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Alimentary Tract

Suboptimal disease control and contributing factors in Italian IBD patients: The IBD-PODCAST Study

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ABSTRACT

Background and Aim: Suboptimal disease control (SDC) and its contributing factors in IBD according to STRIDE-II criteria is unclear. IBD-PODCAST was a non-interventional, international, multicenter real-world study to assess this.

Methods: Data from the Italian IBD cohort (N=220) are presented here. Participants aged ≥19 with confirmed IBD diagnosis of ≥1 year were consecutively enrolled. A retrospective chart review and cross-sectional assessment by physicians and patients within the past 12 months were performed. SDC or optimal disease control was assessed using adapted STRIDE-II criteria.

Results: At the index date, 53.4 % of 116 CD patients and 49.0 % of 104 UC patients had SDC, mainly attributed to a Short Inflammatory Bowel Disease Questionnaire score <50, failure to achieve endoscopic remission, and the presence of active extra-intestinal manifestations in both diseases. Disease monitoring with imaging and/or endoscopy during the previous year was conducted in ~50 % of patients, with endoscopy performed in ~40 %. Potential therapeutic adjustments were reported for half of the patients.

Conclusions: This study highlights SDC in a significant portion of IBD Italian patients. These results emphasize the need for more proactive management strategies in both CD and UC patients.

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1. Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBD), affecting the gastrointestinal tract. Worldwide prevalence of IBD has risen in the past few decades, with Western Europe reporting UC prevalence ranging from 43.1 to 412.0 per 100,000 and 28.2–322.0 per 100,000 for CD [1–3]. UC primarily affects the rectum and colon, while CD can involve any gastrointestinal segment, causing symptoms like abdominal pain and bloody diarrhea. Both diseases can be associated with extraintestinal manifestations (EIMs) [4–6]. Suboptimal disease control (SDC), often due to treatment delays and limited drug effectiveness, can result in severe complications including hospitalization, surgery, and disability [1,2]. Complications for CD include strictures, fistulae, abscesses and cancer [7], while severe UC can lead to colon dilation, strictures [8], bleeding, toxic megacolon, perforation, and cancer [9]. Both may cause irreversible bowel damage and negatively impact upon quality of life (QoL), work and daily activities [1,10–12].

Extensive effort has been placed on the development of disease monitoring techniques and potential therapy decision-guiding tools such as laboratory markers or invasive and non-invasive techniques [13]. This goes along with the development of disease management recommendations advocating a treat-to-target (T2T) approach [14]. The recommendations of the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) initiative published by the International Organization for the Study of IBD (IOIBD) represent a key indication which has recently been updated (STRIDE-II) [15,16]. A central component of STRIDE-II is the definition of criteria, targets, and cut-off values to assess treatment success defining short-term, intermediate and long-term treatment targets for both CD and UC. These targets include clinical response, clinical remission, normalization of inflammatory markers, endoscopic healing and improved QoL [16]. The timing of reaching the targets is dependent on the specific treatment option and its onset of action, therefore, the duration since onset of treatment and assessment of target achievement was defined.

Initial medical treatment options vary by disease type, including corticosteroids (CS) for both diseases and aminosalicylates for UC [17]. Immunomodulators including thiopurines or methotrexate may follow as maintenance therapy. Current therapeutic algorithms introduce various targeted immunotherapies (TIMs, i.e. biologics and small molecules), with EMA-approved TIMs such as anti-tumor necrosis factor (TNF) antibodies, anti-interleukin (IL) 12/23 or anti-IL23, integrin antagonists, anti-S1P receptor, and Janus kinase (JAK) inhibitors [18]. Surgical resection is an option for both diseases [17] unresponsive to medical therapy or UC-related complications, while in CD the patients may undergo multiple surgical resections [19,20].

Among increasing therapeutic options, a key focus has been on developing disease monitoring tools for objective assessment of active inflammation and treatment decisions within a T2T framework [13,21,22]. These include laboratory markers like C-reactive protein (CRP), fecal calprotectin (fCal), digestive endoscopy, and less-invasive imaging techniques like intestinal ultrasound (IUS) and magnetic resonance enterography (MRE) [13,21,22].

Disease control and QoL in UC and CD patients has been described in various studies. In these, inadequate control for CD was defined based on criteria including a Harvey-Bradshaw Index (HBI) score of $\geq$8, a CD Activity Index of $\geq$220, calprotectin levels exceeding 200 μg/g, or evidence of active disease from the previous year's colonoscopy results. For UC, inadequate control was defined by a partial Mayo score of $\geq$5 [10,23–25]. However, there is a lack of studies reporting disease control based on STRIDE-II criteria.

The aim of the international IBD-PODCAST (Proportion of Inadequate Disease Control and Strategy of Treatment in IBD) observational study [26] was to assess "Red Flags" (RFs) based on STRIDE-II recommendations in a real-world setting, evaluating SDC in daily clinical practice among UC and CD patients in multiple countries.

The study also sought to describe the associated impact on QoL and estimate the proportion of CD/UC outpatients with SDC based on different disease management. Here we present data concerning SDC and its determining factors from the Italian population enrolled in the international study.

2. Materials and methods

2.1. Study design and population

The IBD-PODCAST study was a non-interventional, multicenter cross-sectional, retrospective study (Fig. 1). The study was conducted in 103 centers from 10 countries, with a post-hoc multi-country data synthesis [26]. The study population included adult CD/UC outpatients in private practices, centers, and hospitals treating IBD patients. A total of 20 Italian centers were invited to participate of which 17 (14 public and 3 private hospitals accredited to the Italian National Healthcare System) accepted to participate (three did not for practical reasons). Across the 17 centers, the mean number of patients expected to be seen in 2022 were 700±519 CD patients and 812±665 UC patients. The centers were distributed across the Italian peninsula; 6 in the North, 3 in Central regions, 4 in the

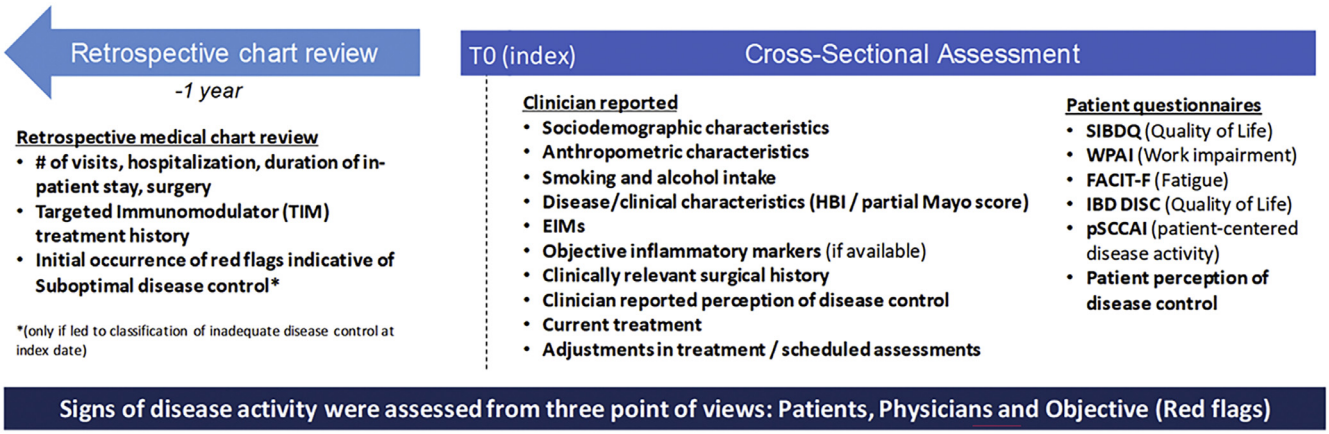

Fig. 1. Study design. TIM, Targeted Immunomodulator; RF, Red Flags; Abd., abdominal; fCal Fecal calprotectin; CRP, C-Reactive Protein; HBI Harvey Bradshaw Index; EIMs, Extra Intestinal Manifestations; SIBDQ, Short inflammatory bowel disease questionnaire; IBD, Inflammatory Bowel Disease; TX1, first treatment.

Table 1
Red Flags indicative of suboptimal disease control and their definitions/cut-offs for Ulcerative Colitis and Chron's Disease, based on STRIDE-II treatment targets.

SHORT-TERM		
	Crohn's disease	Ulcerative colitis
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 since therapy initiation)
INTERMEDIATE-TERM		
	Crohn's disease	Ulcerative colitis
Failure to achieve clinical remission*	PRO-2 stool frequency score >3 OR PRO-2 abdominal pain score >1 OR Harvey-Bradshaw Index >4	Mayo stool frequency subscore >0 OR Mayo rectal bleeding subscore >0
Failure to achieve CRP normalization*	CRP > 5 mg/dl[#]	CRP >5 mg/dl[#]
Failure to achieve sufficient fCal reduction*	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		
	Crohn's disease	Ulcerative colitis
Failure to achieve endoscopic remission	Endoscopic detection of ulcers and or inflammatory stenosis, fistula, or strictures[§]	Mayo ES >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)[§]
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

CD, Chron's Disease; UC, Ulcerative Colitis, SIBDQ Short inflammatory bowel disease questionnaire; AP Abdominal Pain; SF, Stool Frequency; RB, Rectal Bleeding; Hb, Hemoglobin.; fCal, Fecal Calprotectin; CRP, C-Reactive Protein; PRO, patient reported outcomes; Hb, Hemoglobin; MR(E), Magnetic Resonance (Enterography).
* to indicate inadequate disease control both failure to achieve clinical remission and either CRP or fCal above the respective threshold must apply**intermediate Disease Activity Indicator 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.
[§] report acceptable within ±8 weeks of index date.

South and 4 in the Isles. In this analysis undertaken in Italy, patients were consecutively enrolled between April 30th and November 30th, 2022. Patients were eligible for observation in this cohort if the following applied: ≥19 years of age at the time of enrolment; confirmed diagnosis of UC or CD ≥1 year prior to enrolment including documentation at the site, willing and able to provide informed consent; willing and able to read, understand, and complete the patient study materials. Patients were not eligible where: <12 months documentation available; patients currently receiving treatment with any investigational drug/device/intervention; diagnosis of IBDU (IBD unclassified); history of proctocolectomy.

2.2. "Red flags" defining disease control

SDC was determined at index date, defined as the date of the single visit of the cross-sectional assessment, using adapted Red Flags (RFs) indicative of symptomatic disease and/or active inflammation based on STRIDE-II recommendations [15]. RFs were elaborated by a steering committee of 7 international IBD experts. The group agreed on treatment target recommendations for both CD and UC. These recommendations include symptomatic parameters for short-term, symptoms and biochemical parameters for intermediate-term and QoL and imaging for long-term therapeutic targets.

Applicability of short-, intermediate-and long-term targets was based on the duration of treatment with a specific IBD medication. The RFs for CD and UC and their corresponding cut-off values to be applied in this study are shown in Table 1. The cutoff for fecal calprotectin was 250 μg/g, according to Bjarnason [27]. The duration of continued treatment with a specific medication determined if short-, intermediate- or long-term targets/RFs (Supplementary Table 1S) were applied for any individual subject. In a setting where multiple IBD treatments were used, with different induction/maintenance schedules, more stringent time frames for RFs (short-term, intermediate, long-term) were applied. Not all potential RFs were assessed at each visit in clinical practice.

2.3. Treatment patterns

Due to the observational nature of this study, the prescription of a treatment regimen and assessments were at the discre-

tion of the physician in accordance with local clinical practice and guidelines (Supplementary Table 1S). For this study, based on ECCO criteria [4] and Selinger and colleagues [28], the steering committee defined the CS overuse as prolonged (>6 weeks) administration of prednisolone ≥10 mg/d (or equivalent) or ≥1 systemic CS course in current management within the previous 12 months (intermediate RF). CS overuse was only counted as a RF indicative of SDC if: 1) the patient was in the intermediate or long-term treatment window, 2) the patient was classified as current CS overuse, but treatment was not adjusted at index, or 3) despite the patient was classified as current CS overuse, and treatment was adjusted, an additional course of CS was administered.

Dose optimization/intensification was classified according to the Summary of Product Characteristics of the single drugs considered. The maintenance dose of 5 mg kg^{-1} infliximab (every 8 weeks) and escalation dose (10 mg kg^{-1} every 8 weeks or 5 mg kg^{-1} every 4 weeks) were not collected separately as both of these doses are frequently considered as standard dose in real-life clinical practice in several countries in which the study was conducted [Anon., 29]. Therefore, these patients were defined as “undetermined” in subsequent analysis concerning escalation.

2.4. Data collection

According to the requirements for non-interventional or observational studies, no additional diagnostic or monitoring procedures were conducted during patient visits other than those usually performed during the therapeutic strategy. Additional study-specific PROs did interfere with routine office visits.

Data documented in the electronic case report form (eCRF) (during a single visit) were: i) cross-sectional data collection at the study visit as well as patient and health care practitioner (HCP) questionnaires; and ii) retrospective chart review, conducted by a member of the local study team. Patient and HCP questionnaires were provided and collected in electronic format by the local study team after written patient consent was obtained. The cross-sectional assessment included the following clinician reported components: sociodemographic, anthropometric characteristics, disease characteristics and severity, and EIMs to characterize the patient population and assess presence of symptomatic RFs; objective inflammatory markers and laboratory parameters if available (CRP, fCal, endoscopy, histology) to assess presence of objective RFs. Frequency of use of endoscopy with histology, and less invasive techniques like IUS and MRE were also assessed at index. Assessments were documented if samples taken/assessments performed in a timeframe of ±2 weeks from index date. Patient reported components included in the cross-sectional assessment included The Short Inflammatory Bowel Disease Questionnaire (sIBDQ) [30].

The retrospective data collection included the following components: objective inflammatory markers and lab parameters if available (CRP, fCal, endoscopy, histology, MRE, IUS) in case these were RFs at index data to assess initial occurrence; surgical history, TIM treatment (i.e. biological treatment and small molecules) history since diagnosis.

2.5. Outcome measures

The primary outcome variables included optimal/SDC in CD and UC at the index, defined by the presence of RFs indicating suboptimal disease management, as well as QoL assessment via SIBDQ scores for both CD and UC patients.

Secondary outcomes included the evaluation of the patient-reported SDC at the index date, reasons for patient-reported SDC at the index date, assessment of clinician-reported SDC at the index date, the number, dosage, and type of CS prescribed in the 12 months preceding the index date, the number of (TIM) treatments received from the CD/UC diagnosis to the index, the nature of treatment adjustments implemented or scheduled at the index date, the type of monitoring procedures performed or scheduled at the index.

Demographics and clinical characteristics, comorbidities were also recorded.

2.6. Statistical analysis

Analysis was descriptive and performed separately for CD and UC patients. Continuous variables were described by the number of observations (n), median, mean, and standard deviation (SD). Categorical variables were presented as the number and percentage of patients in the total study population, excluding missing data. Since this is a descriptive study, the sample size was not based on a statistical power calculation. All analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

Globally, over 2,000 patients in 10 countries were enrolled in the IBD-Podcast study [26]. The present Italian subset of patients included 220 individuals enrolled across 17 IBD centers (range of 7–23 patients included per center); 116 (53 %) diagnosed with CD and 104 (47 %) with UC. Of 227 patients initially screened, 7 did not participate due to screening failure (not aged ≥19 years; $N = 1$, unconfirmed diagnosis of CD or UC; $N = 4$, and inability or refusal to complete patient consent forms; $N = 2$). All demographic and clinical characteristics are summarized in Table 2.

The mean age was 38±13.3 years for CD and 41.3 ± 14.6 years for UC patients, respectively. In the CD group, 35.3 % were female vs. 46.2 % in the UC group. The proportion of individuals with a smoking history was higher in the CD group (44.0 %) vs. the UC group (26.9 %). No notable differences were observed in alcohol consumption between the two groups. Age at diagnosis (∼30 years old) and disease duration (∼12 years) was similar for both diseases (Table 2).

One-hundred-and-five individuals (90.5 %) with CD and 88 individuals (84.6 %) with UC were classified as having experience with TIM medications. In addition, 100 patients (86.2 %) with CD and 84 patients (80.8 %) with UC were currently using TIM medication at index. The majority of patients (85.6 % of UC and 86.2 % CD, respectively) were in the long-term treatment window.

3.2. Assessment of disease control

According to RF positivity, among 116 CD patients, 62 (53.4 %) exhibited SDC compared with 51/104 UC patients (49.0 %). In the global international pooled analysis involving 10 countries, SDC was detected in 52.2 % of Crohn’s disease and 44.3 % of UC patients [26]. A SIBDQ score <50 (∼63 %), the presence of EIMs (∼24 %) and failure to achieve inactive disease at imaging and/or endoscopic assessment (∼16 %), were the most common reasons for SDC for both diseases. Systemic CS overuse in UC (31.4 %) and perianal disease in CD (19.4 %) also contributed to SDC (Fig. 2).

Considering long-term CD patients with SDC ($n = 59$), 37.3 % had more than one concomitant RF overlapping, compared to 34.0 % of long-term UC patients ($n = 47$). The most represented concomitant RF was impaired QoL for both diseases, as 51 % of CD patients ($N = 19/37$) and 48 % of UC patients ($N = 14/29$) with reduced QoL was positive for at least another concomitant RF.

Table 2
Clinical characteristics of suboptimal control and optimal control subgroups in Crohn's Disease and Ulcerative Colitis study populations.

Patient Characteristic	Crohn's disease			Ulcerative colitis			Total		
	Total $N = 116$	Suboptimal control $N = 62$ (53.4 %)	Optimal control $N = 54$ (46.6 %)	Total $N = 104$	Suboptimal control $N = 51$ (49.0 %)	Optimal control $N = 53$ (51.0 %)	Total $N = 220$	Suboptimal control $N = 113$ (51.4 %)	Optimal control $N = 107$ (48.6 %)
Age at index (years)[a]									
N	116	62	54	104	51	53	220	113	107
Mean (SD)	38.0 (13.29)	39.1 (13.49)	36.7 (13.07)	41.3 (14.56)	37.6 (13.75)	44.8 (14.56)	39.5 (13.97)	38.4 (13.56)	40.7 (14.36)
Sex, n (%)									
Female	41 (35.3 %)	21 (33.9 %)	20 (37.0 %)	48 (46.2 %)	25 (49.0 %)	23 (43.4 %)	89 (40.5 %)	46 (40.7 %)	43 (40.2 %)
Male	75 (64.7 %)	41 (66.1 %)	34 (63.0 %)	56 (53.8 %)	26 (51.0 %)	30 (56.6 %)	131 (59.5 %)	67 (59.3 %)	64 (59.8 %)
BMI (kg/m^2)									
N	98	55	43	84	41	43	182	96	86
Mean (SD)	24.0 (3.70)	24.1 (4.19)	23.8 (3.01)	23.3 (3.59)	23.6 (4.19)	22.9 (2.91)	23.6 (3.66)	23.9 (4.17)	23.4 (2.98)
Smoking history, n (%)									
Yes	51 (44.0 %)	29 (46.8 %)	22 (40.7 %)	28 (26.9 %)	13 (25.5 %)	15 (28.3 %)	79 (35.9 %)	42 (37.2 %)	37 (34.6 %)
Never smoked[b]	54 (46.6 %)	29 (46.8 %)	25 (46.3 %)	63 (60.6 %)	32 (62.7 %)	31 (58.5 %)	117 (53.2 %)	61 (54.0 %)	56 (52.3 %)
Unknown	11 (9.5 %)	4 (6.5 %)	7 (13.0 %)	13 (12.5 %)	6 (11.8 %)	7 (13.2 %)	24 (10.9 %)	10 (8.8 %)	14 (13.1 %)
If yes, number of cigarettes smoked/day									
N	40	21	19	20	7	13	60	28	32
Mean (SD)	12.6 (8.94)	14.3 (8.57)	10.6 (9.15)	13.3 (9.79)	15.7 (13.00)	12.0 (7.88)	12.8 (9.16)	14.7 (9.61)	11.2 (8.55)
Frequency of alcohol consumption, n (%)									
Never	44 (37.9 %)	23 (37.1 %)	21 (38.9 %)	40 (38.5 %)	21 (41.2 %)	19 (35.8 %)	84 (38.2 %)	44 (38.9 %)	40 (37.4 %)
$\leq$1 x per month	29 (25.0 %)	15 (24.2 %)	14 (25.9 %)	32 (30.8 %)	16 (31.4 %)	16 (30.2 %)	61 (27.7 %)	31 (27.4 %)	30 (28.0 %)
2–4 × per month	33 (28.4 %)	17 (27.4 %)	16 (29.6 %)	21 (20.2 %)	9 (17.6 %)	12 (22.6 %)	54 (24.5 %)	26 (23.0 %)	28 (26.2 %)
2–3 × per week	6 (5.2 %)	3 (4.8 %)	3 (5.6 %)	8 (7.7 %)	4 (7.8 %)	4 (7.5 %)	14 (6.4 %)	7 (6.2 %)	7 (6.5 %)
$\geq$ 4 × per week	4 (3.4 %)	4 (6.5 %)	0 (0.0 %)	3 (2.9 %)	1 (2.0 %)	2 (3.8 %)	7 (3.2 %)	5 (4.4 %)	2 (1.9 %)
Age at diagnosis (years)[c]									
N	116	62	54	104	51	53	220	113	107
Mean (SD)	28.5 (11.25)	29.1 (11.27)	27.7 (11.27)	31.2 (13.03)	28.2 (11.92)	34.0 (13.51)	29.7 (12.17)	28.7 (11.53)	30.8 (12.77)
Duration of disease[d]									
N	116	62	54	104	51	53	220	113	107
Mean (SD)	11.5 (7.48)	11.9 (7.81)	11.0 (7.13)	12.1 (8.57)	11.4 (8.01)	12.8 (9.10)	11.8 (8.00)	11.7 (7.87)	11.9 (8.18)

Data are reported as number of individuals (n), mean and standard deviation (SD) or percentage (%).
[a] Note: Age was based on index date and year of birth.
[b] Never smoked refers to anyone who has smoked <100 cigarettes in their lifetime.
[c] year of diagnosis minus year of birth + 1, where year of birth = year of index minus – age at index.
[d] year of index minus year of diagnosis + 1; HBI, Harvey-Bradshaw Index Score; TIM, targeted immunomodulator. Note: A TIM experienced patient is one who is currently and/or previously on a TIM medication; n.a, Not Applicable.

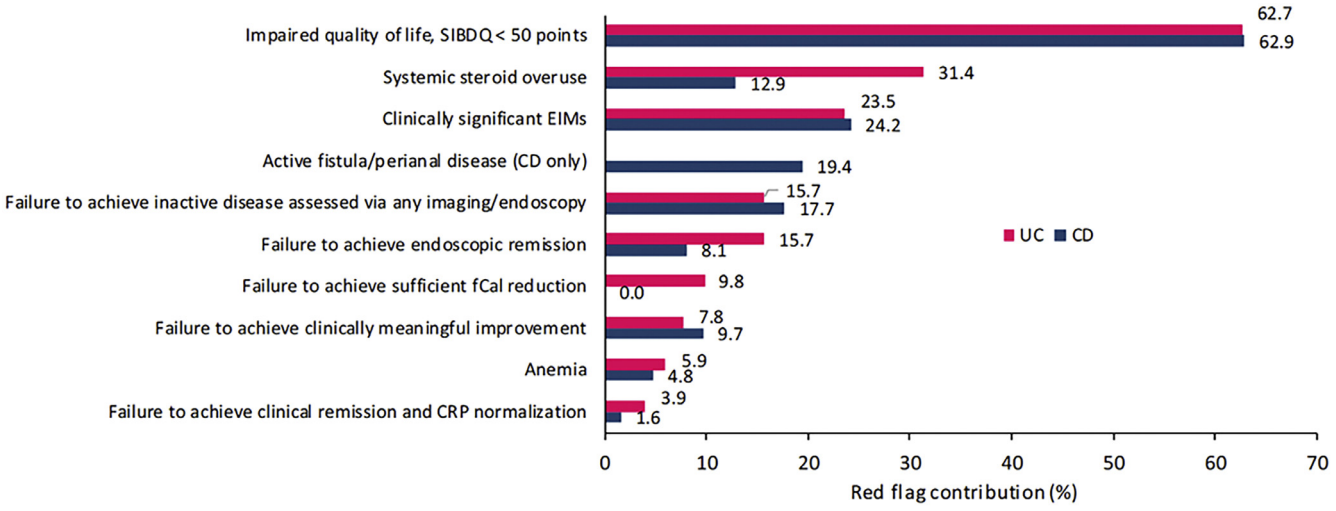

Fig. 2. Red Flags contribution in patients with suboptimal disease control in Crohn's Disease and Ulcerative Colitis. EIMS, Extra-Intestinal Manifestations; MRI, Magnetic Resonance Imaging; MRE, Magnetic Resonance Enterography, CT, Computed Tomography; CRP, C-reactive protein; RF; Red Flags, SIBDQ, Short inflammatory bowel disease questionnaire. A clinically significant EIM was 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 HCP[26]. Clinically significant EIMs ($N = 13$) included the following: peripheral arthritis ($N = 5$), axial arthritis ($N = 5$), psoriasis ($N = 2$) and 1 case hidradentitis suppurativa ($N = 1$).

3.3. Extraintestinal manifestations

A higher percentage of EIMs was observed in patients with SDC compared to those with optimal control. This trend was evident in both CD patients (15/62; 24.2 % in suboptimal control vs. 2/54; 3.7 % in optimal control patients and UC patients (12/51; 23.5 % in SDC vs. 1/53; 1.9 % in optimal control patients.

3.4. Impaired QoL

Mean SIBDQ scores in SDC were lower than in optimally controlled patients in both UC and CD. For long-term CD patients with SDC, mean SIBDQ score ±SD was 47.4 ± 11.11 vs. 61.4 ± 6.09 for optimally controlled CD patients; similarly, in long-term UC patients, mean SIBDQ scores for SDC vs. optimal disease control were 45.6 ± 12.94 vs. 59.8 ± 5.46 (Supplementary Figure 1S, A). Mean scores for all four SIBDQ domains (bowel, systemic, emotional, social) were lower in suboptimally controlled patients (Supplementary Figure 1S, B).

3.5. Disease monitoring

Assessment via imaging/endoscopy was performed in over 50 % of patients with CD and UC within a year prior index date (Fig. 3A). Most of them (39.7 % and 43.9 % in CD and UC, respectively) underwent endoscopy while a smaller subset of patients underwent MRE/MRI/CT or IUS, with a numerically higher percentage in CD (20.2 %) vs. UC (2.9 %). Within two weeks before the index date, biochemical monitoring was conducted using CRP in almost 50 % of both CD and UC patients while 16.4 % of CD patients and 29.8 % of UC patients had fCal levels analyzed (Fig. 3A). When considering biochemical assessment two weeks from the index date and imaging/endoscopic evaluation over 12 months, CD patients received less imaging/endoscopic and biochemical monitoring compared to UC patients (16.4% vs. 33.7 %, respectively, Fig. 3A). This pattern was consistent when analyzing disease monitoring within SDC and optimal control patient groups for both CD and UC (Fig. 3B).

Furthermore, over the past 12 months, actions taken based on imaging/endoscopic findings of inflammation, such as additional monitoring or treatment adjustments, were implemented for half of the patients, including both CD and UC cases (Supplementary Figure 2S).

3.6. Treatment and escalation potential

At the cross-sectional assessment, clinicians examined the treatment patterns including the use of systemic CS (Supplementary Table 2S). In UC, 84.7 % (72/85) of optimally controlled patients had not received more than one course of CS in the past 12 months compared to UC patients with suboptimal control (57.9 %; 11/19). In CD, this occurred in 94/103 (91 %) patients with optimal control vs. 11/15 (73 %) with SDC.

Specific TIMs were administered in all UC patients and in 90.5 % (105 out 116) of CD patients (Supplementary Tables 3S-4S). Approximately 80 % of patients in both groups had received at least one TIM.

In CD patients, out of 62 individuals with SDC, 53 (85 %) had previous experience with TIM therapy (Supplementary Table 5S). For UC patients, out of 51 individuals with SDC, 39 (76 %) had prior experience with TIM therapy (Supplementary Table 5S).

In terms of suboptimal response in UC patients, no difference was observed between naïve (15; 17.0 %) compared to biologic experienced (24; 27.3 %). Similar proportions were seen in for CD patients; in terms of sub-optimal response in CD patients, no difference was observed between naïve (24; 22.9 %) compared to biologic experienced (29; 27.6 %).

Furthermore, patients with SDC who were undergoing TIM therapy showed adjustments in their treatment at the first visit, with 67.9 % (36/53) in CD and 61.5 % (24/39) in UC, respectively. Among these patients, 58 % (21/36) in CD and 54 % (13/24) in UC had the potential for treatment escalation (Supplementary Figure 3S).

4. Discussion

This study represents the first non-interventional, multicenter investigation aimed at assessing disease control based on adapted STRIDE-II criteria in a real-world clinical setting in Italy. Disease assessment revealed that more than half of CD and UC patients exhibited signs of SDC, with common reasons being low SIBDQ scores, systemic CS overuse, failure to achieve remission at imaging/endoscopic assessment, and the presence of clinically

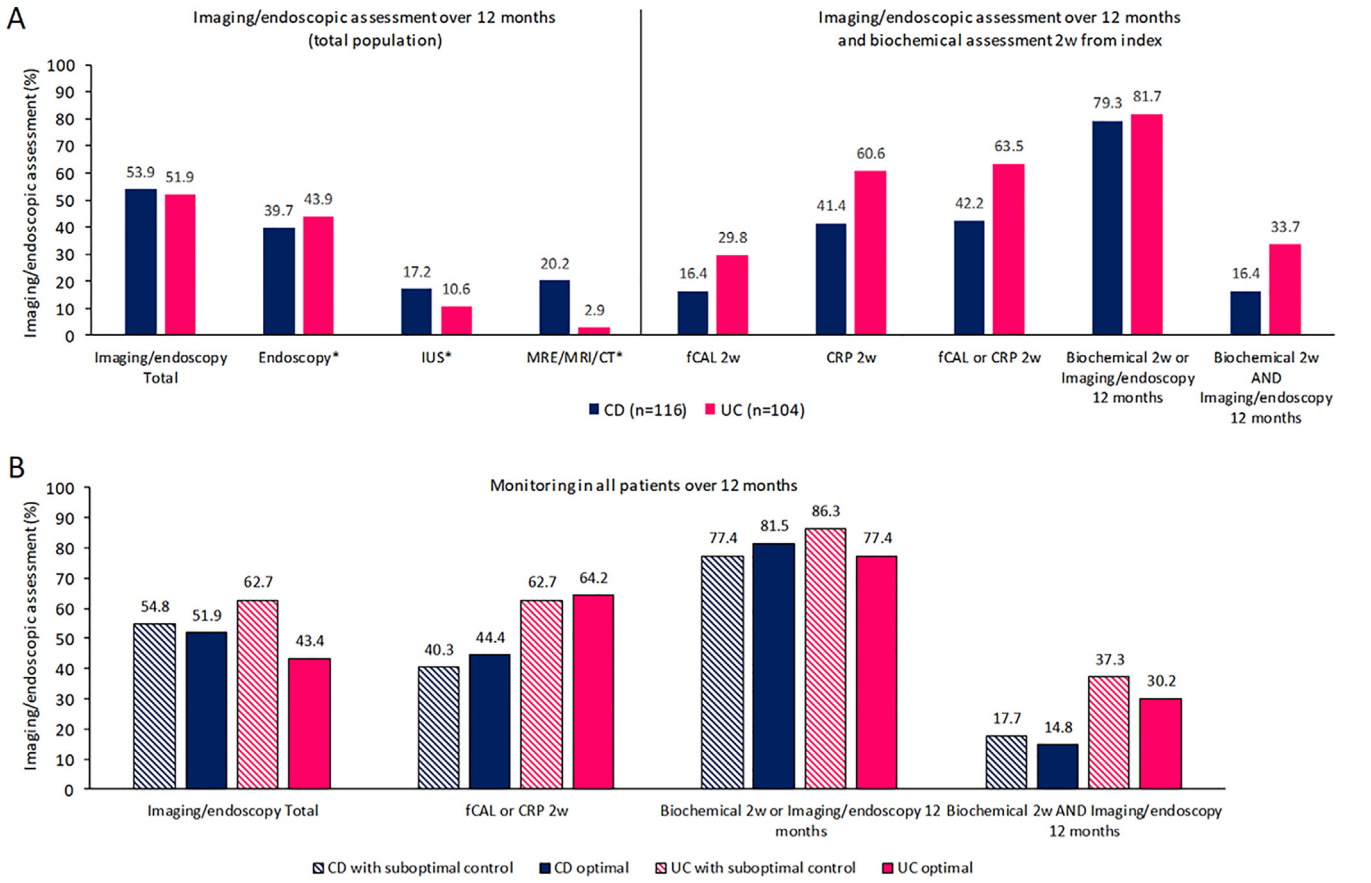

Fig. 3. Imaging/endoscopic and biochemical assessment over a period of 12 months and 2 weeks from the index date (A), and imaging/endoscopic assessment over a 12-month period for both optimally and suboptimally controlled cases of Ulcerative Colitis (UC) and Crohn's Disease (CD) (B). *More than one assessment may occur in the same patient (sum of individual assessments may not equal total).

significant EIMs. These results are in line with those of the multicountry study analysis [26]. Imaging/endoscopic assessment and biochemical markers have been used in a limited number of patients, especially in CD.

Treatment patterns showed that specific disease treatments were administered to most patients; however, a consistent number of patients did not have their treatment adjusted despite potential for therapy escalation and signs of active disease.

Previous studies had different definitions for SDC at enrollment [10,31]. For CD, this included having a HBI score of ≥8, a CD Activity Index of ≥220, calprotectin levels exceeding 200 μg/g, or evidence of active disease based on colonoscopy results from the previous year. For UC, SDC was defined as a partial Mayo score of ≥5. Applying these criteria, it was observed that 44.7 % of CD patients and 25.2 % of UC patients had inadequate disease control [10,31]. However, in our study, when we applied STRIDE-II adapted criteria, we found that more than half of patients did not have optimal disease control, even if it is important to note that direct comparisons may be challenging due to the varying criteria used to define disease control in different studies.

Among suboptimally controlled patients, we observed that low SIBDQ scores were the most prevalent RFs for disease activity. Specifically, 63 % of IBD patients had SIBDQ scores below 50. In a cohort of 185 patients followed for seven years, a significant majority of CD patients (73.1 %) and UC patients (85.0 %) had SIBDQ scores exceeding 50 [32]. This difference in outcomes could be attributed to the longer study duration, during which various efforts were made to achieve disease control.

In a recent systematic review [24], EIMs were documented in 16 publications, showing a prevalence range of 7.0–28.7 % in patients with IBD. EIMs were documented in 16 publications, showing a prevalence range of 7.0–28.7 % in patients with IBD. Among these publications, five reported a higher prevalence of EIMs in patients with CD compared to those with UC. In our study, we observed EIMs in ~24 % of both CD and UC patients, with no significant differences between the two groups.

Limited studies have specifically evaluated the utilization of monitoring methods in the management of CD and UC. In our study, 39.7 % of CD patients and 43.9 % of UC patients underwent endoscopy over a 12-month period. While STRIDE guidelines [15] recommend frequent endoscopic assessments, with three-month intervals during active disease for UC and 6–9 month intervals CD, real-life clinical practice presents several challenges. Endoscopic procedures are expensive for healthcare systems and often face limitations in terms of availability, accessibility, and lengthy waiting lists, particularly in public healthcare systems [33]. Additionally, endoscopy is an invasive procedure, and benefits of frequent assessments must be carefully balanced against the potential risks [34]. Moreover, the necessity for repeated sedation, particularly in elderly patients or those with significant co-morbidities, can make this approach unfeasible [35]. The reliance on endoscopy for assessing mucosal healing poses a barrier to the widespread implementation of T2T approaches in real-world clinical practice. In this context, the utilization of laboratory biomarkers, as CRP and fCal, may facilitate IBD management [36]. When we expanded our analysis to encompass imaging/endoscopic methods, alongside bio-

chemical markers conducted two weeks after the index date, these percentages were 16.4 % for CD and 33.7 % for UC.

These rates may indicate that patients are not receiving tight monitoring. Possible explanations may include costs, waiting lists, and patient non-compliance. For example, some tests, such as calprotectin, are paid for by the patient in certain regions, which may lead to low compliance.

CS use remains an issue in patients with IBD in Italy [37]. Indeed, in our cohort, we observed that systemic CS overuse did contribute largely to define SDC and those patients exhibited a higher percentage of individuals who had received more than one course of CS in the past 12 months, compared to patients with optimal control. Indeed, current guidelines for the treatment of IBD do not recommend CS as maintenance treatment and to avoid prolonged CS use [38]. Despite the availability of guidelines on CS use, studies evaluating the long-term use of CS in IBD is limited and no national IBD registry is available in Italy. Confirming our findings, a recent cross-sectional survey highlighted notable CS use in IBD patients in Italy [37]. It was revealed that 30 % of all IBD patients were treated with oral CS, with an excess rate of 18.9 %; higher rates observed in UC (24.1 %) compared to CD patients (13.6 %). These results confirm findings from other studies performed in the UK [39,40] and Romania [41].

A significant percentage of our patients may require treatment adjustment, with 58 % CD and 54 % of UC patients with the potential for treatment escalation. Sassaki et al. observed that during their follow-up of 9–12 months, 65.3 % of CD patients and 86.1 % of UC patients initiated new treatments at least once. Moreover, discontinuations and dose changes were common, affecting 68.1 % of CD patients and 94.3 % of UC patients. These findings suggest that in our patient population, there is a trend towards a more conservative therapeutic approach, rather than frequent adjustments. This could be enhanced first by raising awareness of the recent IG-IBD consensus for managing EIMs [42], which could assist clinicians in more effectively addressing patients with these issues. In addition, considering the emerging data on IUS, which is increasingly pivotal in disease monitoring, and finally, providing economic incentives (reimbursement) for fecal calprotectin testing, could contribute to improving compliance with testing.

5. Study limitations

The main weakness of this study was the observational and descriptive design, including uncontrolled confounding due to the absence of randomization and challenges related to handling missing data. Causality or correlation analysis was not performed due to the limited sample size. Furthermore, exploratory analysis in subgroups of patients to assess outcome following change in treatment was not assessed due to the limited number of patients. In this regard, formal statistical analysis to assess differences in subgroups was not performed. Since >80 % of patients were in long-term response (even if 48.6 % were in optimal disease control), it is likely that patients with longer follow-up time at specialized centers were included and potentially leading to potential selection bias, a characteristic of these types of studies. Due to difficulty obtaining individual patient data at each centre, the time from the start of the assessed treatment to the index date was not collected. Although geographically distributed across Italy, only 17 centers participated in the study. It is likely that these represent a small proportion of all centers that manage a significant volume of IBD patients in Italy. In addition, it is possible that the total number of patients included per center may not be representative of the population usually attending each institution, due to the long duration of the disease and the fact that most patients were assessed in the long-term response phase (this phase includes the evaluation of QoL). Lastly, the proportion of SDC may be potentially underestimated, as data related to certain RFs (e.g. CRP, fCal, endoscopy, MRE, IUS) may have been missing.

6. Conclusions

This study represents a snapshot of the current management of CD and UC in Italy. Half of patients had SDC and there was room for treatment escalation in a consistent quota of patients. These findings highlight the need for a more holistic, standardized and effective approach in the management and monitoring of IBD patients.

Competing interests

1. **BD, GL, GG, MF and PMA** are AbbVie employees and may own AbbVie stocks/options.
2. **CE** has served as speaker for Abbvie, Takeda, Janssen, Galapagos and Ferring; has served as consultant for Abbvie, Ferring and Galapagos.
3. **CL** has served as speaker for Janssen, Abbvie, Takeda, Pfizer; has served as consultant for Galapagos, Janssen, Abbvie and Sandoz.
4. **CFS** declares lecture fees for Janssen, Pfizer and Ferring.
5. **DF** has served as a speaker for Galapagos, Janssen, Omega Pharma, Sandoz, Takeda, and Tillotts; he also served as consultant for Ferring and as advisory board member for Abbvie, Galapagos, Janssen and Nestlé.
6. **GM** has nothing to disclose.
7. **LG** declares to have received educational and research support from Abbvie, Janssen, Takeda, Ferring, Alfasigma and Chiesi.
8. **MG** declares consultancy for: AbbVie, Amgen, Biogen, Celltrion, Ferring, Galapagos, Janssen, MSD, Sandoz, Takeda, Chiesi, Vifor Pharma and lecture fees for: AbbVie, Amgen, Biogen, Ferring, Janssen, MSD, Sandoz,Takeda, Aurora Biopharma and Omega Pharma.
9. **OS** has served as speaker and/or consultant for Abbvie, Galapagos,Janssen, Pfizer, Takeda.
10. **OA** has served as an advisory board member for AbbVie, Galapagos, MSD, Janssen, Lilly, Pfizer, Takeda, Biogen, and received lecture fees from AbbVie, Biogen, Celltrion, Ferring, Fresenius-Kabi, Galapagos, Lilly, MSD, Sofar, Chiesi, Janssen, Pfizer, Sandoz, and Takeda.
11. **PAC**.has served as consultant for: Amgen, Ferring, Jansen, MSD; he received research support from: Abbvie, Arena, Celtrion, Cristalfarma,Jansen, MSD, Pfizer.
12. **PM** has served as advisory board member and received lecture fees for AbbVie, Galapagos, MSD, Janssen, Lilly, Pfizer, Takeda, Biogen.
13. **RDG** declares the following paid consultancies, lecture fees for the past two years: Abbvie, Janssen, Takeda, Galapagos, Biogen, Celltrion, Pfizer.
14. **SS** declares consultancy, lecture fees, and advisory board for AbbVie, Arena, Ferring, Galapagos, Gilead, Janssen, MSD, Pfizer, and Takeda.
15. **SEV** has served as speaker for Abbvie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly-BiohealthMayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici.

16. **TA** has served as speaker for Abbvie, Takeda, Janssen, Pfizer; has served as a consultant for Abbvie, and Galapagos.
17. **VarA** declares lecture fee from Abbvie, Ferring, Zambon, Janssen-Cilag, Takeda, Pfizer, Alfasigma; advisory board and consultant for Abbvie, Celltrion, Janssen-Cilag, Galapagos, Pfizer, Ferring and Takeda.
18. **VioA** has served as speaker for Abbvie.

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Authors contributions

All authors contributed to the writing, revision and approval of the manuscript.

CE, OS, VAng, RDG, SEV, VAnn, SS, CFS, TA, LG, OA, PA, PM, GM, CL, MG and FDA collected data for study purposes.

CE, OS, RDG, SEV, VA, SS and CFS contributed substantially to the critical analysis and improvement of the manuscript.

BD, PMA, GG and MF contributed to the study design and critical appraisal of data.

GL played a key role in the ideation, design and naming of the study, analysis and critical appraisal of the data.

DF served on the international steering committee that designed and contributed to the development of the study protocol and provided important suggestions and comments during the development of the manuscript.

Data availability

Data are available upon request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.08.040.

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