Asymptomatic Inflammatory Bowel Disease Diagnosed During Colorectal Cancer Population Screening in Catalonia: Characteristics and Natural History

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INTRODUCTION: **Inflammatory bowel disease (IBD) is usually diagnosed when symptomatic. Prognosis and evolution of preclinical IBD is largely unknown. However, colorectal cancer screening programs (CRCSP) detect a subset of patients with IBD with no symptoms. The aim of this study was to describe the natural history of asymptomatic IBD diagnosed through CRCSP.**

METHODS: **An observational, longitudinal, and retrospective study was performed at 22 centers in Catalonia between January 2010 and December 2019 including patients with asymptomatic IBD detected in the CRCSP. Demographic data and IBD characteristics, evolution, and treatment were recorded. Descriptive statistics and Kaplan-Meier analysis were used for the analysis. Data were given separately for IBD, Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBDU).**

RESULTS: **One hundred eighty-eight patients were included: 103 UC (54.8%), 60 CD (31.9%), and 25 IBDU (13.3%). Sixty-six (35.1%) were women, and the average age was 59.9 ± 5.9 years. Sixty-four patients (34.0%) developed symptoms after a median follow-up of 35.6 months. Diarrhea was the most frequent symptom for CD and IBDU (25.4% and 11.5%, respectively) and blood in stools for UC (21.4%). The median time to first symptom was 11.6 months. Treatment was prescribed in 135 patients (72.2%); mesalazine was the most prescribed drug (123 patients; 65.4%). Thirteen patients (6.9%) required biological treatment. None underwent surgery.**

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DISCUSSION: **Around one-third of asymptomatic patients with IBD developed symptoms after a medium follow-up of 3 years. Only 6.9% required biological treatment, and none required surgery. Overall, prognosis of asymptomatic IBD seems better.**

KEYWORDS: inflammatory bowel disease; Crohn's disease; ulcerative colitis; screening; asymptomatic

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic intestinal disorder causing inflammation of the gastrointestinal tract. It is categorized as Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified (IBDU) (1). IBD affects more than 5 million people worldwide and is considered a global disease with progressively increasing incidence and prevalence (2–4). Its peak incidence is between the ages of 20 and 39 years, and a second peak appears between ages 50–70 years (5–7).

IBD is frequently a progressive illness which may present complications requiring surgery or hospitalization (8). The diagnosis is confirmed by endoscopic and histologic findings (9,10). As its initial manifestations are often nonspecific, IBD diagnosis is often delayed for months. Chronic inflammation in IBD may cause strictures, fistulas, or abscesses that could result in irreversible bowel damage. Twelve per cent of patients with CD will require surgery within 5 years of diagnosis and 16% within 10 years (11). Elderly patients usually have a milder course and a slow disease progression but require more frequent hospitalization than younger patients, often related to the increased prevalence of comorbidities (12,13).

Since 2000, the European Union has recommended population screening for colorectal cancer in asymptomatic individuals aged between 50 and 74 years (14). The Spanish National Health System implemented a colorectal cancer screening program (CRCSP) consisting a free biennial immunological fecal occult blood test (iFOBT) screening for people aged between 50 and 69 years (15). When the iFOBT is positive, a colonoscopy is performed. The CRCSP was implemented throughout Catalonia in 2015 (15), and in 2017; 43.6% of the population participated in the program (16,17).

Since the introduction of CRCSP, some patients have been incidentally diagnosed with IBD. Probably, these patients either are at a very initial phase of the disease or have an exceptionally mild condition. Detection of asymptomatic IBD may make it possible to determine the natural history of this group of patients.

It has been suggested that early treatment of IBD correlates with better outcomes (18). However, it is largely unknown whether subclinical chronic inflammation in asymptomatic patients could also progress to symptomatic disease or complications. It may be important to ascertain whether the benefits of aggressive early treatment in asymptomatic patients with IBD outweigh the risks.

The aim of this study was to describe the characteristics, natural history, and management of asymptomatic IBD diagnosed through the Catalan CRCSP between 2000 and 2019. The secondary aim was to determine the prevalence of the condition.

METHODS

Study design, participants, and database

Observational, multicenter retrospective cohort study was performed and reported in accordance with the STrengthening the Reporting OBservational studies in Epidemiology statement for reporting observational studies in epidemiology (19).

Patients were identified from the centralized Catalan CRCSP database. The CRCSP is aimed at women and men with average risk. Population colorectal cancer screening in asymptomatic individuals is conducted by performing an iFOBT every 2 years. Those individuals who test positive in iFOBT receive a recommendation for completing the study by performing a colonoscopy.

People with a history of colorectal cancer, colorectal polyps, or IBD are excluded from the screening program given that they require specific surveillance. Also omitted are people with a family history of colorectal cancer (at least 2 first-degree relatives affected or one first-degree relative diagnosed before the age of 50 years), with a terminal illness or severe disability that contraindicates colonoscopy, or with signs or symptoms suggestive of colorectal cancer. These individuals are referred for specific care.

All the 23 hospitals participating in the Catalan CRCSP were invited to join the study; finally, 22 hospitals provided patients. After identifying patients with suspected IBD in the screening colonoscopy at the CRCSP records, each participating hospital was asked to review the patients' medical records. Patients with a final alternative diagnosis, those who had received previous treatment with nonsteroidal anti-inflammatory drugs or those who did not fulfill the European Crohn's and Colitis Organization (ECCO) criteria for the diagnosis of IBD were excluded. In addition, patients who reported severe symptoms before the colonoscopy or those who were lost to follow-up were also excluded (20).

Data were collected from the clinical records of each participating center and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Asociación Española de Gastroenterología (www.aegastro.es) (21). The Asociación Española de Gastroenterología is a nonprofit scientific and medical society focused on gastroenterology, which provided this service with the sole aim of promoting independent investigator-driven research. REDCap is a secure web-based application designed to support data capture for research studies, providing (i) an intuitive interface for validated data entry, (ii) audit trails for tracking data manipulation and export procedures, (iii) automated export procedures for seamless data downloads to common statistical packages, and (iv) procedures for importing data from external sources (21). The data extraction template is available on reasonable request.

Study variables

The main objective was to analyze the characteristic symptoms developed and treatments prescribed to the patients diagnosed with IBD through the CRCSP. The prevalence of IBD was also assessed.

The clinical variables assessed included age and sex, fecal immunochemical test, date of the screening colonoscopy,

performance of ileoscopy, type of IBD (CD, UC, or IBDU), endoscopic findings, Montreal classification for CD and Mayo score for UC, and histological microscopic findings (including cryptitis, crypt abscesses, mucus depletion, presence of granuloma, and architectural pattern alteration). Histological diagnosis was categorized as *highly suggestive*—mainly CD showing cryptitis, abscess crypts, and granulomas or UC with extensive inflammatory changes, *compatible*—when some of the suggestive histological findings were found, and *nonspecific*. Medical history, smoking habit, previous abdominal surgeries and comorbidities, family history of IBD, extraintestinal manifestations (EIM), studies performed, laboratory tests, symptoms during follow-up and date of first symptom, treatments received, time to first treatment, and follow-up endoscopic results were also recorded. Hemoglobin (Hb), ferritin, and C-reactive protein values at the first visit were collected and standardized using normal values for each center.

Statistical methods

Categorical variables were given as natural frequencies and percentages, and quantitative variables were given as means and SDs (mean ± SD) or medians and interquartile ranges. Kaplan-Meier analysis was used to describe the time to first symptom. A 2-sided alpha level of 0.05 was considered statistically significant. We used SPSS V.25.0 (SPSS, Chicago, IL) to perform the statistical analysis.

Ethical issues

The research used retrospective anonymized data from the technical screening office of Catalonia and from the electronic clinical reports of the participating hospitals. Personal data were not retrieved, and personal identification was not possible once the patients' data were included in the REDCap study database.

Regulations of the Spanish Law 3/2018, of 5 December on the Protection of Personal Data were followed, both during the collection of data and in the analysis, as were the guarantee of digital rights and the provisions of European Regulation 679/2016. The study complied with the ethical guidelines of the Declaration of Helsinki (22).

The study was revised and approved by the local ethics committee of the Hospital Universitari Parc Taulí in Sabadell (CEIC 2021/5006) on February 15, 2021. The protocol was approved by the ethical committees of all participating centers. As the study used retrospective anonymized data and had no impact on patient evolution or treatment, the Ethics Committee waived the requirement for individual informed consent.

RESULTS

Between January 2000 and December 2019, a total of 2,040,865 patients were included in the Catalan CRCSP. Finally, 102,178 individuals underwent colonoscopy in 42 hospitals. In this period, 389 individuals (0.38% of those who underwent colonoscopy) were identified as potential IBD. Medical reports of these individuals were revised at each participating center, and those with alternative diagnoses or who did not fulfill the ECCO diagnostic criteria were excluded. After chart review, 226 (0.2% of those who underwent colonoscopy) patients were diagnosed with IBD. Of these IBD cases, 35 were excluded because they reported significant symptoms before the endoscopy, mainly severe abdominal pain or overt rectal bleeding. Three patients were excluded because they were followed up in private clinics after diagnosis, and clinical reports were not available for review. Finally, 188 patients were included in the analysis (59 CD, 103 UC, and 26 IBDU), representing 0.18% of all the patients included in the CRCSP (0.05% for CD, 1.01% for UC, and 0.03% for IBDU). A flowchart of the study is shown in Figure 1.

The mean follow-up was 35.6 month (range 1 month–9.7 years). Detailed data for CD, UC, and IBDU are presented separately in Table 1.

Patients' characteristics

The prevalence of IBD diagnosed through the CRCSP was 9.2 per 100,000 inhabitants screened with iFOBT (either positive or negative), and 184 per 100,000 colonoscopies were performed in the individuals with a positive iFOBT.

The mean age was 59.9 ± 5.9, and 35.1% (n = 66) of patients were women. The mean fecal immunotest value was 3,363 ± 19,049. Separate data for CD, UC, and IBDU are provided in Table 1.

Eight patients (4.3%) had a family history of IBD, and 35 (18.6%) had previous abdominal surgeries. Thirty-three (17.6%) were active smokers (see Table 1).

Disease characteristics were reported according to the Montreal classification. As screening begins at the age of 50 years, all patients with CD were in the A3 group (n = 59; 100%). Location was ileal (L1) in 21 patients (35.6%), colonic (L2) in 19 (32.2%) (n = 19), and ileocolonic (L3) also in 19 (32.2%). The behavior was inflammatory (B1) in 51 patients (86.4%) and stricturing (B2) in 8 (13.6%); no patients showed a penetrating pattern (B3). Three patients had perianal involvement (5.1%). Regarding UC, extension was proctitis (E1) in 48 patients (46.6%), left-sided colitis in 35 (34%), and pancolitis (E3) in 20 (19.4%).

Most frequent comorbidities were hypertension (n = 72; 38.7%), hypercholesterolemia (n = 43; 22.9%), cardiovascular disease (n = 23; 12.2%), diabetes (n = 22; 11.7%), and lung disease (n = 21; 11.2%) (see Table 1).

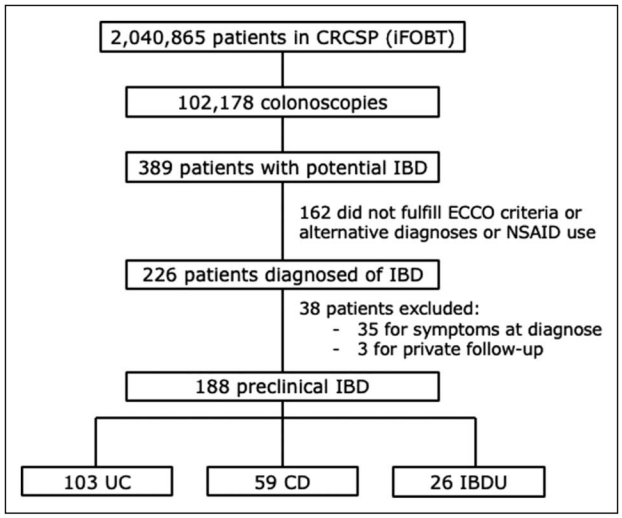

Figure 1. Flowchart of the study. CD, Crohn's disease; CRCSP, colorectal cancer screening programs; ECCO, European Crohn's and Colitis Organization; IBD, inflammatory bowel disease; IBDU, IBD unclassified; iFOBT, immunological fecal occult blood test; NSAID, nonsteroidal anti-inflammatory drugs; UC, ulcerative colitis.

Table 1. Patients' baseline characteristics

	IBD (n = 188)	CD (n = 59)	UC (n = 103)	IBDU (n = 26)
Mean age (yr) (mean ± SD)	59.9 ± 5.9	59.9 ± 6.6	59.9 ± 5.7	59.7 ± 5.7
Women (n, %)	66 (35.1%)	26 (44.1%)	31 (30.1%)	9 (34.6%)
Fecal immunochemical test (ng/mL) (nv < 100 ng/dL) (mean ± SD)	3,362 ± 19,049	958 ± 2,139	5,257 ± 25,540	1,319 ± 2,609
Family history of IBD (n, %)	8 (4.3%)	2 (3.4%)	5 (4.9%)	1 (3.8%)
Previous abdominal surgery (n, %)	35 (18.6%)	22 (13%)	18 (17.5%)	4 (15.4%)
Smokers (n, %)	33 (17.6%)	15 (25.4%)	12 (11.7%)	6 (24%)
Comorbidities (n, %)				
Arterial hypertension	72 (38.3%)	20 (33.9%)	45 (43.7%)	7 (26.9%)
Diabetes	22 (11.7%)	6 (10.2%)	10 (9.7%)	6 (23.1%)
Dyslipidemia	43 (22.9%)	14 (23.7%)	23 (22.3%)	6 (23.1%)
Cardiovascular disease	23 (12.2%)	5 (8.5%)	16 (15.5%)	2 (7.7%)
Lung disease	21 (11.2%)	8 (13.6%)	9 (8.7%)	4 (15.4%)
Rheumatological disease	13 (6.9%)	4 (6.8%)	3 (2.9%)	6 (23.1%)
Neurological disease	10 (5.3%)	6 (10.2%)	3 (2.9%)	1 (3.8%)
Endocrinology disease	8 (4.3%)	5 (8.5%)	1 (1%)	2 (7.7%)
Renal disease	6 (3.2%)	3 (5.1%)	3 (2.9%)	—
Oncological disease	5 (2.7%)	2 (3.4%)	2 (1.9%)	1 (3.8%)
Hepatic disease	5 (2.7%)	2 (3.4%)	1 (1.0%)	2 (7.7%)
Laboratory findings (mean ± SD) (n)				
Hb (g/L)	14.2 ± 1.4 (169)	14 ± 1.5 (56)	14.3 ± 1.5 (90)	14.4 ± 1.1 (23)
Ferritin (mg/dL)	127.1 ± 82.2 (68)	118.8 ± 63.8 (23)	134.2 ± 99.4 (37)	117.6 ± 22.5 (8)
CRP (mg/dL)	0.9 ± 1 (125)	0.8 ± 0.7 (39)	1 ± 1.2 (66)	0.9 ± 0.7 (20)
Calprotectin	367 ± 463 (60)	572 ± 646 (14)	292 ± 395 (37)	361 ± 320 (9)
Follow-up (d) (mean, range)	1,082.32 (29–3,568)	1,270.2 (44–3,568)	1,034.7 (64–3,501)	844.31 (29–2,783)

Data are given for IBD and separately for CD, UC, and IBDU.
CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.

Endoscopic findings

Ileoscopy was performed in 102 patients (54.3%). The severity of UC was evaluated using the Mayo score; 47 patients were rated as Mayo 1 (45.6%), 47 as Mayo 2 (45.6%), and 9 as Mayo 3 (8.8%). The severity of CD at diagnosis was mild to moderate for all patients; no endoscopic scores were provided.

The histological study was highly suggestive of IBD in 44 patients (23.4%), compatible in 105 (55.9%), and unspecific in 39 (20.7%). Alteration of the cellular architectural pattern and presence of cryptitis and crypt abscesses were the most frequent findings (see Table 2).

Laboratory findings

At diagnosis, the mean hemoglobin (Hb) score was analyzed in 169 patients with a result of 14.2 ± 1.4 g/L; ferritin was 127.1 ± 82.2 mg/dL (n = 68), C-reactive protein was 0.9 ± 1.0 mg/dL (n = 125), and calprotectin was 367 ± 463 (n = 60) (see Table 1).

Clinical follow-up

Sixty-four patients (34%) developed symptoms during the follow-up period. The most frequent was diarrhea in CD and IBDU (15 and 3 patients [25.4% and 11.5%], respectively) and blood in stools in UC in 22 patients (21.4%). Other less frequent symptoms were abdominal pain, rectal symptoms, weight loss, and anemia. Detailed data for CD, UC, and IBDU are presented in Table 3.

Time to first symptom was 11.6 months (range 1 month–10.2 years). Survival analysis showed significant statistical differences between IBDU and UC ($P = 0.039$) but no differences between UC and CD ($P = 0.27$) or between CD and IBDU ($P = 0.18$) (Table 3 and Figure 2).

Ten patients with CD (16.9%), one with UC (1.0%), and 3 with IBDU (11.5%) developed EIM (see Table 3).

Regarding additional diagnostic procedures during follow-up, 34 patients (18.1%) underwent abdominal magnetic resonance (MRI), 10 (5.3%) endoscopic capsule, and 10 (5.3%) gastroscopy (see Table 3).

Treatment

Treatment was prescribed in 136 patients (72.2%) with a mean time from diagnosis to prescription of 10.5 months (range 1 month–6.2 years).

The most prescribed drug was mesalazine (oral and/or topical), in 123 patients (65.4%), and the main reason for its prescription was endoscopic activity without symptoms in 107

Table 2. Histological characteristics

	IBD (n = 188)	CD (n = 59)	UC (n = 103)	IBDU (n = 26)
Histological diagnosis (n, %)				
Highly suggestive	44 (23.4%)	11 (18.6%)	32 (31.1%)	1 (3.8%)
Compatible	105 (55.9%)	34 (57.7%)	59 (57.3%)	12 (46.2%)
Nonspecific	39 (20.7%)	14 (23.7%)	12 (11.7%)	13 (50%)
Histological findings (n,%)				
Architectural pattern alteration	132 (70.2%)	41 (69.5%)	77 (74.8%)	14 (53.8%)
Cryptitis	118 (62.8%)	26 (44.1%)	79 (76.7%)	13 (50%)
Abscesses	99 (52.7%)	24 (49.7%)	62 (60.2%)	13 (50%)
Mucus depletion	43 (22.9%)	9 (15.3%)	26 (25.2%)	8 (30.8%)
Granuloma	8 (13.6%)	8 (13.6%)	—	—

Data are given for IBD and separately for CD, UC, and IBDU.
CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.

patients (56.9%), most of them with UC. Topical corticosteroids were prescribed in 18 patients (9.6%), systemic corticosteroids in 17 (9%), and azathioprine in 13 (6.9%). No patients received mercaptopurine or methotrexate. Thirteen (6.9%) required biological treatment. Anti-TNF were the most frequently prescribed agents, with infliximab being prescribed in 4 patients (2.1%) and adalimumab in 11 (5.9%), 2 of these after infliximab failure. One patient with CD received ustekinumab after adalimumab failure (0.5%). No patients required other biological drugs, Janus kinase inhibitors, or surgical treatment (see Table 3).

Endoscopic follow up

Fifty-seven patients (30.7%) underwent endoscopic follow-up (32.2% [n = 19] of patients with CD, 26.6% [n = 27] of UC, and 42.3% [n = 11] of IBDU) after a median time of 25.5 months (range 1.8 months–9.5 years). Clinical activity was the main reason for performing endoscopy.

At the end of follow-up, the Montreal classification for CD was modified in 5 patients (2.7%): one from colonic (L2) to ileocolonic location (L3), 2 developed a stricturing behavior (B2), and one developed a penetrating behavior (B3). Perianal disease appeared in 2 other patients. Extension of UC remained stable in all patients.

DISCUSSION

This study describes the prevalence, characteristics, and evolution of patients diagnosed preclinically with IBD during the CRCSP performed in Catalonia. As screening in our country starts at the age of 50 years, only patients of this age and above were included. The study showed that after a median follow-up of 3 years, most patients presented mild-to-moderate disease. Only a few required immunosuppressive or biological treatment, and none required surgery. These findings suggest that patients with IBD diagnosed during CRCSP represent a subgroup of patients with a relatively good prognosis.

This information is important because the delay between symptom onset and the treatment has been associated with poor outcomes and the need for surgery (23). Early treatment of IBD has been proposed as a tool to improve long-term outcomes (18,24). However, according to our data, the risk-benefit rate of early aggressive treatment in this particular subgroup of patients remains unclear. There may be several reasons for this: for instance, the older age of the patients may be related to the less aggressive behavior (13,25); equally, a delay in the diagnosis and treatment of a symptomatic patient is more serious than in a patient diagnosed when asymptomatic. Probably, the risk of complications is greater in the first case.

Preclinical diagnosis has not been feasible to date. Multiple groups have evaluated different biochemical markers for preclinical IBD, with limited success (26–32). At present, these biochemical markers have little applicability in clinical practice and few patients with IBD are diagnosed today at preclinical stages, those who tend to be diagnosed during CRCSP. The prevalence of preclinical IBD detected during CRCSP is currently unknown; it varies widely from 0.02% to 3.7% of the colonoscopies performed, depending on the study and the geographical area (33–40). We found that 0.2% of colonoscopies performed were diagnostic of IBD, a rate within the previous range described.

The natural history of preclinical IBD diagnosed during CRCSP has been described in only a few studies, which have reported results similar to ours. Butcher et al found 20 asymptomatic preclinical patients with IBD during the UK CRCSP, conducted between 2007 and 2012. During the follow-up, only 7 patients became symptomatic, all of whom were treated with mesalazine (41). In Italy, Bezzio et al described 54 preclinical patients with IBD (40 CD and 14 UC) diagnosed through CRCSP between 2013 and 2019. After a mean follow-up of 26.8 months, treatment was started in 5 patients with CD (4 patients with mesalazine, 3 with topical steroids, one with systemic steroids, one with vedolizumab, and one with thiopurines). All 14 patients with UC received treatment with 5-ASA, 2 of whom required treatment escalation to infliximab and vedolizumab (42). In Spain, Rodríguez-Lago et al evaluated preclinical IBD in the Basque Country, identifying 110 patients with IBD (79 UC, 24 CD, and 7 IBDU). Forty patients (36%) developed symptoms during a median follow-up of 25 months. As in our study, the most frequent symptoms were rectal bleeding and diarrhea. Treatment was prescribed in 97 patients (88%); most of them received mesalazine even though they were asymptomatic (83 patients; 75%). At the end of the follow-up, 7 patients received immunosuppressive treatment, 2 patients anti-TNF, and 2 required surgery (38).

Agrawal et al reported in a meta-analysis that patients incidentally diagnosed of terminal ileitis presented a low rate of

Table 3. Follow-up of patients' characteristics

	IBD (n = 188)	CD (n = 59)	UC (n = 103)	IBDU (n = 26)
Symptoms (n, %)	64 (34%)	20 (33.9%)	40 (38.8%)	4 (15.4%)
Time to first symptom (mean, range)	11.6 (1 mo-10.2 yr)	10.7 (1 mo-4.6 yr)	12.1 (1.5 month-10.2 yr)	10.7 (2.3 month-1.67 yr)
Type of symptom (n, %)				
Diarrhea	39 (20.7%)	15 (25.4%)	21 (20.4%)	3 (11.5%)
Blood in stools	25 (13.3%)	3 (5.1%)	22 (21.4%)	—
Abdominal pain	14 (7.4%)	11 (18.6%)	2 (1.9%)	1 (3.8%)
Rectal symptoms	13 (6.9%)	2 (3.4%)	10 (9.7%)	—
Weight loss	2 (1.1%)	2 (3.4%)	—	1 (3.8%)
Anemia	5 (2.7%)	3 (5.1%)	2 (1.9%)	—
EIM (n, %)				
Rheumatological	10 (5.3%)	6 (10.2%)	1 (1.0%)	3 (11.5%)
Dermatological	4 (2.1%)	3 (5.1%)	—	1 (3.8%)
Ophthalmological	2 (1.1%)	1 (1.7%)	—	1 (3.8%)
Additional studies (n, %)				
MRI	34 (18.1%)	26 (44.1%)	2 (1.9%)	6 (23.1%)
Endoscopic capsule	10 (5.3%)	6 (10.2%)	2 (1.9%)	2 (7.7%)
Gastroscopy	10 (5.3%)	3 (5.1%)	5 (4.9%)	2 (7.7%)
Treatment prescribed (n, %)	135 (72.2%)	34 (57.6%)	90 (87.4%)	12 (46.2%)
Type of treatment (n, %)				
Mesalazine	123 (65.4%)	21 (35.6%)	84 (81.6%)	12 (46.2%)
Topical corticosteroids	18 (9.6%)	12 (20.3%)	6 (5.8%)	—
Systemic corticosteroids	17 (9%)	11 (18.6%)	6 (5.8%)	—
Azathioprine	13 (6.9%)	10 (16.9%)	3 (2.9%)	—
Inflixmab	4 (2.1%)	3 (5.1%)	1 (1%)	—
Adalimumab	11 (5.9%)	10 (16.9%)	1 (1%)	—
Ustekinumab	—	1 (1.7%)	—	—
Endoscopic follow-up (n, %)	57 (30.7%)	19 (32.2%)	27 (26.6%)	11 (42.3%)

Data are given for IBD and separately for CD, UC, and IBDU.
CD, Crohn's disease; EIM, extraintestinal manifestations; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.

progression to overt CD, recommending watchful waiting strategy (43). Other groups have identified patients with preclinical CD from databases not related to CRSCPs, with varying results. Esch et al identified 43 patients with asymptomatic CD, most of them already diagnosed with EIM. Thirty-one patients (72%) developed symptoms, and 10 (23.3%) required surgical treatment after a median follow-up of 46 months (range 2–109) (44). More recently, Grinman et al identified 60 patients with incidental diagnosis of CD from the electronic patient registry of the IBD Unit at Sheba Medical Center in Israel. The most frequent reason for the diagnostic exploration was CRCSP result, followed by iron deficiency (with or without anemia) or abdominal symptoms unrelated to IBD. Most patients did not receive treatment after diagnosis (n = 53; 88.3%), and, after a median follow-up of 4.5 years, only 5 of these patients (9.4%) experienced a flare (45).

To our knowledge, our study is the largest to date in numbers of patients (especially for CD) and has a long follow-up of 3 years on average. However, it has limitations. The first is its retrospective design. Recruitment for a prospective study would be extremely difficult due to the low incidence of preclinical diagnosis of IBD and the need for long-term follow-up; nevertheless, a prospective study analyzing the immunological characteristics of preclinical IBD is currently underway (EARLY study from GETECCU; NCT05698745). Second, there was a risk of both overestimation and underestimation of IBD incidence. To ensure a correct diagnosis of IBD, all patients were evaluated and their diagnoses were confirmed after the initial endoscopic findings. In addition, patients who did not fulfill the ECCO diagnostic criteria, those reporting nonsteroidal anti-inflammatory drugs use, and those with final alternative diagnoses were excluded. Nevertheless, given the retrospective and multicenter design of this study, we cannot absolutely rule out a few cases of IBD misdiagnosis. On the contrary, as ileoscopy was not routinely performed during CRCSP, the prevalence of ileal CD may be underestimated. In addition, biopsies of normal mucosa were not taken during the screening colonoscopy, and so, the prevalence of histological-only early IBD could not be analyzed. Finally, using strict ECCO diagnostic criteria to include the patients in the study

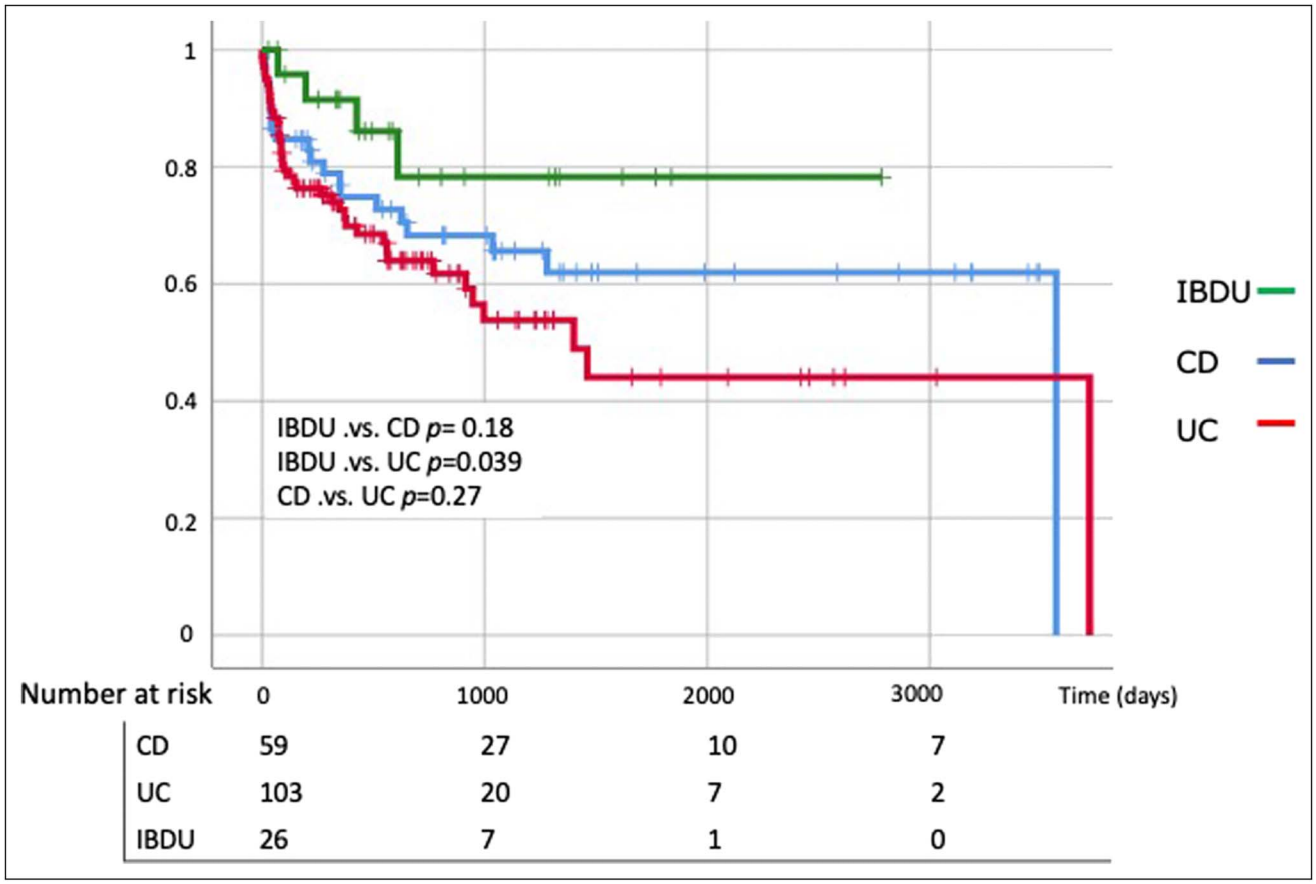

Figure 2. Time to first symptom for CD, UC, and IBDU. CD, Crohn's disease; IBD, inflammatory bowel disease; IBDU, IBD unclassified; UC, ulcerative colitis.

may have excluded a subgroup with very mild IBD who may not fulfill the diagnostic criteria for the disease.

In all, our study suggests that in this subgroup of patients with asymptomatic IBD, the course may be benign and that the risks and costs of early aggressive treatment may be not justified. Careful clinical follow-up (as in all other patients with IBD) may be enough for a large proportion of these individuals. Serial follow-up tests (either invasive or noninvasive) do not appear to be necessary when patients remain asymptomatic. More studies are needed to confirm this impression. In addition, characterizing the molecular reasons for this different behavior may provide further insights into IBD and may possibly help to guide new treatment approaches.

In conclusion, fewer than half of the patients diagnosed with IBD at the preclinical stage had developed symptoms after a medium follow-up of 35.6 months. Only 6.9% required biological treatment, and none required surgery. Overall, the prognosis seems milder than in the case of symptomatic patients with IBD, at least as far as the medium term. These data may justify a conservative approach to these patients.

CONFLICTS OF INTEREST

Guarantor of the article: Xavier Calvet, MD, PhD.

Specific author contributions: E.B.M. designed the study, analyzed data, and wrote the manuscript. E.B.M., A.S., F.B.-C., A.B., B.C., B.G., C.G., D.B., D.M., D.P.V., E.M., G.C., G.T., J.C.-P., J.L., L.G.-G., L.M.-M., M.G., M.E., G.T., S.T., V.R., P.G.-I. provided data. All authors critically reviewed the text and provided important intellectual content; all approve the submitted version.

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Study Highlights

WHAT IS KNOWN

- ✓ The natural history of preclinical inflammatory bowel disease is still unknown.
- ✓ It appears that this subtype of patients may have a better prognosis.

WHAT IS NEW HERE

- ✓ This is the largest cohort of patients with preclinical inflammatory bowel disease to date.
- ✓ Confirms previous theories about the natural history of this subtype of patients.
- ✓ These results should modify the follow-up and treatment of this subtype of patients.

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