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Long-term outcome of pediatric-onset Crohn's disease: a population-based cohort study

Mathurin Fumery[1], Benjamin Pariente[2], Helene Sarter[3,4], Guillaume Savoye[5], Claire Spyckerelle[6], Djamal Djeddi[7], Olivier Mouterde[8], Guillaume Bouguen[9], Delphine Ley[10], Anais Peneau[2], Jean-Louis Dupas[1], Dominique Turck[10], Corinne Gower-Rousseau[3,4] and Epimad Group*

[1] Gastroenterology Unit, Amiens University and Hospital, Université de Picardie Jules Verne, Amiens, France

[2] Gastroenterology Unit, Huriez Hospital, Université Lille Nord de France, Lille, France.

[3] Public Health, Epidemiology and Economic Health Unit, Epimad Registry, Maison Régionale de la Recherche Clinique, Université Lille Nord de France, Lille, France.

[4] Inserm, Lille University, LIRIC UMR 995, Team 5, France

[5] Gastroenterology Unit, Rouen University Hospital, Rouen, France

[6] Department of Pediatrics, St Vincent de Paul Hospital and Lille Catholic University, Lille, France.

[7] Department of Pediatrics, Amiens University Hospital, Amiens, France

[8] Department of Pediatrics, Rouen University Hospital, Rouen, France

[9] Gastroenterology Unit, Rennes University Hospital, Rennes, France

[10] Department of Pediatrics, Jeanne de Flandre Hospital, Université Lille Nord de France, Lille, France.

* *For author footnote see end of the article*

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Mathurin Fumery	Interpretation of data, drafting of the manuscript critical revision and approval of the final version of the manuscript
Benjamin Pariente	Drafting of the manuscript, critical revision and approval of the final version of the manuscript
Hélène Sarter	Statistical analysis and critical revision of the manuscript

Guillaume Savoye	Study design, and critical revision of the manuscript
Claire Spyckerelle	Study design, and critical revision of the manuscript
Djamal Djeddi	Study design, and critical revision of the manuscript
Olivier Mouterde	Study design, and critical revision of the manuscript
Guillaume Bouguen	Data collection and critical revision of the manuscript
Anais Peneau	Data collection and critical revision of the manuscript
Jean-Louis Dupas	Concept and study design, critical revision and approval of the final version of the manuscript
Dominique Turck:	Concept and study design, interpretation of data, drafting and critical revision of the manuscript and approval of the final version of the manuscript.
Corinne Gower-Rousseau:	Concept and study design, interpretation of data, drafting and critical revision of the manuscript and approval of the final version of the manuscript.

Abbreviations: CD, Crohn disease; IBD, Inflammatory bowel disease; CS, Corticosteroids; IS, immunosuppressants; SMR, Standardized mortality ratio; SIR, Standardized incidence ratio; GE, gastroenterologists

Corresponding author: Corinne Gower-Rousseau, MD, PhD
Public Health, Epidemiology and Economic Health Unit, Epimad Registry,
Maison Régionale de la Recherche Clinique
Boulevard Laguesse
CHU de Lille
CS 700001
59037 Lille cedex, France
E-mail: corinne.gower@chru-lille.fr
Phone: +33320445518

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Author footnote

Appendix: Andre JM, Antonietti M, Aoukli A, Armand A, Aroichane I, Aubet JP, Auxenfants E, Bankovski D, Barbry B, Bardoux N, Baron P, Baudet A, Bazin B, Bebahani A, Becqwort JP, Benet V, Benali H, Benguigui C, Ben Soussan E, Bental A, Berkelmans I, Bernet J, Bernou K, Bernou-Dron C, Bertot P, Biron N, Bismuth B, Bleuet M, Blondel F, Bohon F, Boniface E, Bonnière P, Bonvarlet E, Bonvarlet P, Boruchowicz A, Bostvironnois R, Boualit M, Bouche B, Boudaillez C, Bourgeaux C, Bourguet A, Bourienne A, Branche J, Bray G, Brazier F, Breban P, Brung-Lefebvre V, Bulois P, Burgiere P, Butel J, Canva JY, Canva-Delcambre V, Capron JP, Cardot F, Carpentier P, Cartier E, Cassar JF, Cassagnou M, Castex JF, Catala P, Cattan S, Catteau S, Caujolle B, Cayron G, Chandelier C, Chantre M, Charles J, Charneau T, Choteau A, Claerbout JF, Clergue PY, Coevoet H, Cohen G, Collet R, Colombel JF, Coopman S, Corvisart J, Cortot A, Couttenier F, Crinquette JF, Crombe V, Dadamessi I, Dapvril V, Davion T, Debas J, Degrave N, Dehont F, Delatre C, Delcenserie R, Delette O, Delgrange T, Delhoustal L, Delmotte JS, Deregnaucourt G, Descombes P, Desechalliers JP, Desmet P, Desreumaux P, Desseaux G, Desurmont P, Devienne A, Devouge E, Devred M, Devroux A, Dewailly A, Dharancy S, Djedir R, Dubois R, Dubuque C, Ducatillon P, Duclay J, Ducrocq B, Ducrot F, Ducrotte P, Dufilho J, Duhamel C, Dujardin D, Dupont F, Duranton Y, Duriez A, El Ayafi F, El Farisi M, Elie-Legrend MC, Evrard D, Evrard JP, Filoche B, Finet L, Flahaut M, Flamme C, Foissey D, Fournier P, Foutrein- Comes MC, Foutrein P, Fremond D, Frere T, Gallet P, Gamblin C, Ganga-Zandzou M, Geslin G, Gheyssens Y, Ghossini N, Ghrib S, Gilbert T, Gillet B, Godard D, Godard P, Godchaux JM, Godchaux R, Goria O, Gottrand F, Gower P, Grandmaison B, Guedon C, Guillard JF, Guillem L, Guillemot F, Guimberd D, Hanon D, Heckestweiller P, Hedde JP, Hellal H, Henneresse PE, Heyman B, Heraud M, Herve S, Hochain P, Houssin-Bailly L, Houcke P, Huguenin B, Iobagiu S, Ivanovic A, Janicki E, Jarry M, Jeu J, Jonas C, Katherin F, Kerleveo A, Khachfe A, Kiriakos A, Kiriakos J, Klein O, Kornhauser R, Koutsomanis D, Laberenne JE, Laffineur G, Lagarde M, Lannoy P, Lapchin J, Lapand M, Laude D, Leblanc R, Lecieux P, Leclerc N, Le Couteulx C, Ledent J, Lefebvre J, Legrand C, Le Grix A, Lelong P, Lenaerts C, Leplat A, Lepoutre-Dujardin E, Leroi H, Leroy MY, Lesage JP, Lesage X, Lesage J, Lescanne-Darchis I, Lescut J, Lescut D, Leurent B, Lhermie M, Lion A, Lisambert B, Loire F, Louf S, Louvet A, Luciani M, Lucidarme D, Lugand J, Macaigne O, Maetz D, Maillard D, Mancheron H, Manolache O,

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Abstract

Background: Pediatric-onset Crohn's disease (CD) may represent a more severe form of disease. The aim of this study was to describe long-term outcome and identify associated risk factors of complicated behavior in a large population-based pediatric-onset CD cohort.

Patients and methods: Cases included all patients recorded in the EPIMAD registry diagnosed with definite or probable CD between January 1988 and December 2004, under the age of 17 years at the time of diagnosis, with at least two years of follow-up.

Results: Five hundred and thirty-five patients were included. Median follow-up was 11.1 years [IQR, 7.3-15.0]. At the end of follow-up, 8% (n=44) of patients had pure ileal disease (L1), 8% (n=44) had pure colonic disease (L2), and 83% (n=439) had ileocolonic disease (L3). L4 disease and perianal disease were observed in 42% (n=227) and 16% (n=85) of patients, respectively. At the end of follow-up, 58% (n=308) of patients presented complicated disease behavior (B2, 39% and B3, 19%), and 42% (n=163) of patients with inflammatory behavior at diagnosis had evolved to complicated behavior. During follow-up, 86% of patients (n=466) received at least one course of corticosteroids, 67% (n=357) of patients had been exposed to immunosuppressants and 35% (n=187) of patients received at least one anti-TNF agent. Forty-three percent (n=230) of patients underwent at least one intestinal resection. The overall mortality rate was 0.93% and the SMR was 1.6 [0.5-3.8] (p=0.20). Five cancers were reported with a crude cancer incidence rate of 1.1% and an SIR of 3.3 [1.2-7.0] (p = 0.01). In a multivariate Cox model, ileal (HR, 1.87 [1.09 – 3.21], p=0.022) or ileocolonic (HR, 1.54 [1.01 – 2.34], p=0.042) and perianal lesions at diagnosis (HR, 1.81 [1.13- 2.89], p=0.013) were significantly associated with complicated behavior.

Conclusion: About 80% of patients with pediatric-onset CD presented extensive ileocolonic disease during follow-up. The majority of patients evolved to complicated behavior. Surgery, cancer and mortality were observed in 43%, 0.9% and 0.9% of patients, respectively.

Introduction

The incidence of pediatric Crohn's disease (CD) has increased over the last decade (1), and has even doubled among French adolescents since 1998. Pediatric-onset CD currently represents 10% to 25% of all incident cases (2,3). Pediatric-onset CD is often associated with a more severe disease course (4-6), leading to specific complications such as growth retardation, nutritional impairment (7), and a frequent need for surgery (8). Nevertheless, the cumulative probabilities of developing complicated behavior, bowel damage and requiring surgery among pediatric-onset CD patients have been poorly investigated in population-based cohorts. Immunosuppressants (IS) and anti-Tumor Necrosis Factor (TNF) agents are increasingly used to treat pediatric CD (4,9,10). In more recent population-based studies, 30 to 70% of children with CD were exposed to IS. Up to one-third of children diagnosed after 2000 were treated by anti-TNF (4,10-12). Only limited data are available concerning the long-term outcome of pediatric-onset CD patients in the era of biologics. The potential of IS and anti-TNF therapy to induce disease modification in pediatric-onset CD patients has yet to be determined at the population level.

We have previously described the natural history of pediatric-onset CD patients based on the EPIMAD registry that records all incident cases of inflammatory bowel disease (IBD) in Northern France since 1988 (4). The present study was designed to update the description of this cohort and provide information on long-term clinical outcome and long-term cumulative incidence of disease complications in the era of IS and biologics based on updated follow-up until 2009.

Patients and Methods

Patient population

Cases included all patients in the EPIMAD registry with a diagnosis of definite or probable (13) CD between January 1988 and December 2004, under the age of 17 years at the time of diagnosis. The study area was Northern France with 5,916,220 inhabitants according to the 2018 national population census, which represents 9.3% of French population, divided into four administrative areas: Nord (2,613,874 inhabitants), Pas-de-Calais (1,475,142), Somme (570,195) and Seine-Maritime (1,257,009). Only patients who were resident in the defined study area at the time of diagnosis of CD were included. The population under the age of 17 years in this region is distributed as follows: Nord: 593,837, Pas de Calais: 332,228, Somme: 115,969 and Seine-Maritime: 270,107, with a total of 1,312,141 children.

The EPIMAD registry methodology has been previously described in detail (13). Briefly, since 1988, eight interviewing physicians have collected data on all incident IBD patients diagnosed by all gastroenterologists (GE) of the area, regardless of their type of practice (private and/or public sector (n=262). Only patients who were resident in the defined study area at the time of diagnosis are included. Each GE reports all patients consulting for the first time for symptoms compatible with IBD. The interviewing physicians visit the GE's consulting office and collect data from the patient's charts by means of a standardized questionnaire for each new case. The main data collected were age, gender, year of diagnosis, interval between onset of symptoms and diagnosis, and clinical, radiological, endoscopic and histological findings at the time of diagnosis. A final diagnosis of IBD (including CD, ulcerative colitis and indeterminate colitis) is established by two GE experts and is recorded as definite, probable or possible, according to validated and previously published criteria (13). Only patients with definite or probable CD and follow-up ≥2 years were considered in the present study.

Data collection

Data were extracted from the files of adult and pediatric GE and hospital medical records and were collected by means of standardized questionnaires. All records were reviewed for accuracy and completeness and validated by the principal investigator

(CGR).

Description of variables

Data retrospectively collected at diagnosis and at last follow-up included age, gender, date of IBD diagnosis, time between onset of symptoms and diagnosis, CD location and disease behavior according to the Montreal classification (14). Perianal lesions included abscesses and/or fistulae. The following medications were recorded: 5-aminosalicylic acid (5-ASA; oral or topical); corticosteroids (CS) (oral, topical or intravenous); IS (azathioprine/6-mercaptopurine and/or methotrexate) and anti-tumor necrosis factor (anti-TNFα) including infliximab (IFX), adalimumab (ADA) and certolizumab. Patients were considered to be exposed when the medication (at least one prescription) was initiated at diagnosis or during follow-up and the cumulative duration of treatment was recorded. Efficacy or failure of medication and intolerance to treatment were considered at the end of follow-up. CS dependency was defined as continued therapy due to relapse upon reduction, preventing discontinuation of CS and resistance was defined as absence of regression of clinical symptoms. Success of IS therapy was defined as no or weak clinical activity at 3 months, defined as follows: no more than 4 bowel movements per day or blood/pus in the stools less than once daily, little or no abdominal pain less than once daily, no systemic symptoms (fever, weight loss), and no oral corticosteroid treatment. Primary and secondary failures were pooled in the analysis. Intolerance to IS was defined as the occurrence of adverse reactions leading to drug withdrawal. Anti-TNF efficacy was defined as no or only weak clinical activity at 8 weeks. Intolerance to anti-TNF was defined as the occurrence of adverse reactions leading to drug withdrawal. Surgery was restricted to intestinal resection, defined as small bowel resection, and partial or total colectomy that could be either subtotal colectomy with ileorectal anastomosis or with ileoanal anastomosis. Appendectomy, stricturoplasty and elective surgical treatment of anoperineal lesions were excluded. Death, neoplasia, and any conditions requiring hospitalization were also recorded. This study complied with the regulations and instructions established by the Comité National des Registres (approval No. 97107 and No. 983792).

Statistical analysis

Quantitative variables are expressed as median and interquartile ranges (Q1–Q3); qualitative variables are expressed as frequency and percentage. Cumulative probabilities (CP) and 95%CIs of each treatment, surgery and progression to complicated behavior were calculated by the Kaplan-Meier method. Risk factors for complicated behavior were identified by univariate Cox proportional hazards models. Parameters with a p value <0.2 in univariate analyses were introduced into Cox proportional hazards multivariable regression. Results area expressed as Hazard Ratio (HR) with the associated 95% confidence interval. Standardized mortality ratio (SMR) and standardized incidence ratio (SIR) and 95% CI were calculated. Only deaths and cancers occurring during follow-up were taken into account. Reference data were obtained from the French Network of population-based Cancer Registries (FRANCIM) and the regional death rate from National Institute of Statistics and Economic Studies (INSEE; http://www.insee.fr/). Data were analyzed with SAS software V.9.4 (SAS, Chicago, Illinois, USA). P values ≤0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics

From 1988 to 2004, 9,114 patients were diagnosed with inflammatory bowel disease; 724 (7.9%) of these patients were under the age of 17 years at diagnosis, including 535 patients with CD (74% of all pediatric cases), 160 patients with ulcerative colitis (22%), and 29 patients with indeterminate colitis (4%) with a minimum follow-up of 2 years. Among patients with CD, 290 were males and 245 were females (M/F sex ratio: 1.18). Median age at diagnosis was 14.5 years (Q1=12.1–Q3=16.1) and 9% (n=51) of patients were under the age of 10 years at diagnosis. Five hundred and thirty-five CD patients were followed at 31st December 2009 with a median follow-up of 11.1 years (7.3-15.0).

Evolution of CD location

At diagnosis, 13% (n=70) of patients had pure ileal disease (L1), 20% (n=104) had pure colonic disease (L2), and 67% (n=354) had ileocolonic disease (L3). At the end of follow-up, 8% (n=44) of patients had pure ileal disease (L1), 8% (n=44) had pure colonic disease (L2), and 83% (n=439) had ileocolonic disease (L3). Disease extension was reported in 47% of patients with pure ileal or pure colonic disease at diagnosis (**Figure 1**). Thirty-one percent of patients (n=167) had upper gastrointestinal involvement and 10% (n=52) had perianal disease at diagnosis. At the end of follow-up, L4 location and perineal disease were observed in 42% (n=227) and 16% (n=85) of patients, respectively.

Evolution of CD behavior

CD behavior at diagnosis was inflammatory (B1) in 73% (n=387), stricturing (B2) in 24% (n=126), and penetrating (B3) in 3% (n=19) of patients. At the end of follow-up, 58% (n=308) of patients presented complicated behavior (B2: 39% and B3: 19%), indicating that 42% (n=163) of patients had evolved from uncomplicated to complicated behavior (B2 or B3) (**Figure 2**). Median time to evolution from uncomplicated to complicated behavior was 4.1 years [2.2; 7.5] years. Cumulative probabilities of

progression to complicated behavior were 3% at 1 year, 24% at 5 years and 41% at 10 years (**Figure 3**). In multivariate analysis, sex, age, location at diagnosis, presence of extra intestinal manifestations, corticosteroid therapy were not associated with complicated behavior. Ileal CD (HR, 1.87 [1.09 – 3.21], p=0.022) or ileocolonic CD (HR, 1.54 [1.01 – 2.34], p=0.042) and perianal lesions at diagnosis (HR, [1.81 1.13- 2.89], p=0.013) were significantly associated with complicated behavior. (**Table 2)**.

Medications

During follow-up, 86.1% of patients (n=466) received at least one course of corticosteroid therapy; 42% (n=194) of these patients were steroid-dependent and 15% (n=70) were steroid-resistant at 1 year. At the end of follow-up, 67% (n=357) of patients had been exposed to IS therapy, including 66% of patients exposed to thiopurines (n=356) and 19% of patients exposed to methotrexate (n=102); 14% (n=51) experienced drug intolerance and 51% (n=181) experienced IS failure (35 patients experienced failure to both azathioprine and methotrexate). The cumulative probabilities of IS therapy were 22% at 1 year, 50% at 5 years, and 65% at 10 years. Thirty-five percent (n=187) of patients received at least one anti-TNF agent, including infliximab (n=171) and adalimumab (n=55); 14% (n=27) developed intolerance, and 24% (n=45) failed at least one anti-TNF. The cumulative probabilities of anti-TNF therapy were 2% at 1 year, 16% at 5 years, and 29% at 10 years.

Surgery

Two hundred thirty (43%) patients experienced a total of 333 intestinal surgical procedures, including ileocecal resection (n=162, 70%), small bowel resection (n=34, 15%), partial colectomy (n=16, 7%), subtotal colectomy with ileorectal anastomosis (n=16, 7%), total colectomy with ileoanal anastomosis (n=2, 1%). Perianal surgery was performed in 16% (n=85) of patients. The cumulative probabilities of surgery were 9% at 1 year, 30% at 5 years, and 43% at 10 years.

Extraintestinal manifestations

Extraintestinal manifestations were observed in 23.5% (n=126) of patients at diagnosis, including articular manifestations (11%, n=60), skin manifestations (n=86, 15.9%) and hepatobiliary (0.2%, n=1). At the end of follow-up, 29.8% (n=158) patients had developed *de novo* extraintestinal manifestations, including articular manifestations (22.6%, n=121), skin manifestations (13.6%, n=73), uveitis (1.2%, n=6) and hepatobiliary manifestations (0.4%, n=2).

Mortality and cancer

Five deaths were reported during follow-up, including two CD-related deaths: one ascending colon cancer in a 31-year-old woman and one case of multiple organ failure secondary to massive dehydration in a 20-year-old man with a stoma. The overall mortality rate was 0.93% and the SMR was 1.6 [0.5-3.8] (p=0.20). Five cancers were reported after a median disease duration of 15 [10-17] years: basal cell carcinoma (n=1), genital cancer (n=1), leukemia (n=1), cholangiocarcinoma (n=1), adenocarcinoma of the ascending colon (n=1). The crude cancer rate was 0.93%% and the SIR was 3.3 [1.2 to 7.0] (p = 0.01).

DISCUSSION

We report the largest population-based study of pediatric-onset CD cohort, including 535 patients with a median follow-up of 11 years. In this study, early-onset CD was characterized by an extensive phenotype, frequent and rapid progression to complicated behavior, and a high prevalence of extraintestinal manifestations.

As previously described in both population and referral center studies, and in both children (3-5,15) and adults (16,17), most patients presented inflammatory behavior at diagnosis. Only limited long-term data on behavior evolution in pediatric populations are available and population-based studies are needed. In the present study, we showed that two-third of patients presented complicated behavior after a median follow-up of 11 years and 42% of patients evolved from inflammatory to complicated behavior. Similar trends have been reported in adults with progression from inflammatory to complicated behavior in 43% of patients and complicated behavior in 70% of cases 10 years after diagnosis (16,17). In comparison, in the elderly-onset (>60 years) cohort of the EPIMAD registry, complicated behavior was observed in only 32% of patients at 15 years. Two recent studies observed no difference of prevalence of complicated disease behavior between children and adult-onset CD 10 years after diagnosis (9,18). In our cohort, the cumulative probability of evolution from inflammatory to complicated behavior 5 years after diagnosis was 24%. In adults, stricturing complications occurred after a median of 5.5 years and penetrating complications occurred after a median of 6 years (17). Direct comparison of these various reports is difficult because of different population sources, disease classifications and approaches to statistical analysis. Nevertheless, all these studies indicate that complicated behavior is a frequent and early evolution of pediatric CD. Very few data are available regarding location change during the course of CD in children. Two-thirds of patients had ileocolonic location at diagnosis. As previously described, an increased rate of patients with ileal and ileocolonic location was observed over time (19). At the end of follow-up, 83% of patients had ileal or ileocolonic location.

Despite the risk of growth retardation, most children in our population-based cohort received CS, similar to previously reported trends (21,22). Compared to adults, children

are more frequently exposed to steroids and experience higher rates of exposure and steroid dependency than previously reported in children (23,24). Most children (67%) in the present cohort received IS, a higher proportion to that previously reported by Pozler et al. (29%) and Turunen et al. (32%) (22). However, IS exposure in this cohort was similar to that reported by a French adult referral center (16). The first experiences with IFX in pediatric CD were reported in 2001 (26), but only limited long-term data on IFX therapy in the pediatric population are available (27). Although our study was mainly conducted before the widespread use of IFX, patients were followed until 2009. We observed a 10-year cumulative probability of IFX exposure of 29%, reflecting the severity of pediatric CD. Van Limberden et al. (5) also reported a high rate of exposure to IS and/or biologic therapy (90%) in their pediatric referral center study. Surgery rates in the present study were similar to those previously reported in pediatric population (22) and referral center studies (5, 10), with a 10-year cumulative probability of surgery of 43%.

The notion of disease modification in inflammatory bowel disease has recently been brought into the spotlight. Most data from disease modification studies have only evaluated the risk of surgery. To our knowledge, the impact of therapy on disease behavior in pediatric-onset CD is unknown. We did not observe any positive impact of medications on the risk of progression to complicated behavior. Various hypotheses can be proposed to explain these results: the majority of patients had severe disease; IS was initiated too late during the course of the disease. It has been reported that majority of surgery in pediatric patients were performed early in disease course, and that better response to therapy with early disease (29-31). Although IS are increasingly used early in the course of the disease, their effect on the risk of surgery also remains unclear, with conflicting results in the literature in adult CD patients. A meta-analysis of 30 population-based studies showed that the risk of surgery has decreased over the past six decades (32), but this decrease was observed prior to the widespread use of IS and the era of biologics. Cosnes et al. studied IS use between 1978 and 2002. Despite the increased exposure to IS, the cumulative risk of stricturing or penetrating complications and bowel resection remained unchanged (16). On the other hand, several authors have observed

a decreased rate of bowel resection over previous decades. Several authors have attributed the decrease in surgical rates to increased exposure to IS. In a Hungarian population-based cohort, a reduced rate of surgery was independently associated with earlier and increased use of AZA (33). However, non-medication-related factors may also explain the observed decrease in surgery: change of care from surgeons to gastroenterologists, earlier diagnosis, closer endoscopic follow-up, targeting mucosal healing or implementation of practice guidelines. More recently, two randomized controlled trials failed to demonstrate any disease-modifying effect of azathioprine in early CD (34,35). In adults, a recent meta-analysis summarized current data and reported that ant-TNFα agents reduce surgery rates compared to placebo in randomized controlled trials (36). Because our study was mainly conducted before the era of biologics, we could not evaluate the impact of anti-TNF therapy on the natural history of disease. This impact needs to be reassessed subsequently, when data from populations treated with scheduled biologics at an early phase of disease are available.

Some limitations of our study need to be acknowledged. Firstly, our work was mainly conducted before the introduction of scheduled anti-TNF treatments in pediatric CD. No data concerning administration, episodic or scheduled, are available in our study and the impact of scheduled anti-TNF therapy on the course of the disease may be underestimated. Secondly, we have already reported the natural history of pediatric-onset CD EPIMAD cohort (4). However, the present study represents an extension including 134 new CD cases with extended follow-up from 7 to 11 years. Based on prospective data collection from a large pediatric population diagnosed with CD according to well-defined criteria, with a median follow-up of 11 years, our data accurately reflect the course of CD in children and adolescents.

In conclusion, in this large population-based study of pediatric-onset CD cohort, about 80% of patients with pediatric-onset CD presented extensive ileocolonic disease during follow-up. The majority of patients evolved to complicated behavior, resulting in a high risk of surgery. Medications were not associated with a decreased risk of evolution to stricturing or penetrating phenotypes. Further long-term population-based studies are

necessary to more precisely determine the impact of new therapeutic strategies on the natural history of pediatric-onset IBD.

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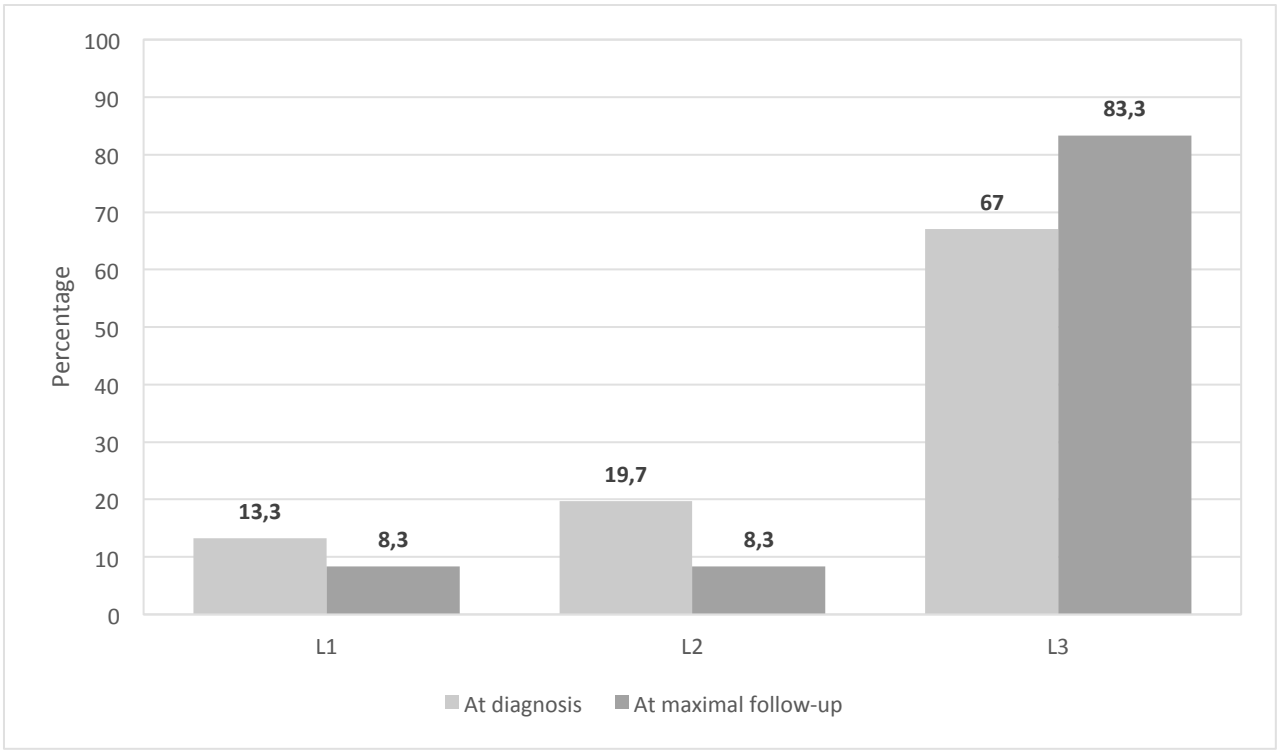
Table 1. Characteristics of the population (Crohn's disease, n=535) at diagnosis.

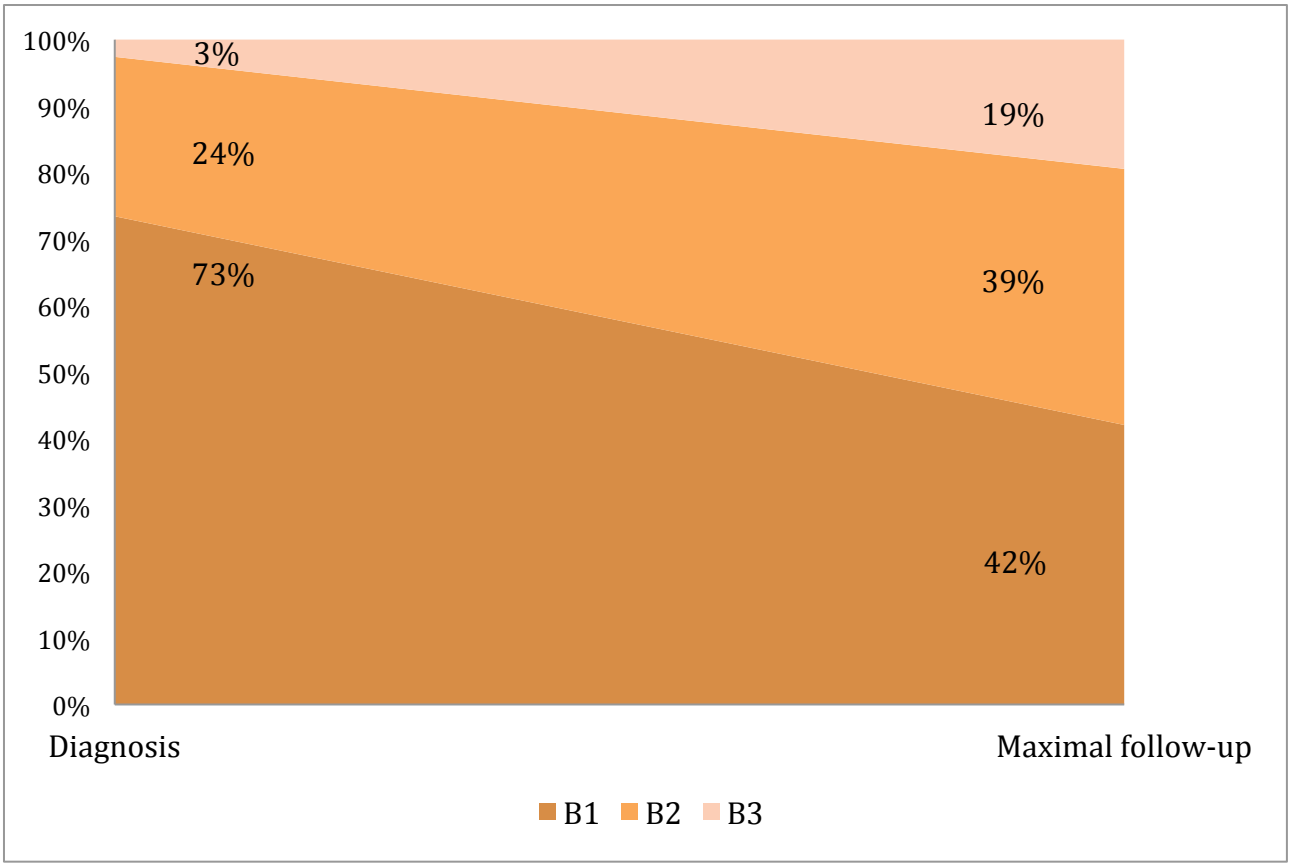
Table 2: Univariate and multivariate analysis of progression to a behaviour in 387 patients with B1 phenotype at diagnosis

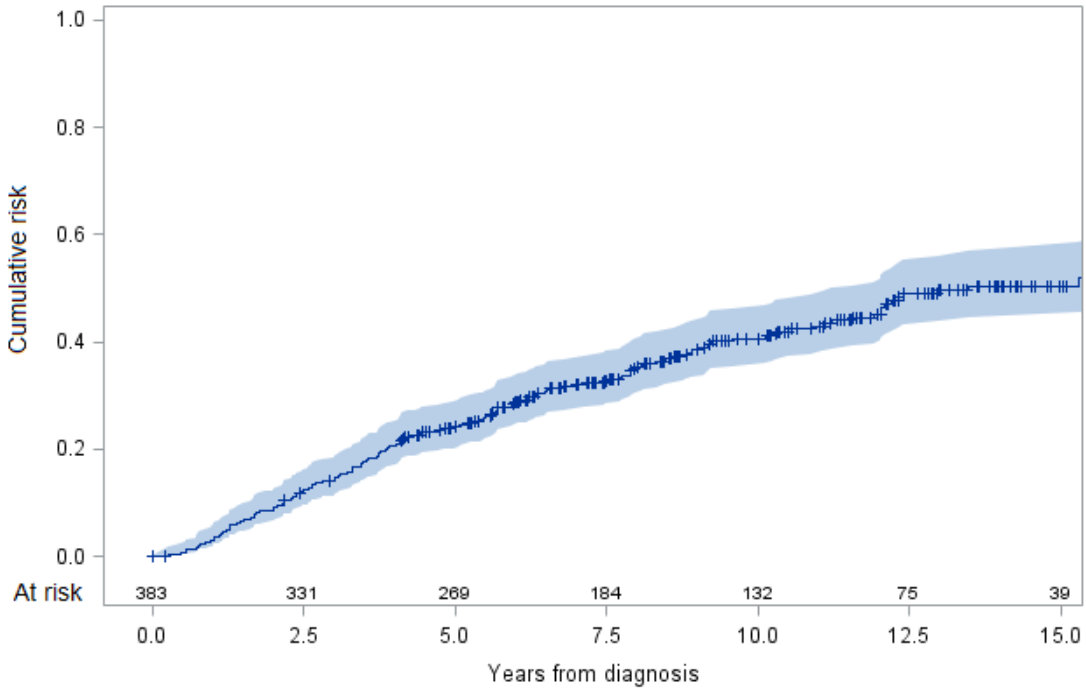
Figure 1. Crohn's disease location according to the Montreal classification at diagnosis and maximum follow-up in 535 pediatric patients with complete gastrointestinal investigation. L1, ileal location; L2, colonic location; L3, ileocolonic location

Figure 2. Cumulative probabilities of inflammatory (B1), stricturing (B2) and penetrating (B3) behavior in 535 patients with pediatric-onset Crohn's disease.

Figure 3: Cumulative probabilities of progression to complicated behavior (stricturing and penetrating) in 535 patients with pediatric-onset Crohn's disease


100
90
80
70
60
50
40
30
20
10
0
Percentage
13,3
8,3
19,7
8,3
67
83,3
L1
L2
L3
At diagnosis
At maximal follow-up


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
3%
24%
73%
19%
39%
42%
Diagnosis
Maximal follow-up
B1
B2
B3


1.0
0.8
0.6
0.4
0.2
0.0
Cumulative risk
At risk
383
331
269
184
132
75
39
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Years from diagnosis

	CD (n=535)
Median age at diagnostic [Q1-Q3] ***(years)***	14.5 [12.1-16.1]
Males (n, %)	290 (54%)
Median follow-up [Q1-Q3] ***(years)***	11,1 [7.3-15.0]
Location at diagnosis (n, %)	**L1 (ileal)** : 70 (13%)
	L2 (colonic) : 104 (20%)
	L3 (ileocolonic) : 354 (67%)
	L4 (upper digestive tract) : 167 (31%)
	Perianal: 52 (10%)
Behavior (n, %)	**B1 (inflammatory)** : 387 (73%)
	B2 (stricturing) : 126 (24%)
	B3 (penetrating) : 19 (3%)
Extra-digestive manifestation (n, %)	124, 23%

Table 1. Characteristics of the population (Crohn's disease, n=535) at diagnosis.

	Univariate analysis		Multivariable analysis	
	HR (IC 95%)	**p**	**HR (IC 95%)**	**p**
Male gender	0.93 [0.68 - 1.27]	0.662		
Age at diagnosis (under 10)	0.63 [0.37 - 1.07]	0.087	0.59 [0.33 - 1.05]	0.072
Extra-intestinal manifestations at diagnosis	0.96 [0.67 - 1.39]	0.836		
Localisation				
L1	1.68 [0.99 - 2.83]	0.054	1.87 [1.09 - 3.21]	0.022
L2	Ref			
L3	1.39 [0.92 - 2.09]	0.116	1.54 [1.01 - 2.34]	0.042
Upper gastrointestinal disease (L4)	1.05 [0.75 - 1.46]	0.774		
Anoperineal disease	1.46 [0.93 - 2.29]	0.100	**1.81 [1.13 - 2.89]**	0.013

Table 2 : Univariate and multivariable analysis of progression to a complicated behaviour in 387 patients B1 at diagnosis