ORIGINAL ARTICLE

IBD-PODCAST Spain: A Close Look at Current Daily Clinical Practice in IBD Management

P. Vega[1] · J. M. Huguet[2] · E. Gómez[3] · S. Rubio[4] · P. Suarez[5] · M. I. Vera[6] · J. M. Paredes[7] · A. Hernández-Camba[8] · R. Plaza[9] · M. Mañosa[10,17] · R. Pajares[11] · B. Sicilia[12] · L. Madero[13] · S. Kolterer[14] · C. Leitner[14] · T. Heatta-Speicher[14] · N. Michelena[14] · R. Santos de Lamadrid[14] · A. Dignass[15] · F. Gomollón[16]

Abstract

Background Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD) that contributes in part to irreversible bowel damage and long-term complications, reduced quality of life, invalidity, and economic burden. Suboptimal control of IBD is associated with higher healthcare resource utilization (HCRU), impaired quality of life (QoL), and reduced work productivity.

Aims The IBD-PODCAST study aimed to assess the proportion of IBD patients with suboptimal control and its associated impact.

Methods IBD-PODCAST is a cross-sectional, multicenter study that aimed to characterize the CD and UC population with optimal or suboptimal control according to the STRIDE-II criteria and patient- and physician-reported measures. Here we present the results of the Spanish cohort ($n = 396$).

Results A total of 104/196 (53.1%) CD and 83/200 (41.5%) UC patients were found to have suboptimal disease control. Long-term treatment targets according to STRIDE-II were applied in 172 (87.8%) CD and 181 (90.5%) UC patients. 125 of 172 (72.7%) CD and 74 of 181 (40.9%) UC patients were currently treated with targeted immunomodulators. Patients with CD and UC and suboptimal disease control showed impaired QoL, higher HCRU and direct costs, and also loss of work productivity compared to those with optimal control.

Conclusion Despite a high rate of targeted immunomodulator therapy, a substantial proportion of IBD patients show suboptimal disease control according to the STRIDE II criteria. Those patients with suboptimal disease control exhibit impaired QoL, less work productivity, and higher HCRU, suggesting that there is considerable need for better treatment approaches in IBD.

Keywords Crohn's disease · Ulcerative colitis · Inflammatory bowel diseases · STRIDE II recommendations · Treat to target strategy

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD) with intestinal symptoms such as abdominal pain, increased stool frequency and diarrhea, rectal bleeding, and urgency and often extraintestinal or general manifestations, such as fatigue, and different pathologies of joints, skin, liver, and eye in a substantial proportion of patients [1–6]. Although the worldwide prevalence of IBD varies across regions [7], in Europe approximately 2.5–3 million people are currently diagnosed of IBD [8] and prevalence is expected to reach 1% in most western countries by 2030 [9, 10], thus constituting a substantial public health issue.

For both CD and UC, the difficulties of disease management and monitoring and the limited efficacy and side effects of available treatments, lead to a suboptimal clinical control in many cases, with steroid overuse, accumulation of intestinal damage, and other serious long-term consequences [11, 12]. Furthermore, suboptimal control of IBD can negatively impact quality of life (QoL) [13], work productivity [14], and activities of daily living [15]. This is associated with a considerable psychosocial and economic burden [16, 17].

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To reduce this burden, clear and standardized definitions of treatment goals are needed, as well as strategies for monitoring and follow-up and therapeutic decision-guiding tools [18, 19].

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) was an International Organization for the Study of IBD (IOIBD) initiative to determine therapeutic goals for treat-to-target strategies in adults with IBD [20], and has been recently updated and improved including time-dependent treat-to-target strategies in Crohn's disease and UC (STRIDE-II) [20, 21]. STRIDE guidelines are based mainly on expert recommendations and need to be adapted to individual patients and local resources in a real-world setting, and thus clinical considerations may require decisions that vary from the suggested algorithm. STRIDE-II defined symptomatic (clinical) response as a short-term target, symptomatic remission and biochemical (CRP/fCal) normalization as intermediate targets, and endoscopic healing or mucosal healing, normalization of QoL, and absence of disability as long-term treatment targets while histological healing for UC and transmural healing for CD were considered as adjunctive goals [21]. In line with the STRIDE-II recommendations, the denominated treat-to-target strategy defines a treatment target and applies tight control to reach this target [22]. For instance, some studies in CD [19, 23–26] have investigated the "treat-to-target" approach and strong evidence was found in the CALM study supporting the value of objective markers of inflammation for therapeutic decision-making [27].

Conversely, in the recent study STARDUST [28] which compared symptom-based to treat-to-target management based on endoscopic findings, no difference in the endoscopic response was found. However, patients with a more severe disease phenotype at baseline achieved higher rates of endoscopic healing [28]. Overall, these data support the use of treat-to-targets in CD particularly in patients with a history of severe/complicated disease [28].

This approach is currently more established in the treatment of CD, but growing evidence supports its usefulness in UC [24].

With this background our goal was to evaluate the proportion of suboptimal disease control in a real-world clinical practice setting, the current use of objective disease monitoring tools and their impact on treatment decision-making. The Proportion of Inadequate Disease Control and Strategy of Treatment in IBD (IBD-PODCAST) study aimed to provide an overview of IBD management in several countries in the context of the STRIDE-II recommendations. Targets based on STRIDE-II were evaluated in patients with CD and UC to identify the proportion of patients with suboptimal control defined by the objective criteria such as clinical activity, elevated fecal calprotectin, or steroid overuse. Additionally, the impact of suboptimal control on QoL and

utilization of health care resources were also evaluated in this cross-sectional study in 14 Spanish hospitals.

Materials and Methods

Study Design and Patients

The IBD-PODCAST study was a cross-sectional, multicenter, non-interventional study of patients with IBD, which included a retrospective component (chart review). The study was conducted in ten countries, with a planned post-hoc multi-country data synthesis in the future. This is the data from the Spanish cohort. Sites were selected across Spanish administrative regions. A total of 14 hospitals participated in the study, with the involvement of more than 30 gastroenterologists with expertise in IBD. Patients were included in the study after giving informed consent that met legal and regulatory requirements according to the Declaration of Helsinki, Good Pharmacoepidemiology Practices, and applicable local regulations. Patients with IBD were recruited consecutively from February 24th, 2022, to June 10th, 2022, in concordance with the structures in place in the IBD units to avoid selection bias.

Inclusion criteria were as follows: (1) confirmed diagnosis (ECCO criteria) of CD or UC ≥ 1 year prior to enrollment, (2) age 19 years or older, (3) full medical documentation available for at least 12 months prior to recruitment, and (4) consent to participate in the study. Patients participating in interventional studies, with a diagnosis of unclassified IBD, or with a history of proctocolectomy were excluded.

"Red Flags" Defining Suboptimal Disease Control

In order to evaluate the degree of compliance with the STRIDE II recommendations, red flags for the identification of suboptimal disease control were defined by a steering committee composed of experts in IBD, based on a systematic review of the literature and interactive surveys of 89 International Organization for the Study of Inflammatory Bowel Diseases members, recommendations were drafted and modified in 2 surveys and 2 voting rounds. Consensus was reached if $\geq 75\%$ of participants scored the recommendation as 7 to 10 on a 10-point rating scale [21]. Several adjustments from the time-dependent treatment targets from the STRIDE II recommendations were made based on the clinical expertise from the steering committee and relevance, such as combining certain red flags, inclusion of steroid overuse (as an intermediate and long-term target) and inclusion of IBD or treatment-associated complications like anemia, clinically significant extraintestinal manifestations, perianal disease or adverse events requiring treatment interruption or termination (as long-term targets) (Table 1).

Table 1 Red flag definitions for the identification of for UC and CD based on STRIDE-II

Red flag[a]	Crohn's disease (CD)	Ulcerative colitis (UC)
Short-term red flag		
Failure to achieve clinically meaningful improvement	At the discretion of the physician (point of reference: <50% reduction of AP/SF since therapy initiation)	At the discretion of the physician (point of reference: <50% reduction of SF/RB criteria since therapy initiation)
Intermediate red flags		
Failure to achieve clinical remission*x	PRO-2 stool frequency score >3 OR PRO-2 abdominal pain score >1 OR Harvey-Bradshaw Index [50] >4	Mayo stool frequency subscore >0 OR Mayo rectal bleeding subscore >0
Failure to achieve CRP normalization*b	CRP>5 mg/dl#	CRP>5 mg/dl#
Failure to achieve sufficient fCal reduction*b	fCal>250 µg/g#	fCal>250 µg/g#
Systemic steroid overuse	Prolonged (>6 weeks) administration of prednisolone ≥10 mg/d (or equivalent) OR >1 steroid course under the current therapy within the previous 12 months	Prolonged (>6 weeks) administration of prednisolone ≥ 10 mg/d (or equivalent) OR >1 steroid course under the current therapy within the previous 12 months
Long-term red flags**		
Failure to achieve endoscopic remission	Endoscopic detection of ulcers and or inflammatory stenosis, fistula, or strictures§	Mayo score>0 or conclusion at the discretion of the investigator in case of no explicit scoring
Impaired quality of life	SIBDQ<50 points	SIBDQ<50 points
MR(E) or ultrasound findings indicative of active disease	At the discretion of the physician (examples: bowel wall thickening, inflammatory stenosis, contrast enhancement, abscess, fistula, free abdominal fluid)	At the discretion of the physician (examples: bowel wall thickening, inflammatory stenosis, contrast enhancement, free abdominal fluid)
CD/UC or treatment-associated complications	Anemia (Hb<11 g/dl for females, <12 g/dl for males), clinically significant extraintestinal manifestations***, perianal disease, adverse events requiring treatment interruption or termination	Anemia (Hb<11 g/dl for females, <12 g/dl for males), clinically significant extraintestinal manifestations, adverse events requiring treatment interruption or termination

AP/SF abdominal pain/stool frequency, *CRP* C-reactive protein, *fCal* fecal calprotectin, *Hb* hemoglobin, *PRO* patient-reported outcomes, *SIBDQ* short inflammatory bowel disease questionnaire, *SF/RB* stool frequency/rectal bleeding

[a] The specific red flags used in this study as well as their respective cut-off values were defined by a steering committee consisting of international IBD experts

[b] Abnormal fecal calprotectin (fCal) and C-reactive protein (CRP) led to classification of inadequate control only in combination with absence of clinical remission ^x

* To indicate inadequate compliance with STRIDE II recommendations both failures to achieve clinical remission and either CRP or fCal above the respective threshold must apply

** Intermediate red flags also apply

*** Clinically significant EIM defined as an EIM needing a specific therapy of its own or one that has an independent negative impact on the patient's well-being/QoL as judged by the physician

Values acceptable within 14 days of index date

Assessment of Optimal/Suboptimal Control

The analysis grouped patients into two categories: patients with no red flag, classified as optimal control and patients with red flag(s), classified as suboptimal control.

The presence of red flags was indicative of suboptimal disease control (Table 1).

Time (mean number of weeks) estimated for achieving the goal after starting treatment for CD and UC and specific red flags corresponding to short-, intermediate-, and long-term targets of STRIDE-II were applied, based on the duration of current treatment (Supplementary Table 1 and 2).

Treatments

Common current treatments for CD and UC included systemic steroids, budesonide, thiopurines, methotrexate (only CD), oral 5-ASA (only for UC), and targeted immunomodulators (TIM). TIM comprised of biologics and small molecules such as anti-tumor necrosis factor α (TNF) antibodies, anti-interleukin (IL) 12/IL23, and integrin antagonists, selective sphingosine-1-phosphate-receptor-1 (S1P1) modulator, and Janus kinase (JAK) inhibitors (Supplementary Table 2).

There is no universally accepted definition of steroid overuse. For this study, based on the ECCO criteria and the previous study of Selinger's group; the steering committee defined the steroid overuse as prolonged (> 6 weeks) administration of prednisolone ≥ 10 mg/d (or equivalent) or more than one systemic steroid course in current management within the previous 12 months (intermediate red flag). Steroid overuse was only counted as a red flag indicative of suboptimal control if: (1) the patient was in the intermediate or long-term treatment window, (2) the patient was classified as current steroid overuse, but treatment was not adjusted at index, or (3) despite the patient was classified as current steroid overuse, and treatment was adjusted, an additional course of steroids was administered [29, 30].

Data Collection

The study comprised a retrospective chart review, and a cross-sectional physician- and patient-completed evaluation. Patient-reported outcomes (PRO) and healthcare practitioner (HCP)-reported outcomes for disease control, health-related QoL, HCRU, work productivity, and monitoring procedures were collected at a single visit. Baseline patient and disease characteristics, objective red flags, inflammatory markers, and information on current treatment and adjustments were collected. The retrospective chart review comprised of the collection of data on HCRU within the last 12 months,

treatment history and initial occurrence of red flags from medical records. Outcome assessments were performed separately for CD and UC.

Outcomes

The primary, secondary objectives and the variables used are described in Supplementary Table 3.

The primary objectives were to estimate (1) the proportion of patients with suboptimal control at the index date for CD and UC by analyzing the presence of red flags, and (2) to describe disease burden on QoL [31].

Physician reported (i) achievement of clinically meaningful improvement since therapy to identify potential short-term red flag; (ii) perception of disease control to assess alignment with patient view and red-flag-based identification of suboptimal control. The assessment of QoL (long-term red flag) was collected during the initial interview where the short IBD questionnaire (SIBDQ) was used, with a cut-off score under 50 indicating impaired QoL (primary definition of suboptimal control) and scores under 45 indicating severely impaired QoL [32–35] (Supplementary Table 4). The impact on QoL was also assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) for the level of fatigue, in which higher scores (0–160) indicate a better QoL, and the IBD Disk tool [36]. Stool urgency was assessed in patients with UC by applying questions 3 and 4 from the validated tool Patient Simple Clinical Colitis Activity Index (pSCCAI) [37].

The secondary objectives were (1) to describe the characteristics of CD/UC patients with optimal control or suboptimal control, (2) to describe IBD monitoring in clinical practice using available results of tests performed, (3) to describe the economic burden of CD/UC of optimal control or suboptimal control, including HCRU, associated costs calculated from the eSalud cost database (Spanish healthcare database), and work productivity measured by the work productivity and activity impairment questionnaire (WPAI), and (4) to evaluate differences in patient-reported and HCP-reported disease activity, and red flag-indicated suboptimal control. The patient-reported disease activity was evaluated by patient perception of their disease control, the duration, and reasons behind their decisions (Supplementary Table 3). Similarly, physicians were asked on their evaluation of disease control of their patients. The aim was to describe the relationship between suboptimal control based on STRIDE II criteria, physician-reported and patient-reported evaluation.

Statistical Analyses

Since this is a descriptive study, the sample size is not based on a statistical power calculation but more on feasibility. In

total 400 subjects with IBD were planned to be included, with CD and UC being analyzed separately.

Baseline demographics and clinical variables were summarized as median or means, standard deviation (SD), and frequency data (proportion), as appropriate. The percentages of patients with suboptimal control and optimal control assessed by on red flags were depicted. Further exploratory analyses were performed in the overall population: Chi-squared (χ^2) or Fisher's exact tests were used for categorical variables. For quantitative variables two-sample t test or Mann–Whitney U tests were used to perform a pairwise comparison. Two-sided p value < 0.05 was considered statistically significant.

Results

Sociodemographic and Clinical Characteristics of the Study Population

In total, 396 patients (196 CD and 200 UC) from 14 Spanish centers were analyzed (Table 2). In the group of 196 CD patients, the mean (SD) HBI score at index was 1.4 (2.3) (Table 3). Active fistulizing and perianal disease status was documented in 27/196 (14%) patients. In the overall CD cohort, 23 (11.7%) showed fCal values > 250 µg/g and 25 (12.8%) showed CRP values > 0.5 mg/dl, but only 13/23 and 17/25 were classed as suboptimal control due to simultaneous failure to achieve clinical remission (Table 4). In the cohort of 200 UC patients, the mean index Mayo score was 0.6 (1.4) (Table 5). A total of 165 (82.5%) UC patients reported a normal stool frequency in the previous 3 days. In the overall UC cohort, 35 (17.5%) patients showed fCal values > 250 µg/g and 19 (9.5%) had CRP values > 0.5 mg/dl, but only 20/35 and 13/19 were classed as suboptimal control due to simultaneous failure to achieve clinical remission.

Most patients were in the long-term treatment window for both patients with CD (87.8%) and UC (90.5%) based on the duration of their current treatment (Table 3).

Suboptimal Control Assessment by Red Flags: Proportion of CD and UC Patients Not Optimally Controlled

Analyzing compliance with STRIDE II recommendations, suboptimal control was identified in 53.1% (104 of 196) patients with CD and in 41.5% (83 of 200) patients with UC (Fig. 1). The study shows higher prevalence of suboptimal control in female patients (Table 2) and as expected, disease severity regarding HBI score, Mayo score, and stool frequency was greater in patients with suboptimal control than with optimal control for both diseases (Table 3). Clinically significant extraintestinal manifestations (EIMs) were present in 30.8% (32/104) CD patients and 26.5% (22/83) UC patients with suboptimal control. The most reported clinically significant EIMs and comorbidities in both UC and CD at the index date are described in Table 3.

The red flag most frequently leading to the identification of suboptimal control in UC and CD was an SIBDQ score below 50 points followed by clinically significant complications or extraintestinal manifestations; in CD specifically, perianal disease; and in UC specifically, corticosteroid overuse (Table 4 and Supplementary Table 4). In long-term patients with CD, the 36.4% (36/99) of red flags were shared and overlapped with other red flags, specifically 60% (33/55) of patients with impaired QoL also had other red flags. In long-term patients with UC, 51.9% (41/79) of red flags were shared and overlapped with other red flags. In fact, 59% (33/56) of patients with impaired QoL also have other red flags.

In the analysis of the subgroup of patients presenting the SIBDQ red flag < 50 is summarized as follows. Patients with CD suboptimal disease control and with SIBDQ < 50 ($N = 58/196$) had a mean (SD) age of 47.8 (13.5) years old, a mean (SD) of disease duration of 15.2 (10.7) years, a mean of BMI (SD) of 27.2(5.2) kg/m², fCal means value (SD) of 850.4 (1494.9) µg/g and CRP means value (SD) of 1.0 (1.9) and 60% of them are treated with TIMs. The comorbidities more frequent in this subgroup of patients were dyslipidemia (12/58) and arterial hypertension (11/58).

For UC, patients with suboptimal control disease and SIBDQ < 50 ($N = 60/200$) had a mean (SD) age of 48 (13.8) years old, a mean (SD) of disease duration of 11.6 (9.2) years, a mean of BMI (SD) of 26.8(4.7) kg/m², fCal means value (SD) of 1362.2 (1349.2) µg/g and CRP means value (SD)of 2.2 (5) and 33% are treated with TIMs. The comorbidities more frequent in this subgroup of patients were dyslipidemia (9/60) and mental disorder (depression, anxiety) (7/60).

Treatments

Most patients in this study received TIM specific treatment: 170/196 (86.7%) CD patients and 187/200 (93.5%) UC patients. Specifically, 71.9% (141/196) of CD and 42.0% (84/200) of UC patients were treated with a TIM (Table 4). Of those, 69/104 (66%) were TIM experienced at the time of the visit in suboptimal control group in CD, and from those who were in maintenance phase, 32/53 (40%) of patients were already escalated, so 21/53 (60%) of patients present with a potential for TIM escalation. In UC, of those, 43/83 (52%) were TIM experienced at the time of the visit in suboptimal control group, 15/35 (43%) of patients were already escalated so 20/35 (57%) % of patients presents with a potential for TIM escalation (Fig. 2).

Table 2 Sociodemographic and clinical characteristics of the overall CD and UC study population (FAS) and suboptimal control and optimal control subgroups

Patient characteristics	Crohn's disease (FAS)		Ulcerative colitis (FAS)	
	Suboptimal control (N=104)	Optimal control (N=92)	Suboptimal control (N=83)	Optimal control (N=117)
Age at index (years)[a]				
Mean (SD)	47.8 (13.6)	50.6 (15.4)	48.7 (14.5)	50.6 (14.1)
Sex, n (%)				
Female	60 (57.7)	37 (40.2)	53 (63.9)	49 (41.9)
Male	44 (42.3)	55 (59.8)	30 (35.7)	68 (58.6)
BMI (kg/m²)				
N*	74	68	52	75
Mean (SD)	25.9 (5.1)	26.0 (5.2)	25.9 (4.7)	26.0 (4.1)
Age at diagnosis (years)[b]				
Mean (SD)	33.4 (13.24)	39.8 (17.1)	37.3 (13.7)	38.4 (13.5)
Duration of disease (years)[c]				
Mean (SD)	16.4 (10.0)	12.8 (8.3)	13.4 (8.9)	14.2 (9.2)
Active nicotine consumption, n (%)				
Yes	29 (27.9)	14 (15.2)	12 (14.5)	7 (6.0)
No or unknown	75 (72.1)	78 (84.9)	71 (85.5)	110 (94.0)
Treatment phase, n (%)				
Short-term	1 (0.9)	10 (10.8)	2 (2.4)	12 (10.3)
Intermediate-term	4 (3.9)	9 (9.7)	2 (2.4)	3(2.5)
Long-term	99 (95.2)	73 79.3)	79 (95.2)	102 (87.2)
Current CD/UC specific treatments, n (%)				
Yes	97 (93.3)	73 (79.3)	81 (97.6)	106 (90.6)
No	7 (6.7)	19 (20.7)	2 (2.4)	11 (9.4)
Current*, n (%)				
TIM[d,e]	69 (66.3)	52 (56.5)	43 (51.8)	36 (31)
First line	40 (38.5)	32 (34.8)	28 (33.7)	20 (17.1)
Second line	16 (15.4)	6 (6.5)	17 (20.5)	12 (10.3)
Third line or more	8 (7.7)	2 (2.2)	7 (8.4)	3 (2.6)
TIM naive[f]	44 (42.3)	29 (31.5)	65 (78.3)	89 (76.1)
Other	18 (12.5)	16 (17.4)	11 (16.)	24 (20.5)
Steroid overuse				
Current prednisolone used at ≥ 10 mg/d for > 6 weeks, n (%)[g]	2 (1.9)	0 (0.0)	1 (1.2)	2 (1.7)
Patient received more than one steroid course in the last 12 months, n (%)[h]				
Yes	13 (12.5)	3 (3.3)	24 (28.9)	5 (4.3)
No	91 (87.5)	89 (96.7)	59 (71.1)	112 (95.7)

Patients may be receiving TIM, non-TIM, and other treatments simultaneously. Data reflect patients who have at least one of the treatments on the index date

BMI body mass index, *CD* Crohn´s disease, *FAS* full analysis set, *HBI* Harvey Bradshaw index, *N* total number of patients in this group, *N** number of patients for whom information was available, *SD* standard deviation, *UC* ulcerative colitis

[a]Note: Age was based on index date and year of birth

[b]Year of diagnosis minus year of birth + 1, where year of birth = year of index minus – age at index

[c]Year of index minus year of diagnosis + 1[d] year of onset minus year of birth + 1

[d]Includes TIM first-time users, total number of patients with at least one TIM. Patients currently not on TIM but previously on TIM were 20 (10 in suboptimal control and 10 in optimal control) in CD and 5 (4 in suboptimal control and 1 in optimal control) in UC

[e]Includes anti-TNFs, vedolizumab, ustekinumab, tofacitinib

[f]TIM naive included: systemic steroids, budesonide, thiopurines, methotrexate (CD only), oral 5-ASA (UC only)

[g]Steroid overuse was not counted as a red flag indicative of suboptimal control if treatment was adjusted at index date

[h]Steroid overuse was not counted as a red flag indicative of suboptimal control if treatment was adjusted in the meantime due to steroid overuse, unless an additional course of steroids was given after treatment adjustment

Steroid overuse based current overuse and on the number of steroid courses in the past 12 months was identified in 16/196 (8.2%) patients with CD, and among 29/200 (14.5%) patients with UC.

Objective Disease Monitoring in Clinical Practice

Objective monitoring via biochemical markers, fCal and/or CRP and hemoglobin was assessed within ± 2 weeks of the index date. fCal was obtained in 88/196 (44.9%) patients with CD and 95/200 (47.5%) patients with UC, and CRP was determined in 112/196 (57.1%) CD and 87/200 (43.5%) in UC. At the current visit (index ± 8 weeks), imaging was performed in 12.2% (24/196) of CD and 12.5% (25/200) of patients with UC. Of those, endoscopy/colonoscopy was performed in 5.1% (10/196) of CD and 11% (22/200) of patients with UC. The use of biochemical markers, fCal and/or CRP, endoscopy and non-invasive techniques (MRE/MRI/IUS/CT) was limited, and the results should not be extrapolated to the entire population.

Annual Imaging and Assessments

Differences in monitoring practice were found between patients with CD and UC. The most frequent imaging techniques over the 12-month period was endoscopy/colonoscopy in both patients with CD (37/62; 59.7%) and UC (53/66; 80.3%), followed by IUS that was more frequently performed in CD than in UC patients (CD: 23/62 [37.1%] UC: 7/66 [10.6%]). MRI/MRE/CT was performed in 12/62 (19.4) CD and in 6/66 (9.1%) UC. Among patients with imaging performed, endoscopic findings indicating ulcers and/or inflammatory stenosis, fistulas, or strictures were observed in 17/62 (27.4%) CD and in 34/66 (51.5%) patients with UC. MRI/MRE or CT findings indicating active disease were observed in 6/62 (9.7%) patients with CD and in 2/66 (3%) with UC and IUS findings suggesting active disease were found in 12/62 (19.4%) CD and in 4/66 (6.1%) patients with UC.

Impact of UC and CD on QoL

The mean SIBDQ score in the overall CD population was 52.8 (11.82), with 33.2% of the patients showing impaired QoL (SIBDQ score < 50). These results were similar in UC patients (Fig. 3a and Table 5).

Mean SIBDQ scores were significantly lower among patients CD and UC with suboptimal control compared to those with optimal control (p < 0.001). Of the CD patients with suboptimal disease control, a significantly higher portion showed impaired QoL compared with optimal control (p < 0.001). Almost three-quarters of UC patients with suboptimal control showed a significantly impaired QoL compared to UC patients with optimal control (p < 0.001). Patients with suboptimal control also reported an impact on all individual SIBDQ items (p < 0.001; Fig. 3b).

The SIBDQ was used as a criterion for suboptimal control, but the impact of suboptimal control was also evaluated on other items of quality of life, including the IBD DISK, PSCCAI and FACIT in order to obtain more information on the burden of disease.

Correspondingly, CD and UC patients with suboptimal control reported significantly higher scores in the IBD Disk assessment, indicating worse QoL for all items, including items related to pain, joint pain, and abdominal pain, compared to those with optimal control (p < 0.05, Supplementary Fig. 1).

Assessment of stool urgency based on pSCCAI revealed that 64/200 (33.2%) UC patients were unable to hold their stool for at least 15 min or reported adjustments to their activities to ensure that there was a toilet nearby.

Finally, for the assessment of fatigue, patients with suboptimal control showed a significant impact on daily activities compared to those with optimal control (p < 0.001). The mean (SD) FACIT-F total score was significantly lower patients with suboptimal control than in those with optimal control in CD [112 (27.4) vs 132 (18.9), respectively; p < 0.001], and in UC [103.3 (26.7) vs 135.8 (14.4); p < 0.001)]. The FACIT-F score showed significantly better QoL in UC and CD patients with optimal control across all subcategories (p < 0.001) except for social/family well-being where no differences were observed in CD patients with optimal control or suboptimal control (p = 0.114).

Use of Health Care Resources

The mean (SD) number of outpatient visits during the 12 months prior to the index date was similar in CD patients with suboptimal control, and optimal control, whereas it was higher in UC patients with suboptimal control, compared to those with optimal control (Table 6). The proportion of patients with emergency department visits, hospitalizations, inpatient days and sick days was greater among both CD and UC patients with suboptimal control than with optimal control.

The mean annual healthcare-related direct cost was €1546.80 in CD patients and €1170.80 in UC patients. Average annual costs were substantially higher in both CD and

Table 3 Disease characteristics of the overall CD and UC study population (FAS) and suboptimal control and optimal control subgroups

Disease characteristics	Crohn's disease		Ulcerative colitis	
	Suboptimal control (N=104)	Optimal control (N=92)	Suboptimal control (N=83)	Optimal control (N=117)
HBI score (CD patients)				
Mean (SD)	2.1 (2.7)	0.6 (1.2)		
Mayo-Score (UC patients)			1.3(1.9)	0.2(0.6)
Mean (SD)			0.0(0.0–2.0)	0.0(0.0–0.0)
Number of liquid stools (on previous day to index date) (CD patients)	104	92		
Mean (SD)	1.1 (2.06)	0.4 (0.91)		
Level of abdominal pain (on previous day to index date) (CD patients), n (%)				
None	85 (81.7)	85 (92.4)		
Mild	13 (12.5)	6 (6.5)		
Moderate	4 (3.8)	1 (1.1)		
Severe	2 (1.9)	0 (0.0)		
Stool frequency per day (UC patients), n (%)				
Normal			53 (63.9)	112 (95.7)
1–2 stools more			15 (18.1)	2 (1.7)
3–4 stools more			11 (13.3)	2 (1.7)
>5 stools more			4 (4.8)	1 (0.9)
Laboratory markers				
Fecal calprotectin fCal>250 µg/g available n (%)	13 (12.5)	10 (10.9)	20 (24.1)	15(12.8)
C-reactive protein CRP>0.5 mg/dl or 5 mg/l available n (%)	17 (16.3)	8 (8.7)	13 (15.7)	6 (5.1)
Hemoglobin Anemia available n (%)	2 (1.9)	1 (1.1)	3 (3.6)	1 (0.9)
Extraintestinal manifestations, n (%)				
Yes[a]	32 (30.8)	2 (2.2)	22 (26.5)	2 (1.7)
Psoriasis	10 (9.6)	0 (0.0)	3 (3.6)	1 (0.9)
Peripheral arthritis	9 (8.7)	1 (1.1)	11 (13.3)	1 (0.9)
Axial arthritis	11 (10.6)	1 (1.1)	5 (6.0)	0 (0.0)
Current comorbidity, n (%)				
Yes[b]	56 (53.8)	46 (50.0)	43 (51.8)	53 (45.3)
No	48 (46.2)	46 (50.0)	40 (48.2)	64 (54.7)
Most frequent comorbidities, n (%)				
Arterial hypertension	18 (17.3)	10 (10.9)	13 (15.7)	19 (16.2)
Anemia	10 (9.6)	5 (5.4)	7 (8.4)	1 (0.9)
Dyslipidemia	17 (16.3)	10 (10.9)	13 (15.7)	16 (13.7)
Type 2 diabetes mellitus	10 (9.6)	4 (4.3)	9 (10.8)	10 (8.5)
Cardiovascular diseases	7 (6.7)	5 (5.4)	4 (4.8)	7 (6.0)
Mental disorder (depression, anxiety, substance abuse)	6 (5.8)	2 (2.2)	8 (9.6)	5 (4.3)

a Percentages may add to more than 100% as patients may be counted in more than one category

CD Crohn's disease, *FAS* full analysis set, *HBI* Harvey Bradshaw index, *SD* standard deviation, *UC* ulcerative colitis, *n* number of patients

*2 patients had selected 'active fistulas' in the HBI, but the HBI was below 5 and therefore excluded from suboptimal control

[a]Patients with at least one extraintestinal manifestation

[b]Patients with at least one current comorbidity

Table 4 Clinical characteristics and number of patients with red flags[a] of the overall CD and UC study population (FAS) and suboptimal control and optimal control subgroups

Number of patients, n (%)	Crohn's disease (N=104)	Ulcerative colitis (N=83)
Failure to achieve clinically meaningful improvement	7 (6.7)	12 (14.5)
Failure to achieve clinical remission and F3. Failure to achieve CRP normalization	5 (4.8)	9 (10.8)
Failure to achieve clinical remission and F4. Failure to achieve sufficient fCal reduction	6 (5.8)	14 (16.9)
Systemic steroid overuse	13 (12.5)	24 (28.9)
Failure to achieve endoscopic remission	2 (1.9)	12 (14.5)
Impaired quality of life, SIBDQ < 50 points	58 (55.8)	60 (72.3)
MRI or MRE (CD) and MRI or CT (UC) findings indicative of active disease	2 (1.9)	1 (1.2)
Ultrasound findings indicative of active disease	6 (5.8)	0 (0.0)
MRI/MRE, CT, or IUS findings indicative of active disease, n (%)	7 (6.8)	1 (1.2)
Failure to achieve inactive disease assessed via imaging (Endoscopy/colonoscopy, MRI/MRE/CT, IUS), n (%)	9 (8.7)	12 (14.5)
CD/UC or treatment-associated complications—anemia	4 (3.8)	4 (4.8)
CD /UC or treatment-associated complications—clinically significant extraintestinal manifestations	32 (30.8)	23 (27.7)
CD or treatment-associated complications—active fistulizing or perianal disease	27 (26.0)	0 (0.0)

CD Crohn's disease; CRP: C-reactive protein, *CT* computer tomography, *F* flag, *FAS* full analysis set, *fCal* fecal calprotectin, *MRE* magnetic resonance enterography, *MRI* magnetic resonance imaging, *SIBDQ* short inflammatory bowel disease questionnaire

[a]Percentages may add to more than 100% as patients may have more than one red flag. All red flags evaluated irrespective of phase

Table 5 Impact of CD and UC on patient's quality of life according to SIBDQ in the overall CD and UC study population (FAS) and long-term treatment phase in the CD and UC study population

SIBDQ score in overall population	Crohn's disease		Ulcerative colitis	
	Suboptimal control (N=104)	Optimal control (N=92)	Suboptimal control (N=83)	Optimal control (N=117)
n	102	91	83	113
Total score				
Mean (SD)*	47.3 (12.2)	58.9 (7.72)	43.2 (12.7)	60.5 (6.5)
SIBDQ with cut-off 50 n (%)				
Score (50–70 points)	44 (43.1)	85 (93.4)	23 (27.7)	108 (95.6)
Impaired, score (10–49 points)	58 (56.9)	6 (6.6)	60 (72.3)	5 (4.4)
SIBDQ long-term treatment phase	Suboptimal control (N=99)	Optimal control (N=73)	Suboptimal control (N=79)	Optimal control (N=102)
n	97	73	79	98
Total score				
Mean (SD)	47.3 (12.1)	60.4 (5.5)	43.7 (12.7)	61.3 (5.7)
SIBDQ with cut-off 50 n (%)				
Score (50–70 points)	42 (43.3)	73 (100)	23 (29.1)	98 (100)
Impaired, score (10–49 points)	55 (56.7)	0 (0)	56 (70.9)	0 (0.0)

SD standard deviation, *SIBDQ* short inflammatory bowel disease questionnaire, *UC* ulcerative colitis, *CD* Crohn's disease, *FAS* full analysis set, *N* total number of patients in this group, *n* number of patients who completed SIBD questionnaires;

*$p < 0.001$

UC patients with suboptimal control (Table 6). This difference was more pronounced in UC patients.

Work productivity assessment showed that 53.9% of CD patients with suboptimal control and 60.4% with optimal control were working at the index date, this difference was not statistically significant ($p > 0.05$). The mean (SD) WPAI results (Fig. 4) showed a higher mean work productivity loss score in CD patients with suboptimal control (19.9% [26.9]) than in those with optimal control (4.8% [10.7], $p < 0.05$). Regarding patients with UC, 53.7% with suboptimal control

Fig. 1 Proportion of patients with suboptimal and optimal control based on red flags according to STRIDE II

Crohn's disease (N=196)

46.9%

53.1%

Ulcerative colitis (N=200)

58.5%

41.5%

■ Suboptimal control ■ Optimal control
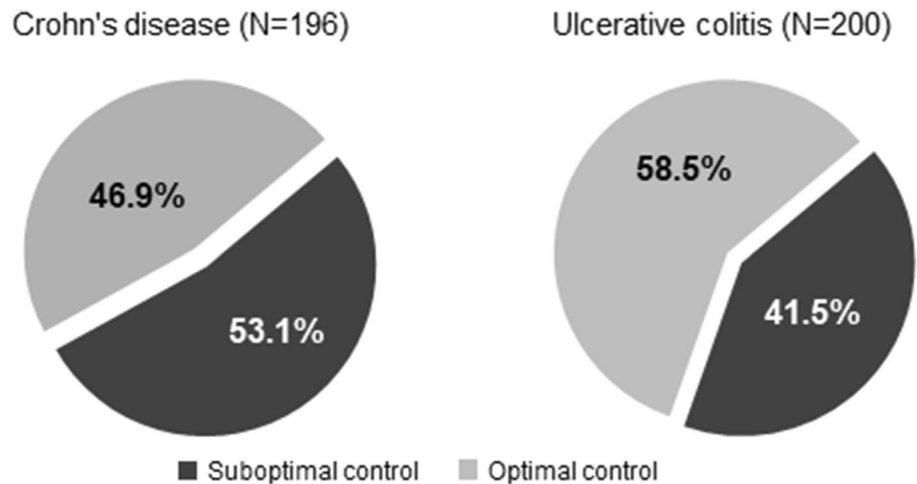
and 65.5% with optimal control were working at the index date ($p < 0.05$). The mean (SD) work productivity loss score in patients with UC was significantly higher in those with suboptimal control (25.5% [28.9]) compared to patients with optimal control (4.9% [11.4], $p < 0.001$).

The differences in mean (SD) scores for absenteeism, presenteeism, and activity impairment in CD were significantly higher in patients with suboptimal control (absenteeism: 5.4% [16.1], presenteeism: 18.5% [25.3], and activity impairment 32.5% [32]) compared to those with optimal control (absenteeism: 2.5% [14.1], presenteeism: 4.4% [9.9], and activity impairment 9.1% [19.6]; $p < 0.05$). Similarly for UC, the

differences in mean (SD) scores of absenteeism, presenteeism, and activity impairment were significantly higher in patients with suboptimal (absenteeism: 18.6% [37.6], presenteeism: 24.4% [28.5], and activity impairment 33% [33.4]) compared to those with optimal control (absenteeism: 0.3% [1.3], presenteeism: 4.6% [11.3], and activity impairment 5.6% [14.6]; $p < 0.05$) (Fig. 4).

HCP-Reported and Patient-Reported Disease Control Status

In addition to the identification of suboptimal control based on red flags (see Fig. 1), HCPs' and patients' perspective of disease control status were also collected. Taking all these evaluations into account, the total number of CD and UC patients with reported suboptimal control was 119/196 (60.7%) and 95/200 (47.5), respectively. Suboptimal control was reported by 26/196 (13.3%) CD patients and 28/200 (14.0%) UC patients, and by HCPs for 28/196 (14.3%) CD and 33/200 (16.5%) UC patients. Alignment between patient-reported and HCP-reported suboptimal control was found in only 12/42 (28.6%) CD and 16/45 (35.6%) UC patients. Suboptimal control suggests inadequate control of disease, however application of red flags based on STRIDE-II represents a more stringent and objective assessment of control of IBD. Alignment on the presence of suboptimal control based on the evaluations of red flags, patient-reported and HCP-reported suboptimal control was only observed in 9/120 (7.5%) CD patients and in 13/95 (13.7%) UC patients (Fig. 5). Sixteen CD patients (16/120; 13.3%) and 12 UC patients (12/95; 12.6%) were identified by either the patient or the physician, but not by the red flags.
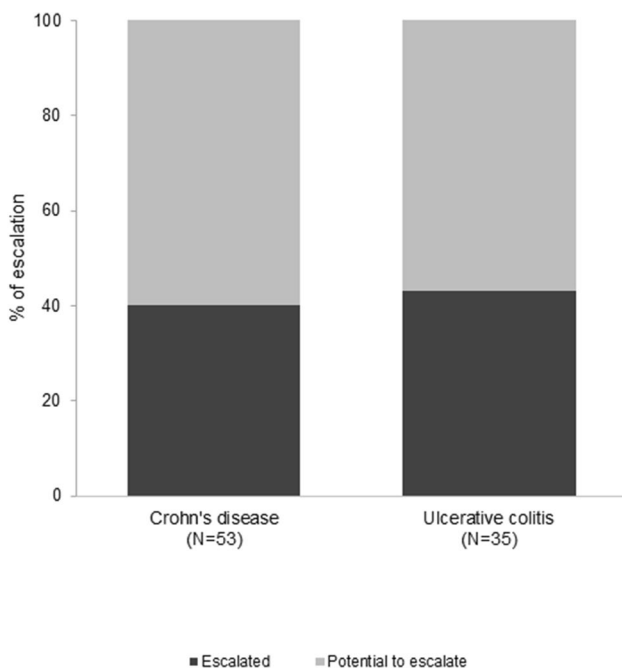
Fig. 2 Escalation of current TIM maintenance therapy of patients with suboptimal disease control in CD and UC. Already escalated: includes escalated TIM therapy only
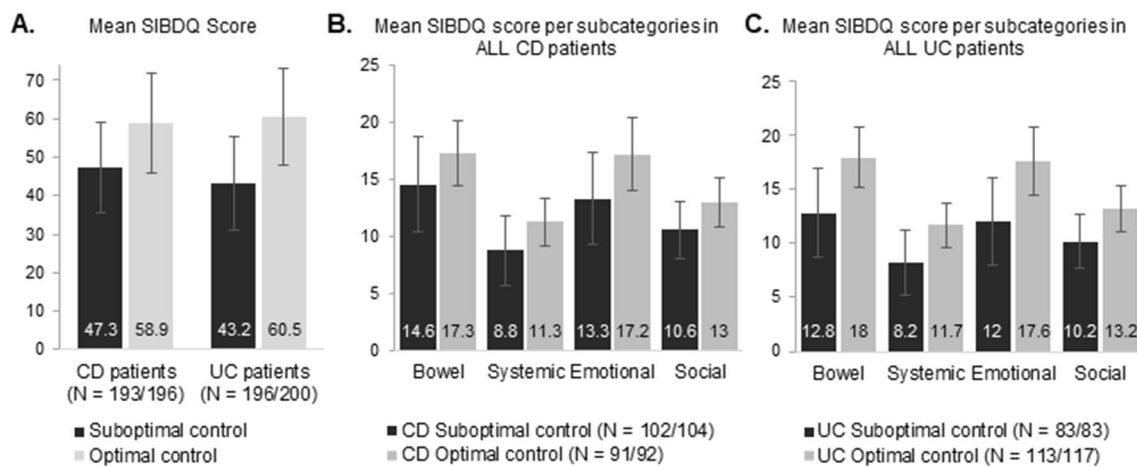
Fig. 3 **a** Short Inflammatory Bowel Disease Questionnaire (SIBDQ) Score in suboptimal control vs optimal control patients. Means and standard deviation were calculated based on total number (*N*) of patients defined as SOC by red flags. **b** Short Inflammatory Bowel Disease Questionnaire Sub Items (SIBDQ) Score in suboptimal vs optimal control of all patients. Means and standard deviation were calculated based on total number (*N*) of patients defined as suboptimal control by red flags

Discussion

This study provided a comprehensive overview of the burden of IBD in Spain within the CD and UC patient population in a real-world setting. This is the first study in a large population assessing the implementation of STRIDE-II recommendations in daily clinical practice by analyzing how IBD is monitored and treated, and if STRIDE-II targets are achieved in daily clinical practice.

We assessed, in addition, the impact of IBD suboptimal control on QoL, the associated costs and HCRU from the clinical records and the cross-sectional evaluation using standardized clinical questionnaires. This multicentric study recruited consecutive patients and shows a close approach to real-world evidence in Spain.

Objective assessments for IBD evaluation (endoscopic, radiologic, and analytical data) from daily clinical practice was only available in a limited number of patients. With this limitation, applying the concept of red flags derived from the STRIDE-II recommendations, approximately half of the patients presented suboptimal disease control.

It is conceivable that the availability of objective disease assessments across all patients of the study would have resulted in a higher percentage of suboptimal controlled disease.

The analysis of the SIBDQ obtained from the clinical questionnaires is the most prominent factor leading to identification of suboptimal control of most patients, but more than the 60% of patients in CD and 50% in UC with impaired QoL have other overlapping red flags. The fact that this questionnaire is collected in all patients may have influenced the results, this red flag being the most common one. Other red flags that led to identification of suboptimal control in IBD patients were the presence of EIMs and perianal disease in patients with CD, and steroid overuse specifically in patients with UC.

Our results of impaired QoL and lower FACIT-F score in suboptimal disease control are consistent with previous reports indicating that severe fatigue and poor QoL are associated with disease activity [38] and, furthermore, could be related to a significant psychosocial burden and reduced social functioning [39] because IBD patients might experience anxiety and depression among other symptoms. In addition, EIMs and perianal disease are associated with morbidity and impaired QoL and higher risk of surgery, leading to high use of health resources [40, 41].

This lack of control highlights the need for holistic monitoring, alternative and effective therapeutic options to improve treatment response rates and long-term treatment effects [42] in order to achieve the therapeutic targets of mucosal healing, normalization of QoL, and absence of disability in those patients with long-term treatments according to STRIDE-II recommendations [21].

Mucosal healing is an important treatment goal because it is associated with improved long-term outcomes [43]: higher rates of long-term clinical remission, and lower rates in hospitalizations, surgeries, and disease relapse [43, 44]. A large percentage of patients do not achieve mucosal healing in our cohort, so they are facing an increased risk of complications from disease progression and steroid overuse, even if treated with TIMs.

Although most of the patients are treated with TIMs, more than half of patients treated with TIM presented suboptimal disease control or failed to respond to treatment and steroid overuse is still high in both patients with CD and UC. The results, however, could be biased by the fact that

Table 6 Use of healthcare resources and total costs (FAS)

Patients with ≥ 1 visit 12 months prior to index	Crohn's disease		Ulcerative colitis	
	Suboptimal control (N = 104)	Optimal control (N = 92)	Suboptimal control (N = 83)	Optimal control (N = 117)
Outpatient visits (all)				
n (%)	103 (99.0)	90 (97.8)	81 (97.6)	107 (91.5)
Mean (SD)	5.1 (3.7)	4.6 (3.6)	6.9 (5.5)	4.0 (4.0)
No. of visits	513	419	571	471
Outpatient visits (elective)				
n (%)	102 (98.1)	84 (91.3)	78 (94.0)	103 (88.0)
Mean (SD)	4.6 (3.5)	3.9 (3.3)	5.8 (4.7)	3.4 (3.4)
No. of visits	3478	362	482	396
Emergency room visits				
n (%)				
Mean (SD)	11 (10.6)	5 (5.4)	14 (16.9)	6 (5.1)
No. of visits	0.1 (0.4)	0.1 (0.2)	0.2 (0.5)	0.1 (0.3)
	12	5	17	7
Hospitalization, all admissions				
n (%)	7 (6.7)	6 (6.5)	10 (12.0)	3 (2.6)
Mean (SD)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.0 (0.2)
No. of visits	9	7	10	3
Hospitalization, elective admissions				
n (%)	1 (1.0)	3 (3.3)	4 (4.8)	1 (0.9)
Mean (SD)	0.0 (0.1)	0.0 (0.3)	0.0 (0.21)	0.0 (0.09)
No. of visits	1	4	4	1
Hospitalization, non-elective admissions				
n (%)	6 (5.8)	3 (3.3)	6 (7.2)	2 (1.7)
Mean (SD)	0.1 (0.3)	0.0 (0.2)	0.1 (0.3)	0.0 (0.1)
No. of visits	8	3	6	2
Inpatient days				
No. of days	69	24	58	21
Mean (SD)	9.9 (6.8)	4.0 (3.2)	5.8 (3.4)	7.0 (3.5)
Patients with ≥ 1 surgery				
n (%)	2 (1.9)	3 (3.3)	0.0	0.0
Mean (SD)	0.0 (0.1)	0.0 (0.3)		
No. of surgeries	2	4		
Patients with ≥ 1 sick days				
n (%)	8 (7.7)	5 (5.4)	6 (7.2)	2 (1.7)
Mean (SD)	1.6 (8.0)	2.1 (11.1)	2.8 (20.0)	0.6 (5.7)
No. of sick days	165	189	229	72
Total annual costs[a]				
Mean (SD)	1612.6 (4371.7)	1472.3 (5461.9)	1944.8 (6874.4)	621.6 (2515.02)

CD Crohn's disease, *FAS* full analysis set, *N* total number of patients in this group, *SD* standard deviation, *UC* ulcerative colitis

[a]Total costs include outpatient visits, emergency room visits, hospital admissions, all surgeries, and sick days

TIM treated patients may have a more severe disease and probably started treatment later during the natural course of the disease.

Furthermore, limited disease monitoring by imaging may lead to undetected inflammation and absence of mucosal healing increasing the potential risk of disease-related complications [45, 46]. In addition, objective disease monitoring using non-invasive biomarkers such as fCal and/or CRP were obtained at a low rate in our cohort. The collection window within ± 14 days from index for lab-based monitoring by fCal and/or CRP may lead to underrepresentation of the monitoring of these biomarkers.
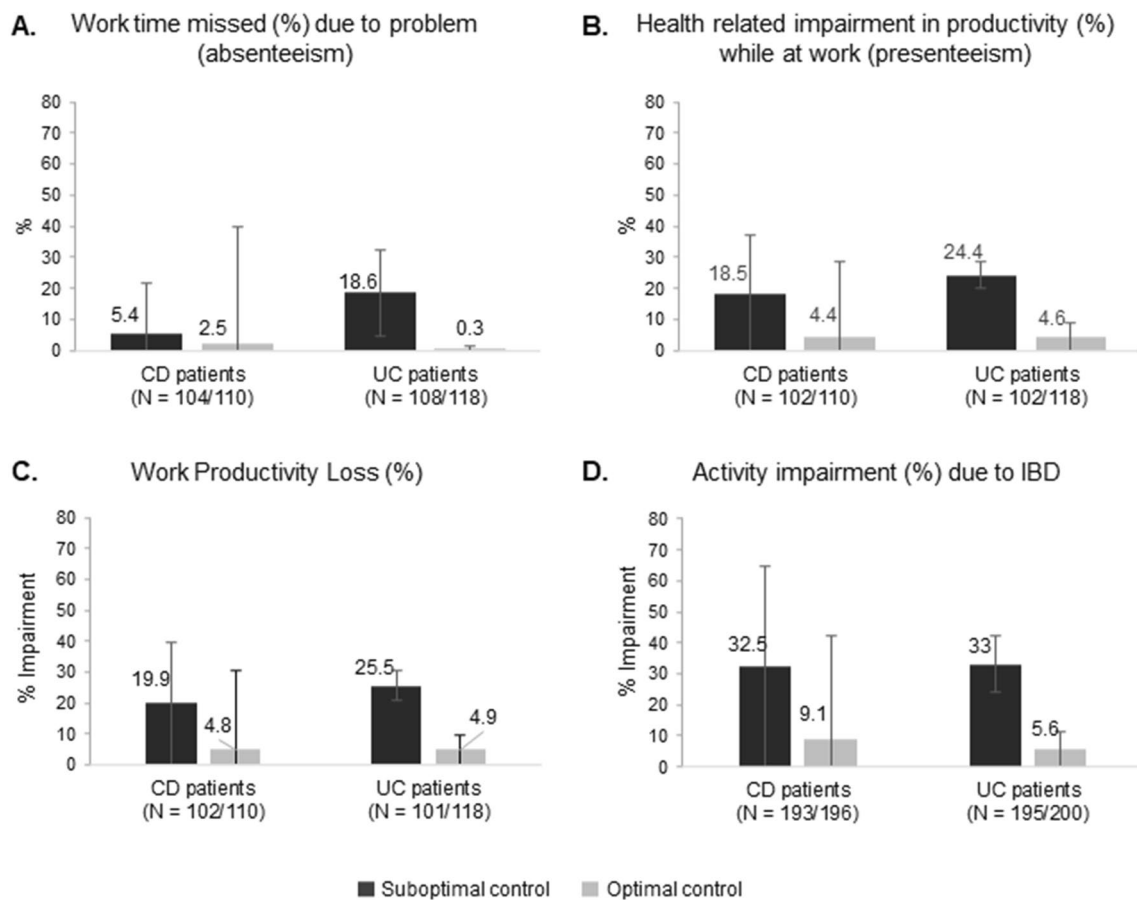
Fig. 4 Work productivity assessment using the Work Productivity and Activity Impairment (WPAI) questionnaire in suboptimal vs optimal control patients. Means and standard deviation were calculated based on total number (*N*) of patients defined as inadequately controlled by red flags. The differences in mean (SD) scores for absenteeism, presenteeism and working productivity loss in CD and UC patients were calculated based on the total number (*N*) of patients working at index date that completed this question in the questionnaire. Means and standard deviation for activity impairment were calculated based on the total number (*N*) of patients that completed this question in the questionnaire

In summary, this study has the limitations inherent of a cross-sectional observational study with a retrospective component. Selection bias was reduced as patients were included consecutively although it is likely that patients with poorer disease control are more likely to have more monitoring visits and may be overrepresented in this study population..In addition, potential biases due to patient-reported and HCP-reported disease evaluations have been minimized with the additional use of objective tools, such as red flags.

Hence, the implementation of objective disease monitoring and compliance with the adaptation of STRIDE-II recommendation remains challenging and should be improved, while more regular assessment of residual inflammation would result in earlier and broader detection of mucosal inflammation. More effective treatments are also needed to reduce mucosal inflammation and improve long-term outcomes.

As expected, in the study population, HCRU (outpatient, emergency visits, and hospitalizations) was higher in patients with suboptimal disease control.

Also, we found striking differences between the objective evaluation of disease control by red flags based on STRIDE-II compared to patient-reported and HCP-reported disease control in line with other studies [47]. Both patients and physicians reported suboptimal control less frequently than it was detected by objective assessment using the red flags. Limited alignment between HCP and patient-reported suboptimal control was also observed, potentially due to different emphasis in IBD care components between the groups, indicating the need for effective communication between patients and HCPs [48, 49].

Therefore, the use of objective criteria (such as the red flags based on STRIDE-II [21] may be more holistic and objective for the assessment of control disease status. Moreover, monitoring the presence of STRIDE-II red flags [19]
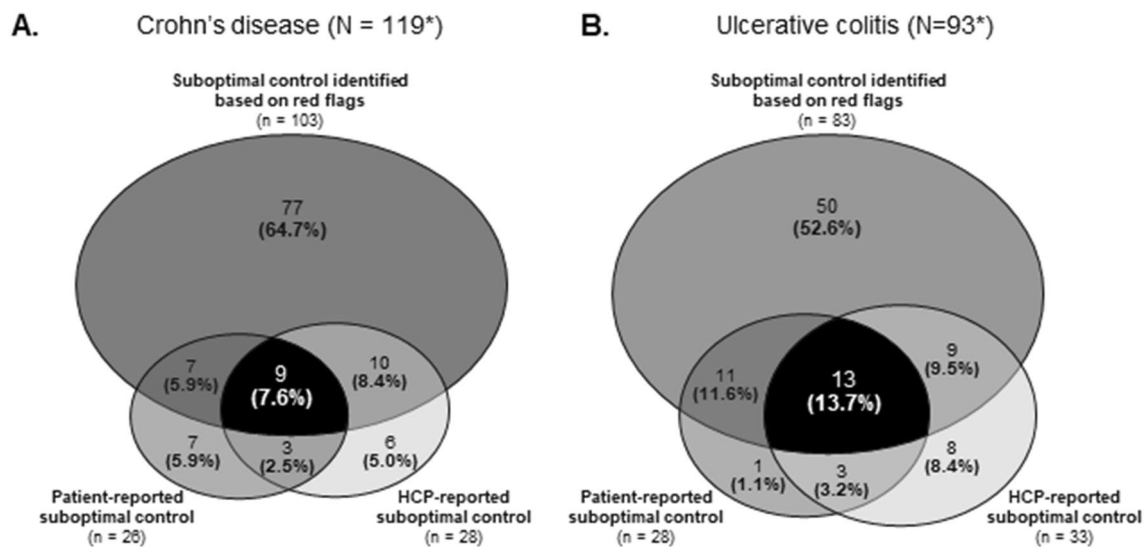
Fig. 5 Three-way Venn diagram of not optimal disease control based on patient view, HCP view, and based on red flags according to STRIDE II. **A** Crohn's disease (*N* = 119). **B** Ulcerative colitis (*N* = 95). Percentages (%) were calculated based on the total number (*N*) of patients defined as suboptimal control by either clinician, patient, or red flags

could ensure that treatment strategies are applied more effective, targets are met, and disease burden is minimized.

Conclusion

Despite the improvement in therapeutic options observed in the past 20 years, a considerable proportion of patients with IBD show suboptimal control. The negative impact on patients' QoL and daily and working lives is a concern for society, and which can have an impact on the overall economic and social cost of IBD.

This study shows that the use of STRIDE-II criteria is useful identifying suboptimal disease control and can help identify opportunities for improvement. The introduction of new alternatives and new therapeutic series should include a prospective assessment of their impact on improving QoL of patients with IBD.

Declarations

as speaker from Takeda and travel expenses from Takeda and Janssen. Míriam Mañosa has served as a speaker, consultant and advisory member for or has received research funding from AbbVie, Janssen, MSD, Pfizer, Galapagos, Faes-Farma, Takeda, Tillots. Beatriz Sicilia reports educational activities, investigational activities and scientific meetings or advisory boards sponsored by Abbvie, FAES, Chiesi, Dr. Falk, MSD, Tillots Pharma, Khern Pharma, Janssen, Pfizer y Takeda. Lucía Madero has received honoraria as speaker from Abbvie. Stefanie Kolterer was employee of AbbVie and is currently employee at GSK and may own stock/options. Tobias Heatta-Speicher, Claudia Leitner, Naiara Michelena, Regina Santos de Lamadrid are employees of AbbVie and may own stock/options. A. Dignass has received fees for participation in clinical trials and for review activities, such as data monitoring boards, statistical analysis and endpoint committees from Abivax, AbbVie, Arena, Celgene/Bristol Myers Squibb, Falk, Gilead, Janssen and Pfizer; consultancy fees from AbbVie, Amgen, Biogen, Boehringer-Ingelheim, Celgene/Bristol Myers Squibb, Celltrion, Falk, Ferring, Fresenius Kabi, Galapagos, Gilead, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Roche/Genentech, Sandoz/Hexal, Takeda, Tillotts and Vifor; and payment for lectures including service on speaker bureaus from AbbVie, Amgen, Biogen, Celltrion, Falk Foundation, Ferring, Gilead/Galapagos, Janssen, Lilly, MSD, Pharmacosmos, Pfizer, Takeda, Tillotts and Vifor. Fernando Gomollón has received honoraria as speaker from Janssen, AbbVie, Takeda and MSD; and participated in advisory panels for Faes-Farma and AbbVie.

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Authors and Affiliations

P. Vega[1] · J. M. Huguet[2] · E. Gómez[3] · S. Rubio[4] · P. Suarez[5] · M. I. Vera[6] · J. M. Paredes[7] · A. Hernández-Camba[8] · R. Plaza[9] · M. Mañosa[10,17] · R. Pajares[11] · B. Sicilia[12] · L. Madero[13] · S. Kolterer[14] · C. Leitner[14] · T. Heatta-Speicher[14] · N. Michelena[14] · R. Santos de Lamadrid[14] · A. Dignass[15] · F. Gomollón[16]

✉ F. Gomollón
fgomollo@unizar.es

1 Complejo Hospitalario Universitario de Ourense, Orense, Spain

2 Hospital General Universitario de Valencia, Valencia, Spain

3 Hospital Universitario Juan Ramon Jimenez, Huelva, Spain

4 Hospital Universitario de Navarra, Pamplona, Spain

5 Complejo Asistencial Universitario de León, León, Spain

6 Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

7 Hospital Universitario Dr. Peset, Valencia, Spain

8 Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

9 Hospital Universitario Infanta Leonor, Madrid, Spain

[10] HHospital Universitario Germans Trias i Pujol, Barcelona, Spain

[11] Hospital Universitario Infanta Sofía, Madrid, Spain

[12] Hospital Universitario de Burgos, Burgos, Spain

[13] Servicio de Medicina Digestiva, Hospital General de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain

[14] AbbVie Inc, North Chicago, IL, USA

[15] Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt am Main, Germany

[16] Hospital Clínico Universitario Lozano Blesa, IIS Aragón, Avda. San Juan Bosco, 15, 50009 Zaragoza, Spain

[17] CIBERehd, Madrid, Spain