study Design and Patient Inclusion. We included all patients diagnosed with IBD before six years of age who were treated at the pediatric department at the Hvidovre University Hospital in Copenhagen in the period from January 1, 2015, to July 1, 2020. Since 2015, the hospital has been the principal department for IBD in patients <10 years of age in the Capital Region and Region Zealand of Denmark (Eastern Denmark) which covered 46%-48% of the Danish population under six years from 2008 to 2020 [10]. Thus, we included all newly diagnosed children with VEO-IBD patients in this geographical area in the period 2015–2020. Children diagnosed prior to 2015 may have been treated at one of the other hospitals in eastern Denmark; thus, the incidence rate of VEO-IBD prior to 2015 was not calculated. All VEO-IBD patients were identified and included by searching for International Classification of Diseases 10th revision (ICD-10) code group K50 (Crohn's disease), K51 (ulcerative colitis), or K52.3 (indeterminate colitis) in the local database. Patients were followed from diagnosis, dating back to 2004, until October 16, 2020, or until death or emigration or for patients with ulcerative colitis (UC) until colectomy. In general, all pediatric patients with IBD in Denmark are diagnosed and followed at the government hospitals free of charge. No children with IBD are treated by adult or private gastroenterologists or pediatricians.

2.2. Data Collection and Definitions. The following data were extracted from the patient charts at end of follow-up: date of birth, IBD diagnosis, sex, family history (defined by either first- or second-degree relative with IBD), date of onset of symptoms, disease localization and phenotype, medical and surgical treatments, and disease activity. Validation of diagnosis and age of diagnosis were performed by patient chart review.

2.3. Diagnostic Criteria and Phenotype. The diagnostic criteria's for CD, UC, and IBDU were based on the Porto criteria [11], and the phenotype was based on the Paris Classification [12].

2.4. Treatment. The start and end date of the following medical treatments were registered as prescriptions in the patient charts: 5-aminosalicylic acid (5-ASA), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), systemic corticosteroid treatment (SCT) (prednisolone, hydrocortisone, methylprednisolone etc.), biological treatment including antitumor necrosis factor alpha (anti-TNF-alpha) and vedolizumab, local treatment (rectal) with 5-ASA and/or steroids, and exclusive enteral nutrition therapy (EEN). The date and type of the following surgical modalities were registered: bowel resections (colectomy and ileocecal resection) and J-pouch surgery.

2.5. Disease Activity. Disease activity at each hospital visit was assessed based on Abbreviated Pediatric Crohn's Disease (abrPCDAI) [13] and Pediatric Ulcerative Colitis Activity Index (PUCAI) [14]. If PUCAI and PCDAI scores were missing, disease activity was graded according to Physician's Global Assessment (ranging from 0 to 3) (PGA) based on the medical record of the hospital visit in question. A good correlation between the disease activity index and the PGA has been demonstrated [15].

2.6. Remission and Relapse. Remission was defined as a period of more than 30 days without disease equivalent to PUCAI < 10, abrPCDAI < 10, or PGA = 0. Relapse was defined as an increase in disease activity or worsening symptoms that resulted in either (1) increase in doses or frequency of the medication already prescribed in response to increased disease activity or worsening symptoms or (2) step-up in treatment in the form a more potent drug or the need of bowel resection [16–18]. An increase in disease activity was defined as PUCAI > 10, abrPCDAI > 10, and PGA > 0 [13–15]. If the disease had not been in remission before a dose increase or step-up treatment, no relapse was recorded. Dose increase due to increase in body weight or suboptimal serum concentrations of medication was not recorded as a relapse.

2.7. Statistics. Categorical data were presented as numbers and percentages while continuous variables as median and interquartile range (IQR). The annual incidence of VEO-IBD per 100,000 children <6 years of age was calculated using the population of children under 6 years in the Capital Region and Region Zealand. Survival analysis (Kaplan-Meier plots) was used to illustrate differences in time to medical or surgical treatment; cumulative risk estimates and incidence rates are presented with 95% confidence intervals (CI). The annual relapse rate after induction of medical treatment among those achieving remission was calculated using Poisson's regression analysis and reported as number of relapses per patient years. Unless otherwise stated, diagnosis at end of follow-up (final diagnosis) was used. A p value <0.05 was considered statistically significant. The statistical analysis was performed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.8. Ethical Considerations. The study was a quality assurance project and was approved by the administration at the Amager-Hvidovre Hospital.

3. Results

We identified 41 patients with VEO-IBD. The chart of one patient was incomplete, and therefore, this patient was excluded from the study. Twenty-one (52.5%) patients were diagnosed between 2004 and 2014, 17 (42.5%) patients between 2015 and 2019, and 2 patients in 2020. Nineteen patients (47.5%) were male (7 CD (63.6%), 7 UC (30.4%), and 5 IBDU (83.3%)), while 21 patients (52.5%) were female

Table 1: Clinical and demographic presentation of patients with VEO-IBD at diagnosis.

	IBD ($N = 40$)		CD ($N = 11$)		UC ($N = 23$)		IBDU ($N = 6$)	
Age in years, median (IQR)	3.3 (2.3-5.0)		3.6 (2.4-5.2)		3.3 (2.2-4.0)		3.2 (1.3-5.1)	
Age at diagnosis, *N* (%)								
0-2 years	7	(17.5)	2	(18.2)	4	(17.4)	1	(16.7)
3-5 years	33	(82.5)	9	(81.8)	19	(82.6)	5	(83.3)
Sex, *N* (%)								
Male	19	(47.5)	7	(63.6)	7	(30.4)	5	(83.3)
Female	21	(52.5)	4	(36.4)	16	(69.6)	1	(16.7)
Time from onset of symptoms and diagnosis, *N* (%)								
<2 mo	11	(27.5)	3	(27.3)	8	(34.8)	0	(0)
≥2 mo and <6 mo	12	(30.0)	3	(27.3)	8	(34.8)	1	(16.7)
≥6 mo	16	(40.0)	5	(45.5)	7	(30.4)	4	(66.7)
NA	1	(2.5)	0	(0)	0	(0)	1	(16.7)
Family history of IBD, *N* (%)								
Parent(s) or sibling(s)	6	(15.0)	2	(18.2)	4	(17.4)	0	(0)
Other relative(s)	8	(20.0)	1	(9.1)	4	(17.4)	3	(50.0)
Screened for primary immunodeficiency, *N* (%)								
No	29	(72.5)	8	(72.7)	17	(73.9)	4	(66.7)
Yes	11	(27.5)	3	(27.3)	6	(26.1)	2	(33.3)

Mo: months; NA: not available; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBDU: IBD unspecified; VEO: very early-onset.

(4 CD (36.4%), 16 UC (69.6%), and 1 IBDU (16.7%)). Seven (17.5%) patients (two CD, four UC, and one IBDU) were aged <2 years at diagnosis (infantile-onset IBD). Demographic and clinical characteristics at diagnosis are presented in Table 1.

3.1. Immunodeficiency Screening. All patients had a normal morphologic presentation but were not systematically screened for immune defects. However, 8 were screened for chronic granulomatous disease, 5 were screened for variants in the interleukin-10 receptor pathway, and 4 underwent whole genome sequencing for primary immunodeficiency. None of the screened patients were identified to have immune defects based on their completed evaluation.

3.2. Phenotype. The Paris Classification of disease location in VEO-IBD at diagnosis categorized 0-2 years and 3-5 years old is presented in Table 2.

3.3. Incidence. As patients were included and followed till October 2020 and not at the end of the year, the annual incidence was calculated for the period 2015-2019. Seventeen new cases of VEO-IBD are presented during 2015-2019. The mean annual incidence of VEO-IBD was 2.0/100,000 (CI 95% 0.8-5.9). The annual incidence is demonstrated in Figure 1.

3.4. Medical Treatment

3.4.1. Systemic Corticosteroid Treatment (SCT). SCT was used in 35 patients (87.5%) during the first year of follow-up. In Table 3, the use of SCT 30 days and 60 days after diagnosis is demonstrated.

3.4.2. Enteral Nutrition Therapy. Four CD patients (36.4%) received EEN therapy, while additional 3 CD patients (27.3%) received enteral nutrition therapy combined with another medication (SCT, anti-TNF-alpha, and vedolizumab).

3.4.3. 5-ASA. Three patients (13.0%) (all UC patients) received 5-ASA as monotherapy during follow-up. The remaining patients who received 5-ASA were also treated with immunomodulators or biologicals.

3.4.4. Immunomodulators. A total of 12 (30.0%) patients (2 CD (18.2%), 8 UC (34.8%), and 2 IBDU (33.3%)) were treated with immunomodulators as monotherapy or combined with 5-ASA. Additional 22 (55.0%) patients (8 CD (72.7%), 12 UC (52.2%), and 2 IBDU (33.3%)) received combination therapy with immunomodulators and biological agents (Table 3).

The median time of treatment with immunomodulators at the end of follow-up was 4.3 years (IQR 3.2-7.9) for CD, 2.4 years (IQR 0.4-8.1) for UC, and 1.8 years (IQR 1.1-2.9) for IBDU.

The cumulative risk of receiving immunomodulators is presented in Figure 2(a).

The number of patients diagnosed prior to 2015 and between 2015 and 2020 who received immunomodulators and biologicals is presented in Table 4.

3.4.5. Biological Treatment. The first-line biological agent used was an anti-TNF-alpha drug (infliximab or adalimumab) in all patients, while anti-integrins (vedolizumab) were used as second-line treatment. A total of 23 IBD (57.5%) patients were treated with an anti-TNF-alpha agent (7 CD

Table 2: Paris classification disease location in VEO-IBD at diagnosis categorized 0-2 years and 3-5 years old.

	Age at diagnosis			
	0-2 years		3-5 years	
Extent of ulcerative colitis, *N* (%)	4	(100)	19	(100)
E1 ulcerative proctitis	0	(100)	2	(10.5)
E2 left sided	0	(0)	0	(0)
E3 extensive UC	1	(25)	4	(21.1)
E4 pancolitis	3	(75)	13	(68.4)
Crohn's disease location, *N* (%)	2	(100)	9	(100)
L2 colonic only	0	(0)	9	(100)
L3 ileocolonic	1	(50.0)	0	(0)
L2 + L4a/b colonic+small bowel	1	(50.0)	0	(0)
Crohn's disease phenotype, *N* (%)				
B1 inflammatory, nonpenetrating, and nonstricturing	2	(100)	9	(100)
P: perianal disease	0	(0)	0	(0)
Extent of inflammatory bowel disease unspecified, *N* (%)	1	(100)	5	(100)
Pancolitis	1	(100)	5	(100)

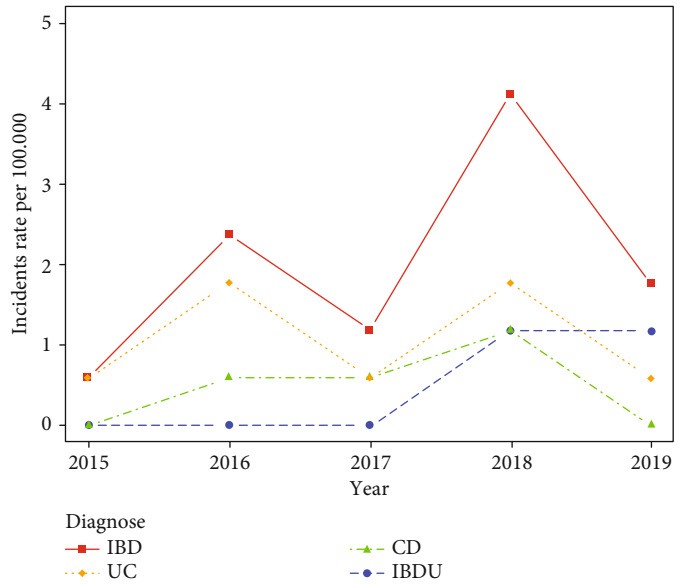

Figure 1: Annual incidence rate per 100.000 of very early-onset inflammatory bowel disease in the period 2015-2019, stratified by Crohn's Disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unspecified (IBDU).

(70.0%), 14 UC (58.3%), and 2 IBDU (33.3%) (Table 3). The median time of treatment with an anti-TNF-alpha agent at the end of follow-up was 7.0 years (IQR 3.5-8.3) for CD, 2.1 years (IQR 1.6-5.4) for UC, and 2.5 years (IQR 1.5-3.5) for IBDU. Figure 2(b) demonstrates the cumulative risk of receiving biological treatment (anti-TNF-alpha and/or anti-integrins).

Six patients received anti-integrins (vedolizumab). The median age when initiating vedolizumab was 7.0 years (IQR 4.6-8.2). The median time of treatment with vedolizumab at the end of follow-up was 17.8 months (IQR 6.7-36.8). Of those who received vedolizumab, 2 (33.3%) with UC never reached remission (defined by calprotectin < 250) and underwent colectomy and ileostomy. One patient (16.7%) had only received vedolizumab treatment for 56 days at the end of follow-up and was not in remission. Three patients (33.3%) were in remission at the end of follow-up, and the time between administration of vedolizumab and remission for these three patients was 2.9 months, 3.2 months, and 7.1 months, respectively.

3.5. Faecal Calprotectin and C-Reactive Protein (CRP) after Induction of Biologicals. The median faecal calprotectin (ranging from 0 to 1800 mg/kg faeces) at 0 days, 30 days, 3 months, 6 months, and 1 year (±14 days) after use of biologicals was 1180.0 (IQR 853.0-2240.0), 996.0 (IQR 282.0-1575.0), 569.5 (IQR 282.0-855), 1415.0 (IQR 615.2-1800.0), and 678.5 (IQR 83.3-1800.0), respectively.

Table 3: Distribution of medical treatment among patients with VEO-IBD (stratified by diagnosis) during follow-up.

	IBD ($N = 40$)		CD ($N = 11$)		UC ($N = 23$)		IBDU ($N = 6$)	
SCT, *N* (%)								
No	5	(12.5)	1	(9.1)	2	(8.7)	2	(33.3)
Yes	35	(87.5)	10	(90.9)	21	(91.3)	4	(66.7)
SCT after 30 days, *N* (%)								
No	18	(45.0)	3	(27.3)	10	(43.5)	5	(83.3)
Yes	22	(55.0)	8	(72.7)	13	(56.5)	1	(16.7)
SCT after 60 days, *N* (%)								
No	14	(35.0)	2	(18.2)	7	(30.4)	5	(83.3)
Yes	26	(65.0)	9	(81.8)	16	(69.6)	1	(16.7)
5-ASA as monotherapy, *N* (%)								
No	37	(92.5)	11	(100)	20	(87.0)	6	(100)
Yes	3	(7.5)	0	(0.0)	3	(13.0)	0	(0.0)
Immunomodulators[a], *N* (%)								
No	6	(15.0)	2	(18.2)	3	(13.0)	2	(33.3)
Yes	34	(85.0)	9	(81.8)	20	(87.0)	4	(66.7)
Immunomodulators only or combined with 5-ASA, *N* (%)								
No	28	(70.0)	9	(81.8)	15	(65.2)	4	(66.7)
Yes	12	(30.0)	2	(18.2)	8	(34.8)	2	(33.3)
Anti-TNF-alpha[b], *N* (%)								
No	17	(42.5)	3	(27.3)	10	(43.5)	4	(66.7)
Yes	23	(57.5)	8	(72.7)	13	(56.5)	2	(33.3)
Vedolizumab, *N* (%)								
No	34	(85.0)	10	(90.9)	18	(78.3)	6	(100)
Yes	6	(15.0)	1	(9.1)	5	(21.7)	0	(0)

5-ASA: 5-aminosalicylic acid; TNF: tumor necrosis factor; SCT: systemic corticoid treatment; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBDU: IBD unspecified; VEO: very early-onset. [a]Total number of children with VEO-IBD treated with immunomodulators. [b]Total number of children with VEO-IBD treated with anti-TNF-alpha.

The median CRP (mg/L) 0 days, 30 days, 3 months, 6 months, and 1 year after use of biologicals was 1.7 (IQR 0.8-13.3), 3.0 (IQR 0.9-6.5), 4.1 (IQR (IQR 1-9), 4.1 (IQR 1.0-9.0), and 2.0 (IQR 0.6-5.6), respectively.

3.6. Hospitalization and Relapse Rate per Patient. The rates of hospitalizations and relapses per year after first use of immunomodulators and biologicals in the cohort are presented in Figure 3. In both UC and CD, a decrease in relapse rates was observed over time with the highest relapse rate in year 1 compared to the relapse rates in the following 6 years after first use of immunomodulators and biologicals. In UC, a decrease in hospitalizations rate was observed over time, while the hospitalization rates were more fluctuating in CD with the highest hospitalization rate in year 5 and 6 after first use of immunomodulators and biologicals.

3.7. Surgical Intervention. A total of 4 patients underwent surgery all diagnosed with UC. Three of the patients 3 (75.0%) underwent subsequent J-pouch surgery. All colectomies were performed within the first 5 years after diagnosis. The cumulative risk of bowel resections for patients with UC at 1, 3, and 5 years was 13.3% (95% CI 0-26.2), 13.3% (95% CI 0-26.2), and 19.5% (95% CI 0-35.2), respectively (Figure 2(d)). No patients with CD had bowel resections. Thus, the cumulative risk of bowel resections for patients with VEO-IBD at 1, 3, and 5 years was 7.6% (95% CI 0-15.6), 7.6% (95% CI 0-15.6), and 11.5% (95% CI 0-21.7), respectively (Figure 2(c)).

3.8. Extraintestinal Manifestations. Five (12.5%) patients (all UC) had EIM at the end of follow-up. Two (40.0%) patients had EIM at diagnosis; 1 patient had uveitis at diagnosis and subsequently developed arthritis during follow-up, while the other patient had arthritis at diagnosis. Three (60.0%) patients developed EIMs after diagnosis; 1 had psoriasis and episcleritis, 1 had oxalate kidney stones, and 1 had primary sclerosing cholangitis.

4. Discussion

In this population-based Danish study of 40 VEO-IBD patients, we found (1) an incidence of 2.0/100,000 from 2015 to 2019, (2) high frequency of treatment with immunomodulators and biological therapy, (3) high surgery rates among UC patients, and (4) low relapse rates over time but high calprotectin levels.

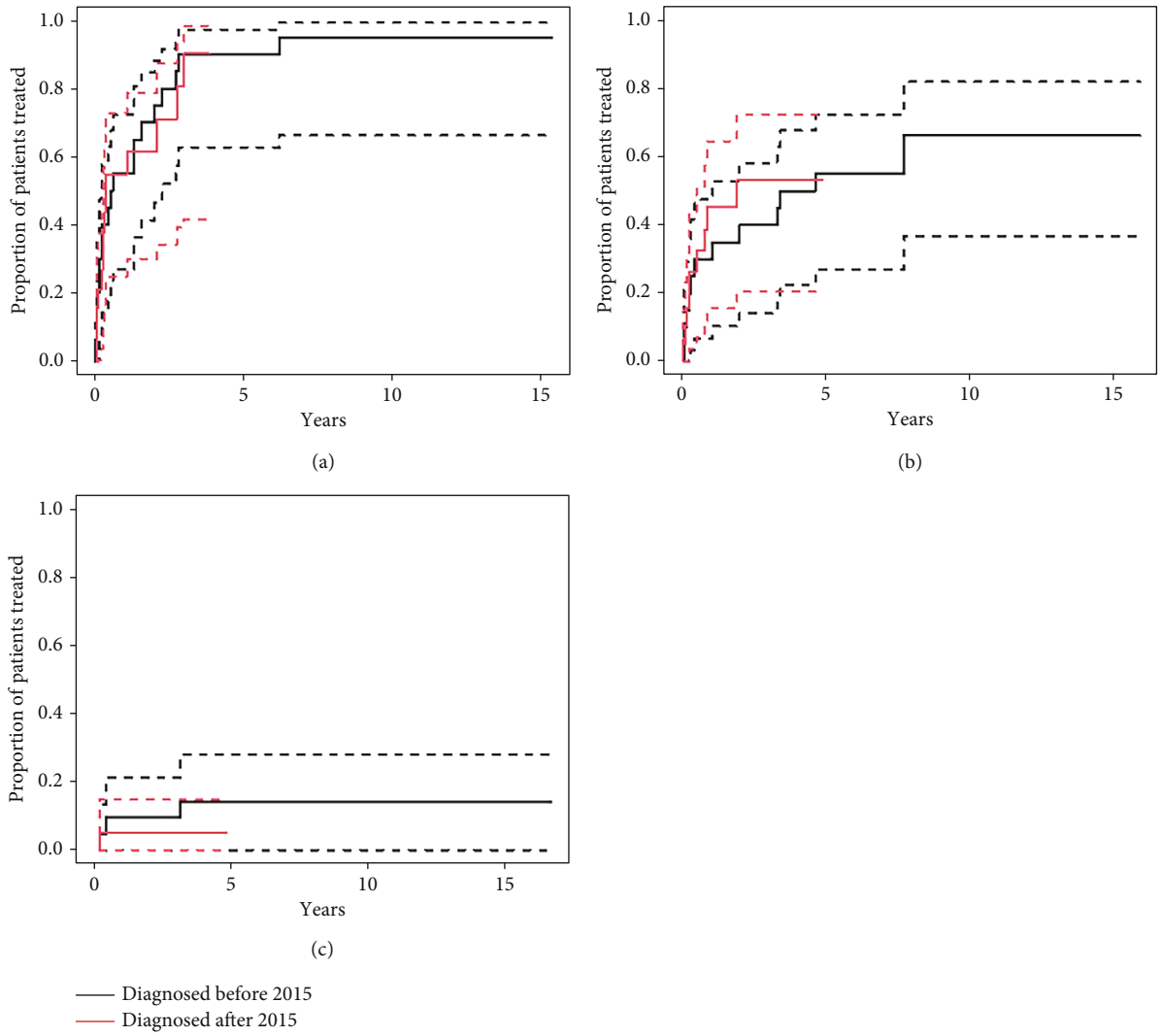

Figure 2: Cumulative incidence of initiation of treatment with (a) immunomodulators, (b) biologicals, and (c) inflammatory bowel disease-related surgery from diagnosis in very early-onset IBD cohort stratified by diagnosed before and after 2015. Dotted lines represent the 95% confidence interval.

Our incidence rate of 2.0/100.000 is similar with the findings in a Canadian study by Benchimol et al., who reported an incidence of VEO-IBD to be 2.1/100.000 in 2009 [3]. Another population-based French study by Bequet et al. reported an incidence of VEO-IBD of 0.4/100.000 in Northern France during 1988-2011 [2].

In our cohort, a total of 34 patients (85.0%) received immunosuppressive therapy and 57.5% received biological therapy which is higher than reported in other studies. Studies from the United States and Canada reported that 35%-60% of patients with VEO-IBD received treatment with immunomodulators 5 years after diagnosis [5, 6, 19]. Additionally, Hemker et al. reported that the cumulative risk of receiving anti-TNF-alpha at 1 year was 5%-17% and 10%-50% at 5 years, while Kerur et al. reported that 42% with VEO-IBD were treated with biologics 5 years after diagnosis [6].

Despite the higher rate of treatment with immunomodulators and biologicals, our surgery rate was similar to other studies: Benchimol et al. reported the cumulative risk of surgery for VEO-IBD patients 1 year, 3 years, and 5 years after diagnosis of 5%, 8%, and 10%, respectively [3]. Aloi et al. reported that 24% of patients with VEO-IBD had surgery at the end of follow-up [20]. A North American study by Kerur et al. reported an observed risk of bowel surgery in VEO-CD patients of 3% at 1 year, 12% at 3 years, and 15% at 5 years [6].

Thus, recent data including our study suggests that VEO-IBD often is treated aggressively which indicates an unexplained treatment-resistant phenotype in this population. Studies in which the biological treatment frequency between children with VEO-IBD and pediatric IBD is compared are needed to confirm this.

The current guidelines from 2018 to 2020 regarding the treatment of children with IBD (including children with VEO-IBD) from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) describe an approach that involves individualization and risk

Table 4: Distribution of medical treatment among patients with VEO-IBD (stratified by diagnosis, period of diagnosis, and years after diagnosis) during follow-up.

	Diagnosis 2015-2020						Diagnosis before 2015					
	CD ($N = 4$)		UC ($N = 10$)		IBDU ($N = 5$)		CD ($N = 7$)		UC ($N = 13$)		IBDU ($N = 1$)	
SCT	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
0-1 yr after diagnosis												
Yes	3	75.0	3	30.0	2	40.0	7	100	12	92.3	0	0
End of follow-up	0	0	0	0	0	0	0	0	0	0	0	0
1-3 yrs after diagnosis												
Yes	1	25.0	3	30.0	1	20.0	6	85.7	8	61.5	1	100
End- f follow-up	0	0	3	30.0	3	60.0	0	0	2	15.4	0	0
3-5 yrs after diagnosis												
Yes	1	25.0	0	0	0	0	2	28.6	6	46.15	0	0
End of follow-up	2	50.0	8	80.0	5	100	0	0	2	15.4	0	0
>5 yrs after diagnosis												
Yes	0	0	0	0	0	0	2	28.6	3	23.1	1	100
End of follow-up	4	100	10	100	5	100	0	0	2	15.4	0	0
5-ASA												
0-1 yr after diagnosis												
Yes	1	25.0	9	90.0	4	80.0	5	71.4	12	92.3	1	100
End of follow-up	0	0	0	0	0	0	0	0	2	15.4	0	0
1-3 yrs after diagnosis												
Yes	2	50.0	4	40.0	1	20.0	5	71.4	10	76.7	1	100
End of follow-up	0	0	3	30.0	3	60.0	0	0	2	15.4	0	0
3-5 yrs after diagnosis												
Yes	0		2	20.0	0		4	57.1	10	76.7	1	100
End of follow-up	2	50.0	8	80.0	5	100	0	0	2	15.4	0	0
>5 yrs after diagnosis												
Yes	0	0	0	0	0	0	3	42.9	11	84.6	1	100
End of follow-up	4	100	10	100	5	100	0	0	2	15.4	0	0
Immunomodulators												
0-1 yr after diagnosis												
Yes	3	75.0	5	50.0	2	40.0	5	71.4	7	53.8	0	0
End of follow-up	0	0	0	0	0	0	0	0	0	0	0	0
1-3 yrs after diagnosis												
Yes	1	25.0	4	40.0	2	40.0	7	100	7	53.8	1	100
End of follow-up	0	0	3	30.0	3	60.0	0	0	2	15.4	0	0
3-5 yrs after diagnosis												
Yes	1	25.0	1	10.0	0	0	6	85.7	8	61.5	1	100
End of follow-up	2	50.0	8	80.0	5	100	0	0	2	15.4	0	0
>5 yrs after diagnosis												
Yes	0	100	0	0	0	0	6	85.7	8	61.5	1	100
End of follow-up	4	100	10	100	5	100	0	0	2	15.4	0	0
Anti-TNF-alpha												
0-1 yr after diagnosis												
Yes	3	75.0	5	50.0	0	0	2	28.6	4	30.8	0	0
End of follow-up	0	0	0	0	0	0	0	0	0	0	0	0
1-3 yrs after diagnosis												
Yes	3	75.0	2	40.0	1	20.0	3	42.3	2	15.4	0	0
End of follow-up	0	0	3	60.0	3	60.0	0	0	2	15.4	0	0

Table 4: Continued.

	Diagnosis 2015-2020						Diagnosis before 2015					
	CD ($N = 4$)		UC ($N = 10$)		IBDU ($N = 5$)		CD ($N = 7$)		UC ($N = 13$)		IBDU ($N = 1$)	
3-5 yrs after diagnosis												
Yes	2	50.0	0	0	0	0	4	57.1	3	23.1	0	0
End of follow-up	2	50.0	8	80.0	5	100	0	0	2	15.4	0	0
>5 yrs after diagnosis												
Yes	0	0	0	0	0	0	4	57.1	5	38.5	0	0
End of follow-up	4	100	10	100	5	100	0	0	2	15.4	0	0
Vedolizumab, *N* (%)												
0-1 yr after diagnosis												
Yes	0	0	2	20.0	0	0	0	0	0	0	0	0
End of follow-up	0	0	0	0	0	0	0	0	0	0	0	0
1-3 yrs after diagnosis												
Yes	0	0	2	40.0	0	0	0	0	0	0	0	0
End of follow-up	0	0	3	60.0	3	60.0	0	0	2	15.4	0	0
3-5 yrs after diagnosis												
Yes	0	0	0	0	0	0	0	0	1	7.7	0	0
End of follow-up	2	50.0	8	80.0	5	100	0	0	2	15.4	0	0
>5 yrs after diagnosis												
Yes	0	0	0	0	0	0	0	0	2	15.4	0	0
End of follow-up	4	100	10	100	5	100	0	0	2	15.4	0	0
Operation												
0-1 yr after diagnosis												
Yes	0	0	1	10.0	0	0	0	0	2	15.4	0	0
End of follow-up	0	0	0	0	0	0	0	0	0	0	0	0
1-3 yrs after diagnosis												
Yes	0	0	0	0	0	0	0	0	0	0	0	0
End of follow-up	0	0	3	30.0	3	60.0	0	0	2	15.4	0	0
3-5 yrs after diagnosis												
Yes	0	0	0	0	0	0	0	0	0	0	0	0
End of follow-up	2	50.0	8	80.0	5	0	0	0	2	15.4	0	0
>5 yrs after diagnosis												
Yes	0	0	0	0	0	0	0	0	0	0	0	0
End of follow-up	4	100	10	100	5	100	0	0	2	15.4	0	0

5-ASA: 5-aminosalicylic acid; TNF: tumor necrosis factor; SCT: systemic corticoid treatment; yrs: years; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IBDU: IBD unspecified; VEO: very early-onset.*End of follow-up reached before the specific period.

assessment of the individual IBD patient. Immunomodulators and biological therapy are only recommended for patients who are at high risk for disease complications [21, 22]. In Denmark, ECCO guidelines are followed, which recommend a step-up approach, where patients with activity in disease or symptoms are either increased in dose or frequency of the already prescribed medication or put into step-up treatment in the form of a new drug (5-ASA/EEN therapy ⟶ immunomodulators ⟶ biologicals) [9]. This approach may explain the difference in the use of immunosuppressive agents and biological therapy between the studies of Kelsen et al. and Hemker et al. both of which are from the United States and our study. Furthermore, as biologicals are free to the patients in Denmark, there is greater possibility to prescribe biologicals following failure of treatment with 5-ASA and immunomodulators, respectively, to achieve remission of disease, compared to the United States.

Six patients in our cohort were treated with vedolizumab as second-line biological therapy. Data on vedolizumab treatment in patients with VEO-IBD is still lacking. Currently vedolizumab is an off-label drug for VEO-IBD, and there has only been one study regarding vedolizumab treatment for this group of patients [23]. This recent study by Fabiszewsja et al. reported clinical response in more than 40% of patients after induction therapy with vedolizumab. This is higher than our study in which 33% were in remission at the end of follow-up. Thus, vedolizumab seems to

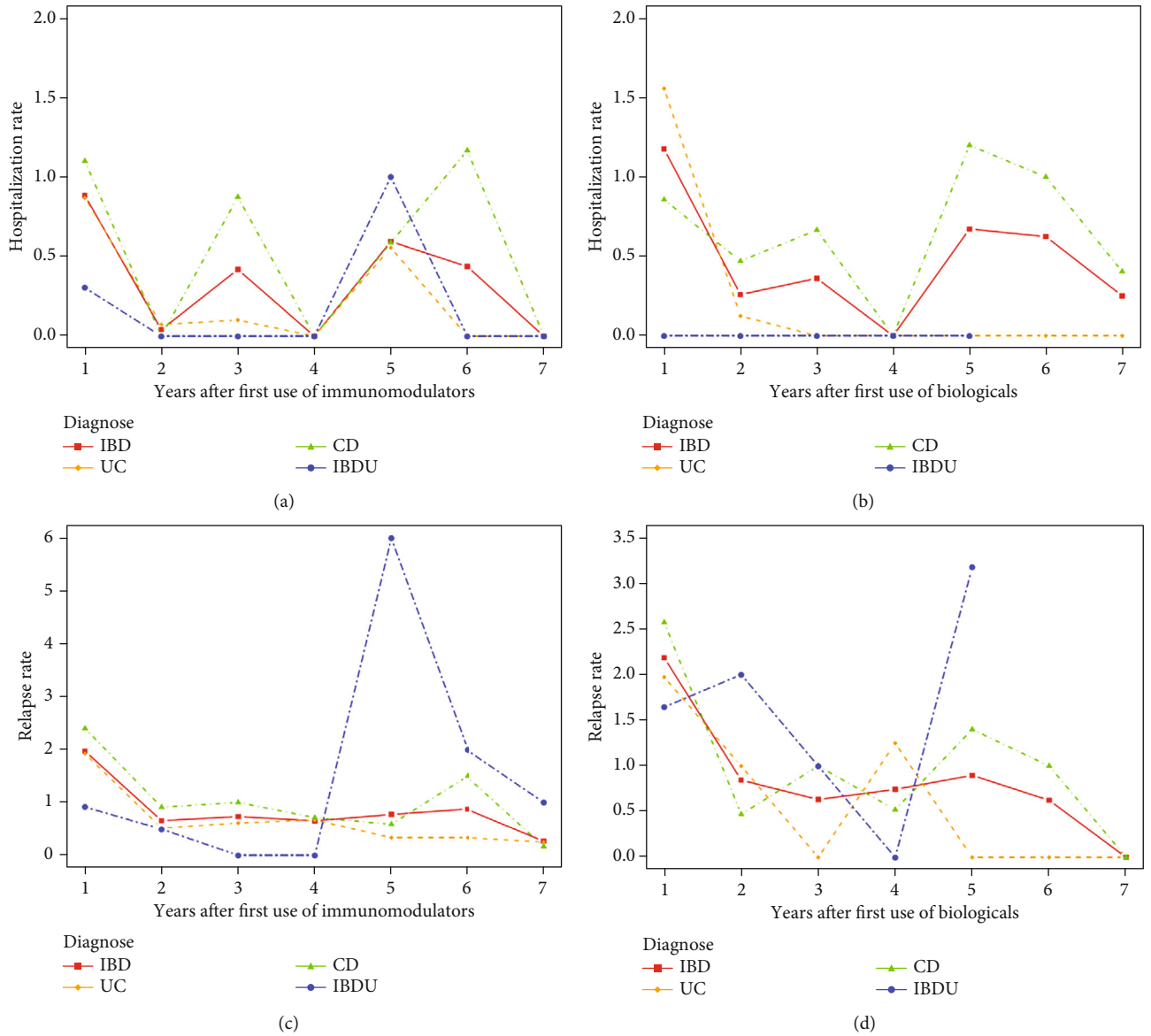

Figure 3: Annual hospitalization and relapse rate per patient year for VEO-IBD patients after induction of immunomodulators and biological treatment.

be a promising second-line biological agent in the treatment of VEO-IBD and is certainly worth further evaluation, especially in the group of youngest patients.

Our data suggest no difference in the use of immunomodulators in patients diagnosed between 2015 and 2020 and those diagnosed prior to 2015 during the first years after diagnosis. However, there seems to be a more frequent use of biological therapy among the patients diagnosed between 2015 and 2020 at 3-5 years after diagnosis compared to patients diagnosed prior to 2015. This difference is likely due to more reluctance from treating physicians to start biological treatment in the youngest group of patients with IBD prior to 2015.

The goal of aggressive medical treatment with immunomodulators and biologicals is to achieve clinical remission and prevent IBD-related surgery. The question remains whether the aggressive medical approach in the treatment of children with VEO-IBD reduces the risk of IBD-related surgeries or simply postpone them.

Furthermore, one could speculate if this aggressive treatment could increase the risk for treatment-related cancers during follow-up.

As the consumption of immunomodulators and biologicals increases, studies have shown an increased risk of opportunistic infections with Epstein-Barr virus and cytomegalovirus [21] and malignancy such as Non-Hodgkin's lymphoma and hepatosplenic T-cell lymphoma in young men [24, 25].

Untreated UC is associated with an increased risk of developing colorectal cancer (CRC) [24]. A meta-analysis by Eaden et al. found that early disease onset IBD (<10 years of age), long duration of the disease, and pancolitis at the time of diagnosis were independent risk factors for developing CRC, making children with VEO-IBD a potential high-

risk group [26]. Currently, there are no longitudinal studies on CRC in VEO-IBD.

Two recent longitudinal population-based studies by Malham et al. from Denmark/Finland and by Olen et al. from Sweden found a 2.5-fold increase in the risk of cancer in pediatric onset IBD (<15 years) compared to the general population with identical risk estimates in CD and UC [27, 28]. Finally, a recent nationwide Israeli study by Atia et al. showed that the absolute malignancy risk among pediatric onset IBD is very low and no differences in risk with specific therapies were apparent [29]. While the rate of surgery remains high despite higher utility of biologics, patients may benefit from early advanced therapy as reduction of symptoms may improve the quality of life (QoL), growth, and development. However, this was not assessed in the current or previous studies.

Thus, medical treatment with immunosuppressive agents and biological therapy of this complicated and treatment-resistant group of patients is a difficult balancing of effect (anti-inflammatory), complications (cancer and infections), and surgery in early childhood.

The aggressive treatment with immunomodulators and biologicals resulted in low relapse rates during the follow-up period, but the calprotectin levels remained relatively high suggesting clinical remission but not mucosal healing. To our knowledge, no study has addressed the treatment effect on mucosal healing over time in VEO-IBD.

The most important strength of our study is the population-based nature of the study covering 48% of the Danish population aged <6 years. In addition, we reviewed all patient records and thus increased the reliability of the registered data. Limitations of this study are the retrospective nature of data recording and the relatively small number of patients included.

In conclusion, our population-based study showed an incidence of VEO-IBD comparable with the incidence in other countries. The population was treated intensively with immunomodulators and biologicals—including off-label vedolizumab—resulting in decreasing relapse rates over time but not mucosal healing as indicated by elevated calprotectin levels over time. The risk of surgery was comparable to results from the previous cohorts. Future studies in VEO-IBD are needed to investigate if this high medication burden leads to a change in the natural history of the disease or merely keeps the disease in a low-grade inflammation state with potential devastating consequences during the patient's life span (surgery, cancer, and low QoL).

Data Availability

The data underlying this article cannot be shared publicly due to the privacy of the individuals that were included in the study. The data will be shared on reasonable request to the corresponding author.

Conflicts of Interest

There are no conflicts of interest.

Authors' Contributions

G.N was responsible for the study design, acquisition of data, analysis, and interpretation of data; drafted the article; approved the final version to be published; and agreed to be accountable for all aspects of the work. T.K was responsible for the analysis and interpretation of data; revised the article critically; approved the final version to be submitted; and agreed to be accountable for all aspects of the work. V.W was responsible for the study design and interpretation of data; revised the article critically; approved the final version to be published; and agreed to be accountable for all aspects of the work. C.J was responsible for the study design, acquisition of data, analysis, and interpretation of data; revised the article critically; approved the final version to be published; and agreed to be accountable for all aspects of the work.

References

[1] M. J. Rosen, A. Dhawan, and S. A. Saeed, "Inflammatory bowel disease in children and adolescents," *JAMA Pediatrics*, vol. 169, no. 11, pp. 1053–1060, 2015.

[2] E. Bequet, H. Sarter, M. Fumery et al., "Incidence and phenotype at diagnosis of very-early-onset compared with later-onset paediatric inflammatory bowel disease: a population-based study [1988-2011]," *Journal of Crohn's & Colitis*, vol. 11, no. 5, pp. 519–526, 2017.

[3] E. I. Benchimol, D. R. Mack, G. C. Nguyen et al., "Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease," *Gastroenterology*, vol. 147, no. 4, pp. 803–813.e7, 2014.

[4] J. Ouahed, E. Spencer, D. Kotlarz et al., "Very early onset inflammatory bowel disease: a clinical approach with a focus on the role of genetics and underlying immune deficiencies," *Inflammatory Bowel Diseases*, vol. 26, no. 6, pp. 820–842, 2020.

[5] J. R. Kelsen, M. A. Conrad, N. Dawany et al., "The unique disease course of children with very early onset-inflammatory bowel disease," *Inflammatory Bowel Diseases*, vol. 26, no. 6, pp. 909–918, 2020.

[6] B. Kerur, E. I. Benchimol, K. Fiedler et al., "Natural history of very early onset inflammatory bowel disease in North America: a retrospective cohort study," *Inflammatory Bowel Diseases*, vol. 27, no. 3, pp. 295–302, 2021.

[7] C. Nordenvall, O. Rosvall, M. Bottai et al., "Surgical treatment in childhood-onset inflammatory bowel disease-a nationwide register-based study of 4695 incident patients in Sweden 2002-2014," *Journal of Crohn's & Colitis*, vol. 12, no. 2, pp. 157–166, 2018.

[8] N. Gupta, A. G. Bostrom, B. S. Kirschner et al., "Presentation and disease course in early- compared to later-onset pediatric Crohn's disease," *The American Journal of Gastroenterology*, vol. 103, no. 8, pp. 2092–2098, 2008.

[9] ECCO Guidelines, https://www.ecco-ibd.eu/publications/ecco-guidelines-science/published-ecco-guidelines.html.

[10] Statistics Denmark, https://www.statbank.dk/statbank5a/default.asp?w=1920.

[11] J. C. Escher, "Inflammatory bowel disease in children and adolescents: recommendations for diagnosis - the Porto criteria," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 41, no. 1, pp. 1–7, 2005.

[12] A. Levine, A. Griffiths, J. Markowitz et al., "Pediatric Modification of the Montreal Classification for Inflammatory Bowel Disease : The Paris Classification," *Inflammatory Bowel Diseases*, vol. 17, no. 6, pp. 1314–1321, 2011.

[13] H. J. Loonen, A. M. Griffiths, M. P. Merkus, and H. H. F. Derkx, "A critical assessment of items on the pediatric Crohn's disease activity index," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 36, no. 1, pp. 90–95, 2003.

[14] D. Turner, A. R. Otley, D. Mack et al., "Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study," *Gastroenterology*, vol. 133, no. 2, pp. 423–432, 2007.

[15] D. Turner, J. Hyams, J. Markowitz et al., "Appraisal of the pediatric ulcerative colitis activity index (PUCAI)," *Inflammatory Bowel Diseases*, vol. 15, no. 8, pp. 1218–1223, 2009.

[16] M. Malham, C. Jakobsen, M. K. Vester-Andersen et al., "Paediatric onset inflammatory bowel disease is a distinct and aggressive phenotype—a comparative population-based study," *GastroHep.*, vol. 1, no. 6, pp. 266–273, 2019.

[17] C. Jakobsen, A. Paerregaard, P. Munkholm, and V. Wewer, "Paediatric inflammatory bowel disease during a 44-year period in Copenhagen County: occurrence, course and prognosis - a population-based study from the Danish Crohn colitis database," *European Journal of Gastroenterology & Hepatology*, vol. 21, no. 11, pp. 1291–1301, 2009.

[18] C. Jakobsen, A. Paerregaard, P. Munkholm et al., "Pediatric inflammatory bowel disease: increasing incidence, decreasing surgery rate, and compromised nutritional status: a prospective population-based cohort study 2007-2009," *Inflammatory Bowel Diseases*, vol. 17, no. 12, pp. 2541–2550, 2011.

[19] M. Oliva-Hemker, S. Hutfless, E. S. Al Kazzi et al., "Clinical presentation and five-year therapeutic management of very early-onset inflammatory bowel disease in a large North American cohort," *The Journal of Pediatrics*, vol. 167, no. 3, pp. 527–532.e3, 2015.

[20] M. Aloi, P. Lionetti, A. Barabino et al., "Phenotype and disease course of early-onset pediatric inflammatory bowel disease," *Inflammatory Bowel Diseases*, vol. 20, no. 4, pp. 597–605, 2014.

[21] A. S. Day, A. S. Gulati, N. Patel, B. Boyle, K. T. Park, and S. A. Saeed, "The role of combination therapy in pediatric inflammatory bowel disease: a clinical report from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 66, no. 2, pp. 361–368, 2018.

[22] J. R. Kelsen, K. E. Sullivan, S. Rabizadeh et al., "North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition position paper on the evaluation and management for patients with very early-onset inflammatory bowel disease," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 70, no. 3, pp. 389–403, 2020.

[23] S. Fabiszewska, E. Derda, E. Szymanska, M. Osiecki, and J. Kierkus, "Safety and effectiveness of vedolizumab for the treatment of pediatric patients with very early onset inflammatory bowel diseases," *Journal of Clinical Medicine*, vol. 10, no. 13, p. 2997, 2021.

[24] T. Jess, J. Simonsen, K. T. Jorgensen, B. V. Pedersen, N. M. Nielsen, and M. Frisch, "Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years," *Gastroenterology*, vol. 143, no. 2, pp. 375–381.e1, 2012.

[25] L. Beaugerie and S. H. Itzkowitz, "Cancers complicating inflammatory bowel disease," *The New England Journal of Medicine*, vol. 372, no. 15, pp. 1441–1452, 2015.

[26] J. A. Eaden, K. R. Abrams, and J. F. Mayberry, "The risk of colorectal cancer in ulcerative colitis in a population-based setting," *Gastroenterology*, vol. 48, no. 4, p. 526, 2001.

[27] M. Malham, C. Jakobsen, A. Paerregaard, L. J. Virta, K. L. Kolho, and V. Wewer, "The incidence of cancer and mortality in paediatric onset inflammatory bowel disease in Denmark and Finland during a 23-year period: a population-based study," *Alimentary Pharmacology & Therapeutics*, vol. 50, no. 1, pp. 33–39, 2019.

[28] O. Olén, J. Askling, M. C. Sachs et al., "Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014," *BMJ*, vol. 358, article j3951, 2017.

[29] O. Atia, S. Harel, S. Greenfeld et al., "Risk of cancer in pediatric-onset inflammatory bowel diseases: a nation-wide study from the epi-IIRN," *SSRN Electronic Journal*, 2021.