



Alimentary Tract

Epidemiological features and disease-related concerns of a large cohort of Italian patients with active Crohn's disease

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ABSTRACT

Background-Aims: The SOLE study was conducted on a large cohort of Italian patients with moderate-severe Crohn's disease (CD) to assess epidemiological and disease characteristics and their correlation with disease-related worries, treatment satisfaction and adherence, workability.

Methods: The following tools were used over 12 months to assess:

- disease-related worries: Rating Form of Inflammatory Bowel Disease Patient Concerns,
- impact on workability: Work Productivity and Activity Impairment-CD,
- satisfaction: Treatment Satisfaction Questionnaire for Medication,
- adherence: Medication Adherence Rating Scale.

Results were correlated with demographic and clinical variables with linear regression models.

Results: 552 patients with active CD (51% men) were recruited. Higher worries were having an ostomy bag and undergoing surgery. Variables associated with a higher RFIPC score included female sex, higher disease activity, lower treatment adherence ($p < 0.001$), previous surgical treatments ($p = 0.003$). 60% of patients claimed difficulties with activities of daily living. Lower VAS scores were reported by patients with disease duration > 6 years; treatment satisfaction/adherence was higher with anti-TNF- α treatment. Decreased hospitalizations during follow-up and improved workability/daily activities occurred with adalimumab, infliximab, azathioprine ($p < 0.001$).

Conclusion: Worries included having an ostomy bag, undergoing surgery, developing cancer: conditions significantly associated with worsened disease activity and low treatment adherence. Higher treatment adherence scores/greater workability improvements were observed in patients treated with anti-TNF- α agents.

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1. Introduction

Recently there has been increasing interest on the impact of chronic diseases on patients' general well-being and health-related quality of life (HRQoL) [1]. Symptoms and objective measures of disease are not sufficient to fully describe the complex and multidimensional aspects of chronic diseases, that have a dramatic impact on the quality of life (QoL) of patients, their relatives and caregivers.

Crohn's disease (CD) is a relapsing-remitting chronic condition whose symptoms heavily affect patients' daily activities [1]. Patients with CD are frequently diagnosed at a young age [2], with most of their lives ahead with the disease, affecting their choices about work, lifestyle, and personal relationships. Several therapeutic options are currently available to manage inflammatory bowel diseases (IBDs) and QoL assessment may enhance their global evaluation, enabling a more comprehensive planning of disease management [3–5]. The evaluation of the patient's feelings and concerns about the disease and its management may allow clinicians to identify major areas of discomfort and distress and to tailor treatment strategies, considering the patient's perspective. A correlation between corticosteroids and QoL impairment has been demonstrated in CD, while traditional immunosuppressants and biological therapies have been associated with QoL improvement and increase in quality-adjusted life-years, respectively [6].

The Rating Form of IBD Patient Concerns (RFIPC) questionnaire measures IBD-related worries [7], a major dimension of HRQoL in IBD. Compliance to lifelong treatment strategies is critical in chronic diseases: self-administered questionnaires have been developed to evaluate patients' satisfaction and adherence to therapy (Treatment Satisfaction Questionnaire for Medication –TSQM [8], and Medication Adherence Rating Scale –MARS-5-I [9]). The impact of CD on the daily working activities of patients is heavily affecting not only the patients' QoL, but also social costs: it can be assessed through the Work Productivity and Activity Impairment (WPAI), validated also in CD [10,11].

The SOLE study, “Survey on Quality Of Life in Crohn's PatiEnts” was conducted in Italy with a large cohort of patients with moderate-severe CD to assess disease evolution and its relationship with work ability-efficiency, disease activity, disease-related worries, treatment satisfaction and compliance.

2. Materials and methods

2.1. Study design

A prospective observational cohort study was conducted in 38 Italian IBD centers (Feb2012–Nov2013). Clinical sites, evenly distributed over the national territory (12/11/15 respectively in the north/center/south of Italy), were experienced in the management of patients with IBD and were selected on the basis of the availability of CD patients and of an internet connection.

2.2. Patients

Patients were consecutively recruited during routine outpatient visits in the participating centers, according to the following inclusion criteria: (1) confirmed diagnosis of CD supported by clinical, radiological, histological, and endoscopic criteria; (2) adults with Harvey-Bradshaw Index (HBI) score ≥ 8 ; (3) written informed consent for participation in the study and processing of personal data. Exclusion criteria included: (1) active fistulas (requiring medical and surgical intervention); (2) New York Heart Association class III/IV congestive heart failure; (3) active malignancies that required therapy; (4) inability to understand/complete the survey-related questionnaires (according to the clinician's judgment).

2.3. Data collection

Baseline data (clinical history, medications, HBI score, demographic, socioeconomic data, and lifestyle) were collected at study entry (M0) based on patient interviews and review of medical records. Follow-up visits were scheduled 3, 6, and 12 months after study entry (M3, M6, M12, respectively). At each visit, the physician collected study data and rated the disease activity through the HBI.

For analyses involving the impact of drug therapy, increasing levels of treatment were defined: no drugs at all for CD were assigned to Level 0; Level 1 included non-specific treatment regimens (antidiarrheal, antimicrobial, and 5-aminosalicylic acid); systemic corticosteroid therapy, alone or with other Level 1 drugs, were assigned to Level 2; Level 3 therapy included non-biological immunosuppressants (thiopurines, methotrexate), alone or with lower level therapies; Level 4 regimens were based on anti-tumor necrosis factor (TNF)- α therapy (adalimumab and infliximab, alone or with lower level drugs).

2.4. Self-administered questionnaires

Patients were asked to complete the following questionnaires in the validated Italian translation:

- The EuroQoL 5 Dimensions (EQ-5D) assesses generic HRQoL. Component 1 focuses on patients' perceptions of the difficulties experienced in mobility, self-care, usual activities, pain/discomfort, anxiety/depression, rated from 1 = no problems to 3 = severe/extreme problems. In Component 2, patients rate their own health using a visual analog scale (VAS) ranging from 0 to 100 (worst to best imaginable health) [12].
- The RFIPC assesses worries related specifically to Crohn disease. The questionnaire contains 25 items related to: body stigma, complications, sexual intimacy, and impact of the disease, each rated from 0 to 100 (not concerned at all/very concerned) on a VAS. The final result is the mean of the scores [7].
- The WPAI-CD evaluates the impact of CD on normal activities of daily living (Total Activity Impairment-TAI) and productivity in the work setting (for employed patients: absenteeism, presenteeism, overall loss of productivity [10]). The score for each item varies from 0 to 100, (higher scores = greater impact of CD). The minimally clinical important difference has been estimated to be approximately 7% [13].
- The 14-item TSQM explores patients' assessments of the effectiveness, side effects, and convenience of the main drug of their treatment regimen, as well as their overall satisfaction with that drug; scores range from 0 to 100 (higher scores indicate greater satisfaction) [8].
- The MARS captures the frequency of 5 types of nonadherence to the prescribed treatment; the overall index ranges from 5 to 25 (poor to optimal adherence) [9].

2.5. Statistical analysis

Data analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC, USA), and Stata version 12.0 software (StataCorp, College Station, TX, USA). Descriptive statistics were used to summarize data as frequencies (categorical variables) or mean $\pm$ SD (continuous variables) as appropriate. $P < 0.05$ was considered statistically significant. An analysis of variance model was used to evaluate differences between groups. Mixed-effects linear regression models were used to evaluate temporal trends for outcomes and to measure their association with covariates (e.g., HBI, age). The effects of the covariates and their standard errors were esti-

Table 1
Clinical and socioeconomic characteristics of the cohort.

Clinical and socioeconomic characteristics	Baseline (N = 552)
Age in years, median (range)	41 (18–84)
Females, n (%)	271 (49)
Years from CD diagnosis, median (range)	6 (0–49)
Harvey-Bradshaw Index, median score (range)	9 (8–39)
History of >1 operations for CD, n (%)	248 (45)
Disease extension, n (%)	
Ileum	237 (43)
Colon	81 (15)
Ileum and colon	235 (43)
Other	20 (4)
Extraintestinal manifestations, n (%)	214 (39)
Disease phenotype, n (%)	
Inflammatory	262 (53)
Strictureing	219 (45)
Penetrating	9 (2)
Living arrangements, n (%)	
Living alone	59 (11)
Living with family/significant others	478 (87)
Other	15 (3)
Education, no (%)	
High school diploma	287 (52)
University or post-graduate degree	84 (15)
Occupational status, n (%)	
Employed	300 (54)
Student	49 (9)
Homemaker	78 (14)
Retired or unemployed	125 (23)
Smoking status, n (%)	
Never smoked	213 (39)
Current smoker	214 (39)
Former smoker (for >6 months)	125 (23)
Alcohol consumption, n (%)	110 (20)

CD, Crohn's disease.

mated taking into account the hierarchical structure of the data (i.e., patients, visits, and clinical centers).

3. Results

3.1. Baseline

3.1.1. Clinical and socioeconomic profiles

Five hundred fifty-two adults with moderately-to-severely active CD (median age, 41 [18–84] years; 49% women; median HBI score of 9; range, 8–39) were consecutively enrolled. The patients distribution at baseline was as follows: North n = 137 (24.8%), Centre n = 178 (32.3%) and South n = 237 (42.9%) out of 12/11/15 respectively recruiting sites. Patient characteristics are summarized in Table 1. At study entry, the median time from CD diagnosis was 6 years (interquartile range, 3–14 years) and 36 patients (6.5%) had been diagnosed <12 months before study entry.

The majority of participants had ileocolic or ileal disease (43% each); 53% of patients had inflammatory behaviour. Twenty percent of patients had at least 1 EIM of IBD, mainly musculoskeletal; 55% reported ≥ 1 concomitant disease (Supplementary Table 1). Two hundred forty-eight patients (45%) had undergone ≥ 1 surgery for CD, most commonly intestinal resection (73%, Supplementary Table 2). Seventeen (6.9%) and 3 patients (1.2%) had undergone fecal diversion procedures with creation of temporary or permanent ostomy, respectively.

Four hundred seventy-eight participants (87%) lived in family, but 84 (15%) were assisted by a paid caregiver. Almost two-thirds worked or were engaged in active study. More than half of women (56.8%) and 34.9% of men did not work. The majority of patients (80%) denied alcohol consumption, but 61% were current or former smokers (Table 1).

3.1.2. Treatment regimens, patient satisfaction, and adherence

At baseline, 42% of patients (n = 233) were being treated with TNF- α antagonists (infliximab: 96; adalimumab: 137; Level4 regimens; Table 2). A similar cumulative percentage (40%) were receiving nonspecific drug therapy (Level1) or no drugs at all (Level0). One out of 10 patients was receiving a non-biological immunosuppressant (thiopurine or methotrexate, Level3) and a smaller group was treated with systemic steroid therapy (Level2).

Overall satisfaction with the prescribed drug regimens, according to the TSQM, was 50.1/100 (Table 2A). At baseline, patients showed greater satisfaction for their treatments' side effects. Level4 drugs showed higher scores in overall satisfaction (Table 2B). Self-reported adherence to therapy was excellent, with mean MARS scores indicative of almost complete adherence. The most common nonadherence was related to forgetfulness. Higher scores for Level4 vs lower level drugs were reported for adherence and satisfaction (Table 2B).

3.1.3. HRQoL and CD-related concerns

Generic QoL was measured using the EQ-5D questionnaire (Table 3). Pain/discomfort was the most common complaint: 90% of the respondents experienced some degree of difficulty: almost 20% rated these problems as extreme (data not shown). Anxiety/depression was also a prevalent concern: 53% reported some and 10% severe problems (data not shown). The mean VAS rating of overall health was mediocre (54/100). VAS scores were lower in patients who had previously undergone a surgical treatment for CD (52.4 ± 21.0 vs. 55.9 ± 20.4 ; $p = 0.05$) and for those who had a disease duration >6 years at diagnosis (52.4 ± 21.0 vs. 56.1 ± 20.4 ; $p = 0.041$); no differences were observed comparing the drug classes (data not shown).

The responses to the RFIPC are summarized in Table 4. At baseline, the top 2 CD-specific worries involved undergoing surgery and having to use an ostomy bag. The mean total RFIPC score at baseline was 47.5 ± 21.9 . The demographic and clinical variables associated with higher scores were female sex ($p < 0.0001$), disease activity ($p < 0.0001$), suboptimal adherence to treatment (defined as MARS <25; $p < 0.0001$), and current smoking ($p < 0.0001$). The stratifications of RFIPC scores with time from diagnosis (</ ≥ 12 , $\leq$ / > 12 and $\leq$ / > 24 months) did not reveal any statistical difference between early and late CD patients (Supplementary Table 3).

More detailed characterization of the smokers in the study (Supplementary Table 4) revealed that their mean baseline HBI score was significantly higher than that of nonsmokers (10.9 vs. 9.9; $p = 0.003$) and former smokers (10.1, not statistically significant). Former smokers were older (mean age, 45 years vs. 41 years), predominantly male (62% vs. 46%), had longer-standing disease (mean years from diagnosis, 8 years vs. 6 years) and had higher ratings of overall health (mean EQ-5D VAS scores, 55 vs. 51) compared with current smokers. Current smokers were significantly more concerned about CD than former smokers (mean scores, 51 vs. 45, $p = 0.039$), with particular concern about the impact of the disease on their lives (mean score, 58 vs. 50) and its complications (mean domain scores, 64 vs. 58).

3.1.4. Work productivity and activity impairment

Roughly half the participants were employed: mean age and HBI score of working and not working patients were similar (40.9 ± 10.5 and 41.8 ± 16.9 years; 10.1 ± 2.8 and 10.6 ± 3.5 , respectively); 83% of workers had full time jobs.

The WPAI-CD responses (Table 5) showed that work productivity was reduced by approximately 25%, mainly due to presenteeism (e.g., job effectiveness) rather than absenteeism (hours of work lost). TAI, rated by all participants, was 55%. A statistically significant improvement was observed in the association between TAI and use of TNF inhibitors and azathioprine ($p < 0.01$). All 4 impair-

Table 2

Treatment regimens, patient satisfaction, and adherence and their stratifications.

(A) Treatment regimens, patient satisfaction, and adherence.											
Variable		Baseline				M3		M6		M12	
Treatment regimens, n (%)											
Level 4. Anti-TNF inhibitors ^a		233 (42)				270 (55)		267 (57)		251 (53) [†]	
Level 3. Nonbiological immunosuppressants ^b		62 (11)				57 (12)		55 (12)		46 (10)	
Level 2. Systemic corticosteroids ^c		37 (7)				32 (7)		19 (4)		14 (3)	
Level 1. Nonspecific regimens ^d		138 (25)				83 (17)		80 (17)		81 (17)	
Level 0. No drugs for CD		82 (15)				52 (11)		48 (10)		79 (17)	
TSQM 14 scores, mean (SD)											
Global satisfaction		50.1 (21.3)				57.7 (18.4)		57.1 (18.4)		59.2 (19.2)	
Effectiveness		52.0 (21.5)				57.8 (20.8)		56.7 (22.1)		58.7 (22.2)	
Side effects		85.9 (23.6)				91.1 (19.8)		92.1 (18.9)		92.1 (20.1)	
Convenience		69.2 (17.7)				69.3 (17.4)		69.2 (16.9)		69.8 (17.9)	
MARS scores, mean (SD)											
Total score		22.7 (4.2)				23.2 (3.5)		23.6 (3.1)		23.5 (3.2)	
Forgetting to use drug		4.4 (0.8)				4.4 (0.8)		4.5 (0.7)		4.5 (0.8)	
Altering dose		4.8 (0.6)				4.8 (0.7)		4.9 (0.5)		4.8 (0.5)	
Stop taking it for a while		4.7 (0.7)				4.7 (0.6)		4.8 (0.5)		4.8 (0.6)	
Skipping a dose		4.7 (0.7)				4.7 (0.6)		4.8 (0.5)		4.8 (0.6)	
Taking less than instructed		4.8 (0.6)				4.8 (0.7)		4.9 (0.4)		4.8 (0.6)	
B) TSQM and MARS scores by treatment regimens											
		TSQM				MARS					
		Baseline	M3	M6	M12	Baseline	M3	M6	M12		
L0	N	13	1	0	0	13	2	0	1		
	Mean (SD)	53.85 (22.5)	42.86			22.31 (5.7)	21.5 (4.9)		13		
L1	N	108	73	67	76	137	90	81	79		
	Mean (SD)	44.3 (18.8)	52.35 (19.5)	53.41(17.6)	54.79 (16.9)	21.54 (4.6)	22.16 (4.2)	22.62 (4.6)	22.59 (3.9)		
L2	N	96	43	27	22	85	49	25	22		
	Mean (SD)	42.93 (22.5)	53.16 (21.9)	49.47 (19.3)	55.2 (22.7)	22.81 (4.2)	21.8 (4.8)	22.96 (3.3)	23.14 (3.8)		
L3	N	74	67	63	64	74	70	65	68		
	Mean (SD)	44.5 (19.6)	57.89 (17.9)	57.03 (20.2)	59.82 (19.2)	22.65 (4.2)	23.5 (1.9)	23.51 (2.1)	23.49 (2.2)		
L4	N	224	286	291	285	210	255	270	271		
	Mean (SD)	57.65 (20.0)	59.71 (17.4)	58.66 (17.4)	60.48 (19.4)	23.43 (3.7)	23.74 (3.0)	24 (2.7)	23.8 (3.1)		

CD, Crohn's disease; MARS, Medication Adherence Rating Scale (scores 5–25; higher scores = better adherence); SD, standard deviation; TNF, tumor necrosis factor; TSQM, Treatment Satisfaction Questionnaire for Medication (scores 0–100; higher scores = greater satisfaction).

^a Includes adalimumab, golimumab, and infliximab.

^b Includes azathioprine and methotrexate.

^c Includes corticosteroids.

^d Includes antidiarrheal, antimicrobial, and/or anti-inflammatory drugs.

* $p < 0.001$ vs. baseline values.

Table 3

EQ-5D assessments of generic health-related quality of life.

EQ-5D Results	Baseline ^a	M3 ^b	M6 ^c	M12 ^d
Percentage with problems ^e related to:				
Mobility	33%	24%	24%	21%
Self-care	15%	11%	11%	10%
Usual activity	60%	46%	42%	38%
Pain/discomfort	87%	67%	60%	58%
Anxiety/depression	64%	53%	51%	51%
Overall health rating (VAS), mean (SD) ^f	54.3 (20.8)	66.2 (17.4)	67.4 (17.2)	68.8 (17.5)

EQ-5D, EuroQol 5 Dimensions; SD, standard deviation; VAS, visual analog scale.

^a No. of participants who rated the 5 dimensions: 535–538; no. who rated overall health (VAS): 536.

^b No. of participants who rated the 5 dimensions: 480–482, no. who rated overall health (VAS): 480.

^c No. of participants who rated the 5 dimensions: 457–459, no. who rated overall health (VAS): 457.

^d No. of participants who rated the 5 dimensions: 459–462, no. who rated overall health (VAS): 462.

^e Includes Level 2 (some problems) and Level 3 (extreme problems) responses.

^f Inverse correlation with Harvey-Bradshaw Index score at all time points ($p < 0.0001$).

ment scores were significantly correlated with increasing HBI score ($p < 0.01$), increasing age (>55 vs. 18–25 years; $p < 0.01$), and female sex ($p < 0.01$).

3.2. Follow-up

Eighty-six percent of patients completed the study. The 78 non-completers included 2 deaths (post-surgery complications), 18 protocol deviations (10 enrolled in clinical trials, 2 neoplasia,

6 informed consent withdrawal), and 58 lost to follow-up. The baseline profiles of the non-completer and completer subgroups were not significantly different in age, gender, HBI, EQ-5D VAS, or treatment level (data not shown).

3.2.1. Disease evolution

At M12 the mean HBI was less than half the score recorded at baseline (4.4 vs. 10.3; $p < 0.001$; Table 6). Among all treatments, patients treated with anti-TNF- α inhibitors had lower mean

Table 4
Mean scores of patients' CD-related concerns during the study^a.

Concern	Baseline ^b	M3	M9	M12	Score Δ^c	P value ^d
Having an ostomy bag	68.6	68.6	66.4	66.8	↔	0.325
Having surgery	67.9	68.2	65.9	68.3	↔	0.852
Achieving full potential	65.9	61.0	57.8	56.6	↓	<0.01
Pain or suffering	64.9	61.2	59.1	57.5	↓	<0.01
Energy level	63.1	58.3	56.9	54.7	↓	<0.01
Being a burden on others	60.6	57.7	54.2	52.1	↓	<0.01
Loss of bowel control	60.4	57.7	56.2	54.5	↓	<0.01
Uncertain nature of disease	60.0	57.8	56.98	56.2	↓	0.015
Effects of medication	59.2	55.6	55.4	52.1	↓	<0.01
Developing cancer	56.3	58.5	56.8	57.2	↔	0.767
Access to quality care	52.1	49.3	46.9	45.5	↓	<0.01
Financial difficulties	51.9	47.9	47.9	47.2	↓	0.006
Body feelings	46.7	44.0	41.4	39.7	↓	<0.01
Unpleasant odors	46.0	45.2	42.9	41.7	↓	0.02
Dying early	45.8	48.2	46.7	47.0	↔	0.675
Feeling out of control	43.3	41.5	41.9	39.7	↓	0.01
Intimacy	39.3	40.4	37.9	35.2	↓	0.013
Feeling alone	38.1	39.7	38.1	36.3	↔	0.438
Loss of sexual drive	36.0	37.0	35.0	34.4	↔	0.361
Performing sexually	32.7	35.1	34.2	33.8	↔	0.568
Attractiveness	32.1	35.5	34.5	33.3	↔	0.537
Feeling dirty	29.1	35.3	35.5	34.5	↑	<0.01
Ability to have a child	27.8	28.9	28.4	27.7	↔	0.804
Being treated as different	23.4	27.4	26.6	26.4	↔	0.079
Passing the disease to others	14.0	16.1	14.7	13.3	↔	0.5
Sum score, mean (SD)	47.5	47.0	45.5	44.5	↓	0.001

^a Based on responses to the RFIPC questionnaire. Each item was rated using a 100-mm VAS (from 0 = no concern to 100 mm = highest concern). The sum score represents the mean of the 25 individual concern scores.

^b Baseline concerns are listed in decreasing order of rank.

^c Direction of significant score changes M12 vs. baseline: no significant change: ↔; decrease indicating less concern: ↓; increase indicating growing concern: ↑.

^d Overall trend during study (model for repeated measures).

Table 5
Work Productivity and Activity Impairment questionnaire: Crohn's Disease (WPAI-CD).

Variable	Baseline	M3	M6	M12
WPAI-CD scores, mean (SD)				
Work productivity loss	24.5 (34.6)	18.2 (29.4)	17.4 (27.4)	15.7 (26.1)
Absenteeism scores	5.5 (16.0)	3.4 (10.9)	2.9 (9.9)	2.8 (10.6)
Presenteeism scores	22.9 (32.8)	16.9 (28.0)	16.2 (25.9)	14.7 (24.6)
Daily activity impairment	55.1 (30.1)	38.5 (29.5)	37.4 (29.2)	32.8 (29.2)
Participants with paid employment, n (%)	267 (49.9)	238 (50.5)	235 (52.6)	243 (54.9)

CI, confidence interval; WPAI-CD, Work Productivity and Activity Impairment – Crohn's Disease.

WPAI-CD scores are expressed as a percentage of impairment; higher scores indicate greater impairment and reduced productivity. For absenteeism, presenteeism, and work productivity, scores are based on responses from participants with paid employment. Daily activity scores are based on responses by all participants. Mean changes from M0 to M12 (95% CI) can be reported in the text and correlated with other variables. (Larger negative changes indicate greater improvement.).

Table 6
Clinical evolution of CD during the study.

Variable	Baseline	M3	M6	M12	Delta (M12-Baseline)
HBI score, mean (SD)	10.3 (3.2)	5.6 (3.2)	5 (3.3)	4.4 (3.2)	↓57%
Non-HBI manifestations ^a	n = 552	n = 494	n = 469	n = 471	
Asthenia	298 (54.0)	138 (27.9)	120 (25.6)	103 (21.9)	↓59%
Weight loss	179 (32.4)	58 (11.7)	34 (18.2)	31 (6.6)	↓80%
Nausea	79 (14.3)	36 (7.3)	25 (7.2)	25 (5.3)	↓63%
Fever	70 (12.7)	13 (2.6)	17 (3.6)	16 (3.4)	↓73%
Vomiting	41 (7.4)	14 (2.8)	9 (1.9)	3 (0.6)	↓92%
Other	113 (20.5)	60 (12.1)	45 (9.6)	47 (10.0)	↓58%
No. of flares/year, mean (SD)	1.8 (1.4)	0.4 (0.7)	0.3 (0.6)	0.4 (0.6)	↓78%
Hospitalization rate (average per subject/year)	–	0.65	0.33	0.32	p < 0.001

HBI, Harvey-Bradshaw Index; SD, standard deviation.

^a Percentages calculated as%/total respondents.

HBI scores during the entire study ($p < 0.05$). A consistent number of patients (40% at baseline – 56% at the last visit) in this cohort reached indices of ≤ 4 , indicating clinical remission. Clinical improvement was also reflected by a significant decreases of flares ($p < 0.001$) and disease manifestations (asthenia, weight loss, nausea, fever, vomiting). The overall number of hospitalizations occurring during the study was 221, with a progressive decrease

from an average of 0.65 events per subject/year from baseline to M3, to 0.32 events per subject/year from M6 to M12 ($p < 0.001$).

As clinical parameters improved, there was a significant increase in the EQ-5D VAS ratings ($p < 0.0001$), and a significant decrease in the percentages of participants reporting problems in each of the 5 domains, although pain/discomfort and anxiety/depression remained at the top of the list (Table 3). Disease-related worries also

diminished (Table 4), as reflected by a significant drop in the mean RFIPC score from 47.5 at baseline to 44.5 at 12 months ($p=0.001$). Nine of the 12 concerns rated highest at baseline diminished significantly during the study.

3.2.2. Treatment regimens, patient satisfaction, and adherence

During the study, the percentage of patients on Level4 therapy increased significantly, while on Level1 regimens decreased. The increased reliance on biological agents was already evident by M3 (55% vs. 42%), and remained stable through the study (Table 2).

This trend was paralleled by an increase in overall satisfaction with the therapy, mainly efficacy (Table 2), although scores remained moderate. Mean TSQM scores were lowest at baseline (50.1), increased significantly ($p<0.001$) at M3 (57.7), and remained stable thereafter (59.2 at M12). In each regimen level, a moderate increase of the overall satisfaction was noted. In contrast, self-reported adherence was excellent from the start, with median overall scores indicative of complete-near complete adherence. No change in adherence was detected within each regimen, although higher scores were maintained for increasingly complex therapies (from Level1-4; Table 2). Variables associated in a linear regression model with a higher RFIPC score included female sex, higher disease activity, lower treatment adherence ($p<0.001$), previous surgical treatments ($p=0.003$).

The data on the scores of all the questionnaires stratified by the different levels of treatment are reported in Supplementary Table 5. No difference was noted comparing the mean values of MARS and TSQM of the three regions at each visit (Supplementary Table 6).

3.2.3. Work productivity and activity impairment

By the end of the study, CD-related impairment had diminished significantly in all areas considered (Table 5). The mean TAI score dropped by 40%, as confirmed also by the decreases in participants reporting problems in this area in the EQ-5D (Table 3). The improvement in work productivity was similar (overall score reduction of 36%, 49% in absenteeism and 36% for presenteeism). A statistically significant association was observed only for reduction of TAI and use of anti-TNF therapies and thiopurines ($p<0.01$).

4. Discussion

Many aspects of long-standing active CD impact patients' daily functioning, emotional/social well-being, overall quality of life, and work productivity. These complications contribute to the significant economic and HRQoL burdens associated with CD [14–17].

This study shows that in our CD population the highest worries were having an ostomy bag and undergoing surgery, and the variables significantly associated with a higher global RFIPC score included female sex, previous surgical treatments, disease activity, and lower treatment adherence. A significant improvement in workability and daily activities during the follow-up was observed, particularly in patients treated with anti-TNF- α and azathioprine.

Observational studies on HRQoL in Italian IBD patients have been extremely limited until now: 2 studies focused on differences in HRQoL following surgery [18,9] and a third study evaluated a small patient population [20]. A multinational study that included Italian patients with CD found cross-cultural variations in disease-related concerns [21]. To our knowledge, this is the first observational study conducted with a large cohort of Italian moderate-severe active CD patients.

An overall reduction in the clinical and psychological burden of disease was observed during the study in disease activity, flares, hospitalizations, and disease concerns, with a correlation between improvement in disease burden and biologic treatment, possibly due to the effect of newly initiated therapy. Since patients with HBI

score ≥ 8 were enrolled, it was very likely that the physician decided to change the initial therapy, fostering an improvement; furthermore, the effect of “being in a study,” with regular follow-up visits and accurate evaluations could have resulted in the “Hawthorne effect”, (“the observer effect”) that is a type of reactivity in which individuals improve an aspect of their behaviour in response to their awareness of being observed [22].

The highest rated worries in our cohort were having an ostomy bag, undergoing surgery, and not being able to achieve “full potential”. Previous studies reported the top 3 concerns as ostomy, energy level, and bowel control [23,24], and unpredictable flares-ups, need for an ostomy bag and risk of surgery [25]. This confirms that surgery and its consequences are the biggest worries for CD patients. Several concerns significantly decreased during follow-up, consistently with the clinical improvement. This can be explained by the fact that most worries refer to physical impairments due to the disease activity. On the other hand, fear of having surgery, developing cancer, dying early, being treated as different, or not being capable to have a child, tended to remain stable or increase probably due to an increasing awareness of disease chronicity and burden.

The variables significantly associated with a higher global RFIPC score included female sex, previous surgical treatments, disease activity, and lower treatment adherence. Female sex has been reported to be associated with higher concerns in several IBD studies [23,25], particularly related to self-image and relationships [26]. Other authors reported a higher level of concern over sexual performance and intimacy in women [26,27]. Blondel-Kucharski et al. [15] found that greater concerns and the psychological impact of IBD resulted in a lower HRQoL in women, hypothesizing greater worries in female patients about physical and cosmetic adverse events of drug therapy, especially steroids.

Patients' satisfaction is subjective: in our study a rather high treatment satisfaction, with higher scores for anti-TNF- α agents was shown. Consistent with treatment satisfaction, adherence to therapy was also high. Previous studies reported a non-satisfactory adherence to therapy in patients with IBD [28–30], suggesting that optimizing the information on disease/treatment strategies could enhance therapeutic compliance. The better results observed in our cohort may be due to the fact that patients were recruited in an observational study within routine visits with physicians more prone to explain study and CD-management characteristics.

It is well known that the course of CD is unfavorable for smokers [15,31]: active smoking has also been associated with a high prevalence of EIMs in patients with CD [32] and is recognized as the most significant factor affecting post-operative recurrence [33]. Despite the high level of concern about CD at baseline, the percentage of active smokers was high in our cohort, even though cessation of smoking is a major recommendation made to patients. Active smoking in our patient population was associated with higher disease activity and impact of disease, higher worries, and more complications.

Studies of the impact of anti-TNF- α therapy on work productivity in CD patients are limited: statistically significant and clinically meaningful improvements in all components of the WPAI were observed following adalimumab therapy in the CHOICE study [34]. Anti-TNF- α agents are effective in improving HRQoL and reducing the risk of hospitalization and surgery in moderate-severe active CD-patients, both in naïve patients and in those who failed prior anti-TNF- α agents [34]. In addition to the direct medical costs associated with hospitalization and surgery, CD is associated with substantial indirect costs due to disease-related work and activity impairment, particularly because the onset of CD is typically during early adulthood. A French meta-analysis of clinical trials assessed the effect of anti-TNF- α agents on work productivity and indirect costs in CD patients and concluded that these drugs provided clin-

ically meaningful improvements in work productivity, which may translate into substantial indirect cost savings from an employer's perspective [35]. In our study, we observed a significant improvement in workability and daily activities in patients treated with adalimumab, infliximab, and thiopurines.

A limitation of our study is that it was an observational, non-controlled trial in a real-world clinical practice setting. This does not allow us to draw conclusions about treatment changes and their effects; on the other hand, this study provides a picture of a large Italian cohort of patients with CD, not affected by the usual strict selection criteria of a controlled trial. Other limitations of our study are the selection bias, as the investigational sites in our study were of medium/high experience in IBD management (regional reference centers) and might have followed more severe patients than the average population, and the lack of assessment of IBD-unrelated psychiatric comorbidities, despite anxiety/depression was reported by 5% of patients. Crohn's disease causes a significant decrease in HRQoL and has a considerable economic cost to society, mainly due to hospitalizations and loss of productivity [36]. This analysis found that the major determinants of disease-related worries in Italian CD patients include female sex, degree of disease activity, previous surgical treatments, and lower adherence to treatment. The mix of patients on conventional treatment and anti-TNF- α inhibitors (both biologic-experienced and -naïve) reflects a real-world representation of patients with moderate-severe CD.

These results help to illustrate the importance of having a holistic view of patients, considering both clinical and psychological features, and empowering the patient–physician relationship. The burden of CD makes health programs and interventions essential for the reduction of the heavy impact of the disease on both patients and society.

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Conflicts of interest

Authors S. Di Fino, G. Gualberti, and R. Merolla are AbbVie employees and may own stocks and options. All other author's institutions received payment from AbbVie for participation in the study. No payments were made for drafting or reviewing this publication.

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Ethical approval

The SOLE study has been approved by local Ethics Committees according to Italian regulations.

Informed consent

Informed consent was obtained from all individual participants included in the study

Research involving human participants

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.dld.2018.12.019>.

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