Annals of Gastroenterology (2025) **38,** 629-640

Disease burden and unmet medical need in patients with Crohn's disease in Greece: a cross-sectional patient survey

Charalampos Tzanetakos[a], Vasiliki-Rafaela Vakouftsi[b], George Mavridoglou[c], Marina Psarra[a], George Gourzoulidis[a]

Health Through Evidence GP, Athens; Hellenic Society of Crohn's Disease's and Ulcerative Colitis' patients (HELLESCC), Athens; University of Peloponnese, Kalamata, Greece

Abstract

Background Improving Crohn's disease (CD) management requires a comprehensive understanding of the disease's full impact. This real-world, patient-reported survey investigated the disease burden and unmet medical needs among Greek patients with CD.

Methods Between October 2023 and January 2024, members of the Hellenic Society of Crohn's Disease and Ulcerative Colitis Patients (HELLESCC) completed a structured questionnaire. The questionnaire captured demographics, disease and treatment characteristics, as well as patient-reported outcomes: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Work Productivity and Activity Impairment (WPAI), Patient Health Questionnaire-9 (PHQ-9), treatment satisfaction, and treatment adherence. To determine associated factors, both univariate and multivariate logistic regression analyses were carried out.

Results Among 240 CD patients, 52.9% had active disease and 83.7% were treated with advanced therapies (biological/small molecule agents). Approximately 73.1% reported impaired quality of life (QoL) (SIBDQ <60), 30.9% reduced work productivity, and 36.0% limitations in daily activities. Nearly half (46.1%) reported moderate-to-severe depressive symptoms (PHQ-9 ≥10). Four of 10 patients expressed dissatisfaction with their treatment and 9.9% reported reduced adherence. Higher disease activity was associated with poorer QoL, reduced work productivity, worse mental health, and lower treatment satisfaction. Notably, 76.3% of patients on advanced therapies reported impaired QoL. Of these, 30.9% were in clinical remission.

Conclusions In Greece, CD patients continue to bear a substantial disease burden, evidenced by reduced QoL, impaired work productivity and daily activity, high rates of depression, and persistent disease activity. A significant proportion also reported dissatisfaction with their treatment, underscoring ongoing unmet needs in disease management.

Keywords Crohn's disease, disease burden, unmet medical need, patient-reported outcomes

Ann Gastroenterol 2025; 38 (6): 629-640

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by periods of remission and recrudescence [1]. The burden of CD extends beyond the clinical manifestations, adversely affecting employment, work productivity and social engagement [2]. Consequently, patients experience a significant deterioration in psychological functioning and health-related quality of life (HRQoL) [2,3].

According to global research, patients often perceive their disease burden differently from clinicians, prioritizing symptom severity and HRQoL outcomes over traditional clinical metrics [4,5]. Fatigue, for example, is identified as the most distressing symptom, affecting over 80% of patients and approximately 50% of those in remission [6]. In response to these challenges, initiatives such as STRIDE-II, by the

Conflict of Interest: VRV is the president of HELLESCC. GG and CT are owners of Health Through Evidence. The other authors have no conflicts of interest that are directly relevant to the content of this study.

Funding: This work was supported by the Hellenic Society of Crohn's disease's and Ulcerative Colitis' patients (HELLESCC)

Correspondence to: Charalampos Tzanetakos, Health Through Evidence, Athens, Greece, 25, Agiou Panteleimonos St, Alimos, Athens 17456, Greece, e-mail: c.tzanetakos@hte.gr

Received 5 June 2025; accepted 4 September 2025; published online 10 October 2025

DOI: https://doi.org/10.20524/aog.2025.1013

International Organization for the Study of Inflammatory Bowel Disease, recognize improvement of HRQoL as an essential long-term treatment target [7]. The European Crohn's and Colitis Organisation (ECCO) also underlines the need to assess HRQoL and patient satisfaction as part of optimal standards of care [8].

Patient-reported outcomes (PROs) capture patient's perception of their HRQoL, work efficiency and mental health [9]. These measures are increasingly required by regulatory agencies, and are used as primary endpoints in clinical trials [10,11]. Validated tools for assessing PROs in CD include the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) for disease-specific QoL [2,12-14], the CD-related Work Productivity and Activity Impairment (WPAI) questionnaire for absenteeism, presenteeism and activity impairment [15-17], and the Patient Health Questionnaire-9 (PHQ-9) for depressive symptoms [18-20].

Real-world PRO data are particularly valuable, as they can identify unmet needs, inform shared decision-making, and support value-based care strategies. Moreover, they provide critical insights into the actual impact of disease and treatment beyond controlled clinical settings, guiding the development of more patient-centered healthcare approaches. In Greece, however, evidence on patient-reported burden and unmet needs in CD remains scarce. Hence, the primary objective of this survey was to assess the overall disease burden and unmet medical needs of CD patients, using a comprehensive set of validated PRO instruments. The study also investigated the associations between demographic and disease-related factors and these PROs.

Materials and methods

Study design and population

Between October 2023 and January 2024, a cross-sectional survey was conducted using a structured questionnaire, in collaboration with Hellenic Society of Crohn's disease and Ulcerative Colitis patients (HELLESCC). Eligible participants were adults diagnosed with CD and members of the association. All candidates received the questionnaire as a link via email or phone. Recruitment was managed by HELLESCC staff without collecting personal data. All participants were informed of the study's purpose, provided consent, and participated voluntarily, with the option to withdraw at any time. Responses were anonymous and treated with strict confidentiality.

Questionnaire and variables

The questionnaire was developed in the Greek language. Data were collected for sociodemographic characteristics, smoking status, comorbidity history, disease activity and other characteristics, current CD treatments, and PROs, including SIBDQ, WPAI-CD, PHQ-9, treatment satisfaction, and treatment adherence. Disease activity was assessed using the Harvey-Bradshaw Index (HBI), and the following categories were defined based on score: remission (0-4), mild (5-7), moderate (8-16) and severe (>16) [21]. All prescribed CD therapies available at the time of the survey were recorded and classified as advanced (tumor necrosis factor inhibitors [TNFi], α4-integrin inhibitor, interleukin-12/23 inhibitor [IL-12/23i], and Janus kinase inhibitors [JAKi]) or non-advanced (5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics) treatments.

The questionnaire included validated measures for the evaluation of the following PROs: QoL (SIBDQ), work productivity (WPAI), and psychological burden (PHQ-9) [13,15,18]. The SIBDQ ranges from 10-70, with scores interpreted as follows: 60-70 (mild/no impairment), 45-59 (moderate impairment) or 10-44 (severe impairment) [2,14,22]. In this study, a score lower than 60 indicated moderate-to-severe QoL impairment, while scores of 60 or higher reflected normal QoL. The WPAI score (0-100%), measures absenteeism (work time missed), presenteeism (impairment at work), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment [2,15,16]. Although thresholds have not been established, severity was categorized following Williet *et al*, [2] as mild (0-19%), moderate (20-49%), or severe (≥50%). The PHQ-9 score ranges from 0-27, with increasing scores indicating more severe depressive symptoms: 0-4 (none or minimal), 5-9 (mild), 10-14 (moderate), 15-19 (moderately severe), or 20-27 (severe). The cutoff point of 10 or greater corresponds to a moderate-to-severe condition, potentially indicating clinically significant depression [18,20,22]. This study employed the validated Greek versions of the HBI, SIBDQ, WPAI-CD and PHQ-9 questionnaires, which are all freely available [23-26].

Treatment satisfaction was evaluated with a 5-scale Likert study-specific question (not at all; not very; quite; very; extremely satisfied). Participants who reported dissatisfaction (responses of "not at all," "not very," or "quite") were asked to provide the reasons. Treatment adherence was assessed using a separate, study-specific 5-point Likert scale (I follow my treatment regularly; occasionally I forget to/do not take my treatment; sometimes I forget to/do not take my treatment; often I forget to/do not take my treatment; I never take my treatment). Patients who did not follow their treatment regularly selected from a list of reasons for their non-adherence.

Statistical analysis

Categorical variables were reported using frequencies (n) and percentages (%), while continuous variables were described using means and standard deviations (SD). Socio-demographic variables, clinical variables, and PROs (SIBDQ, WPAI-UC, PHQ-9, treatment satisfaction, and treatment adherence) were categorized by treatment type (advanced or

[a]Health Through Evidence GP, Athens, Greece (Charalampos Tzanetakos, Marina Psarra, George Gourzoulidis); [b]Hellenic Society of Crohn's Disease's and Ulcerative Colitis' patients (HELLESCC), Athens, Greece (Vasiliki-Rafaela Vakouftsi); [c]University of Peloponnese, Kalamata (George Mavridoglou), Greece

non-advanced). Associations between treatment type and sociodemographic and disease characteristics were assessed using Pearson's chi-squared test for categorical variables and the Mann–Whitney U test for continuous variables. Differences in means or proportions between the advanced and non-advanced treatment groups were also calculated, along with their respective 95% confidence intervals (CIs). CIs improve clinical interpretation by providing a plausible range of values and reflecting both the magnitude and direction of the effect [27]. It is essential to emphasize that these comparisons are cross-sectional and should not be interpreted as reflecting treatment response. Relationships between PROs and disease activity were quantified using Spearman's correlation coefficient (SCC). In addition, the relationship between PROs and sociodemographic and disease characteristics was examined through both bivariate and multivariate logistic regression analyses. Variables with a P-value <0.15 in the bivariate analysis were entered into a multivariate logistic regression model using stepwise selection. Results are presented as odds ratios (ORs) with 95%CIs. Statistical significance was defined as P<0.05. All data processing and analyses were performed using IBM SPSS Statistics version 29.0.

Results

Participants' characteristics

The questionnaire was sent to 871 CD patients and returned by 275 (participation rate: 31.5%). The final analysis included 240 CD patients (35 respondents who were not receiving any drug therapy for CD were excluded), with 47.1% in remission, 25% with mild disease, and 27.9% in moderate-to-severe disease. The mean age (±SD) was 42.5±10.5 years, and 41.7% of patients were male. Approximately 4 of 10 were active smokers (40.8%), and a similar percentage (37.1%) had undergone CD-related surgery. The mean age at diagnosis was 31.1±10.7 years and the mean disease duration was 11.4±7.8 years. Interestingly, the mean time between symptom onset and diagnosis was 14.8±17.9 months. Over the previous year, the mean number of gastroenterologist visits was 3.1±3.6, and 14.1% were hospitalized at least once. One or more comorbidities were reported in 63.9% of patients (Supplementary Table 1). These and other patients' characteristics are presented in Table 1.

The majority of the participants (83.7%) were treated with advanced therapies (alone or in combination with non-advanced therapies), while 16.2% received non-advanced treatment. In the advanced therapy group, patients were younger (41.8 vs. 46.5 years, P=0.029) and had lower rates of being married (50.4% vs. 71%, P=0.037) and in paid employment (53.9% vs. 71%, P=0.082). The mean age at diagnosis was significantly lower in advanced treatment recipients (30.5 vs. 34.3 years, P=0.042) and the delay from symptom onset to diagnosis was longer (15.6 vs. 11.0 months, P=0.036). During the previous 12 months, surgery (40.3% vs. 22.6%, P=0.039) and gastroenterologist visits (3.7 vs. 2.1, P=0.002) were more common in the advanced group, and hospitalizations occurred exclusively among patients receiving advanced therapies (17.3% vs. 0%, P<0.001). Higher disease activity (moderate-to-severe: 31.3% vs. 10.2%, P=0.011) was reported in advanced treatment patients.

Patient-reported outcomes

Table 2 presents the data on PROs. The mean SIBDQ score was estimated at 46.7±15.0. The majority of participants (73.1%) reported moderately to severely impaired QoL (SIBDQ<60), with a significantly higher proportion in the advanced treatment group compared to the non-advanced group (76.3% vs. 58.8%, P=0.038). Notably, among patients in the advanced treatment group who reported impaired QoL, 30.9% were in remission.

Of 182 patients who completed the WPAI questionnaire, 107 (58.8%) were in paid employment and eligible to respond. The mean absenteeism was 10.4±21.9%, while nearly a third of the participants reported presenteeism (25±27.7%), work productivity loss (30.9±32.4%), and activity impairment (36±32.5%). Moderate-to-severe absenteeism, presenteeism, work productivity and activity impairment were reported by 17.5%, 53.2%, 55.7% and 63.5% of patients, respectively. Moderate-to-severe activity impairment was significantly more common in the advanced group (68.3% vs. 42.4%, P=0.005).

Around half of the participants (46.1%) reported moderate-to-severe depressive symptoms. The mean PHQ-9 score was 9.7±7.6, which is just under the borderline (≥10) of moderate-to-severe depression.

Overall, 39.2% of the participants were "not at all," "not very" or "quite" satisfied with their treatment. Four in 10 of advanced recipients were dissatisfied, with "increasing fatigue" being the primary reason (17%) (Supplementary Table 2). Almost one tenth (9.9%) of the total population were non-adherent, as were one third of the patients (33.3%) in the non-advanced treatment group (Supplementary Table 3).

Univariate and multivariate analyses

Univariate and multivariate logistic regression analyses were conducted to determine the factors linked to moderately to severely impaired quality of life (SIBDQ<60), moderate-to-severe overall work impairment (WPAI≥20%), moderate-to-severe depressive symptoms (PHQ-9≥10), as well as low levels of treatment satisfaction and adherence (Tables 3-5 and Supplementary Tables 4 and 5).

In the multivariate analyses, the risk of moderately to severely impaired QoL was significantly higher in patients without paid employment (OR 5.07, 95%CI 1.74-14.79; P=0.003) and those with active disease (OR 19.71, 95%CI 5.99-64.81; P<0.001). The risk of moderate-to-severe overall work impairment was significantly greater in women, who had a more than threefold risk compared to men (OR 3.30, 95%CI 1.06-10.27; P=0.04), and in patients with active disease (OR 11.16, 95%CI 3.14-39.74; P<0.001).

Table 1 Characteristics of the study population

Characteristics	Total (n=240)	Advanced therapies[a] (n=201)	Non-advanced therapies[b] (n=39)	Difference (95%CI) [c]	P-value[d]
Age, years					
Mean±SD	42.5±10.6	41.8±10.1	46.5±12.3	-4.7 (-8.3 to -1.1)	0.029
Sex, n (%)					
Male	100 (41.7%)	81 (40.3%)	19 (48.7%)	-8.4% (-25.1 to 8.3%)	0.329
BMI, n (%)					
Underweight (<18.5)	10 (4.2%)	9 (4.5%)	1 (2.6%)	1.9% (-7.2% to 7.3%)	0.584
Normal (18.5-25)	84 (35.0%)	71 (35.3%)	13 (33.3%)	2.0% (-14.7 to 17.3%)	0.812
Overweight (25-30)	100 (41.7%)	84 (41.8%)	16 (41.0%)	0.8% (-16.1 to 16.9%)	0.929
Obese (≥30)	46 (19.2%)	37 (18.4%)	9 (23.1%)	7.3% (-19.9 to 8.5%)	0.498
Residence, n (%)					
Urban area (>10.000)	204 (85%)	172 (85.6%)	32 (82.1%)	3.5% (-8.3 to -17.8%)	0.573
Family status, n (%)	n=172	n=141	n=31	-20.6% (-37.0 to -1.7%)	0.037
Married	93 (54.1%)	71 (50.4%)	22 (71.0%)		
Socioeconomic status, n (%)	n=172	n=141	n=31		
In paid employment[§]	98 (57.0%)	76 (53.9%)	22 (71.0%)	-17.1% (-33.5 to -1.8%)	0.082
Education level, n (%)	n=172	n=141	n=31	-12.7% (-30.2 to 9.5%)	0.197
Bachelor degree or more, n (%)	93 (54.1%)	73 (51.8%)	20 (64.5%)		
Smoker, n (%)					
Current smoker	98 (40.8%)	83 (41.3%)	15 (38.5%)	2.8% (-1.0 to 18.8%)	0.742
Former smoker	64 (26.7%)	50 (24.9%)	14 (35.9%)	-11.0% (-27.4 to 4.4%)	0.154
Never smoker	78 (32.5%)	68 (33.8%)	10 (25.6%)	8.2% (-8.4 to 21.2%)	0.318
Age at diagnosis, years					
Age at diagnosis, Mean±SD	31.1±10.7	30.5±10.5	34.3±11.2	-3.8 (-7.5 to -0.2)	0.042
Disease duration, years					
Disease duration, Mean±SD	11.4±7.8	11.3±7.6	12.2±8.8	-0.9 (-3.6 to 1.8)	0.337
Time from symptoms' onset to diagnosis, months					
Time on onset, Mean±SD	14.8±17.9	15.6±19.0	11.0±10.4	4.5 (0.3 to 8.9)	0.036
Surgery, n (%)	n=170	n=139	n=31		
Surgery	63 (37.1%)	56 (40.3%)	7 (22.6%)	17.7% (2.5 to 32.9%)	0.039
Gastroenterologist visits in the past 12 months	n=170	n=139	n=31	2.2 (0.8 to 3.5)	0.002
Number of visits, Mean±SD	3.1±3.6	3.5±3.7	1.4±2.1		
Hospitalization in the past 12 months, n (%)	n=170	n=139	n=31		
Hospitalization	24 (14.1%)	24 (17.3%)	0 (0%)	17.3% (6.1 to 23.3%)	<0.001
Comorbidities, n (%)	n=169	n=138	n=31		
One or more	108 (63.9%)	91 (65.9%)	17 (54.8%)	11.1% (-6.9 to 29.7%)	0.245
Disease Activity*, n (%)					
Remission	113 (47.1%)	87 (43.3%)	26 (66.7%)	-23.4% (-31.5 to -8.4%)	0.007
Mild	60 (25%)	51 (25.4%)	9 (23.1%)	2.3% (-13.2 to 15.7%)	0.762
Moderate-to-severe	67 (27.9%)	63 (31.3%)	4 (10.2%)	21.1% (7.5 to 31.2%)	0.007
Moderate	64 (26.7%)	60 (29.9%)	4 (10.3%)	--	--
Severe	3 (1.3%)	3 (1.5%)	0 (0%)	--	--
Ongoing treatment					
Non-advanced therapies, n (%)					
5-ASA	25 (10.4%)	14 (7%)	11 (28.2%)		
Corticosteroids	17 (7.1%)	15 (7.5%)	2 (5.1%)		
Immunosuppressants	64 (26.7%)	36 (17.9%)	28 (71.8%)		
Antibiotics	10 (4.2%)	8 (4%)	2 (5.1%)		

(Contd...)

Table 1 *(Continued)*

Characteristics	Total (n=240)	Advanced therapies[a] (n=201)	Non-advanced therapies[b] (n=39)	Difference (95%CI) [c]	P-value[d]
Advanced therapies, n (%)					
TNF inhibitors	145 (60.4%)	145 (72.1%)			
Integrin α4 inhibitor	11 (4.6%)	11 (5.5%)			
Interleukin-12/23 inhibitor	43 (17.9%)	43 (21.4%)			
JAK inhibitors	2 (0.8%)	2 (1%)			

*Harvey-Bradshaw Index (HBI): remission: <4; mild: 5-7; moderate: 8-16; severe: >16
[§]Full- or part-time employment or self-employed
[a]Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitor, interleukin-12/23 inhibitors, and Janus kinase inhibitors
[b]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics
[c]Unadjusted mean difference (95%CI) between groups for continuous variables and difference in percentage points (95%CI) between groups for categorical variables
[d]Pearson's χ^2 test or Mann-Whitney test
5-ASA, 5-aminosalicylic acid; BMI, body mass index; JAK, Janus kinase; SD, standard deviation; TNF, tumor necrosis factor

Table 2 Patient-reported outcomes in the study population

Outcomes	Total (n=240)	Advanced Therapies[a] (n=201)	Non-advanced Therapies[b] (n=39)	Difference (95%CI) [c]	P-value[d]
Quality of life					
SIBDQ	n=182	n=148	n=34		
Mean±SD	46.7±15.0	45.4±15.4	52.7±11.8	-7.4 (-12.9 to -1.8)	0.003
Moderate-to-severe impact<60, n (%)	133 (73.1%)	113 (76.3%)	20 (58.8%)	17.5% (0.2 to 35.2%)	0.038
Productivity loss					
WPAI					
Absenteeism	n=97	n=77	n=20		
Mean±SD	10.4±21.9%	11.8±23.6%	5.1±12.2%	6.7% (-4.2 to 17.6%)	0.084
Moderate-to-severe impact≥20%, n (%)	17 (17.5%)	15 (19.5%)	2 (10%)	9.5% (-10.2 to 23.5%)	0.235
Presenteeism	n=94	n=74	n=20		
Mean±SD	25.0±27.7%	22.4±25.1%	34.5±34.7%	-12.1% (-29.2 to 5.0%)	0.158
Moderate-to-severe impact≥20%, n (%)	50 (53.2%)	38 (51.4%)	12 (60.0%)	-8.6% (-31.2 to 15.6%)	0.492
Work productivity loss	n=97	n=77	n=20		
Mean±SD	30.9±32.4%	29.4±31.4%	36.5±36,2%	-7.1% [-23.2 to 9.1%]	0.386
Moderate-to-severe impact≥20%, n (%)	54 (55.7%)	42 (54.5%)	12 (60.0%)	-5.5% (-28.0 to 18.6%)	0.662
Activity impairment	n=178	n=145	n=33		
Mean±SD	36.0±32.5%	37.9±32.0%	27.6±34.1%	10.4% (-2.0 to 23.4%)	0.099
Moderate-to-severe impact≥20%, n (%)	113 (63.5%)	99 (68.3%)	14 (42.4%)	25.9% (7.1 to 43.2%)	0.005
Psychological burden					
PHQ-9	n=178	n=145	n=33		
Mean±SD	9.7±7.6	10.1±7.7	7.8±7.1	2.3 (-0.6 to 5.1)	0.061
Moderate-to-severe impact≥10, n (%)	82 (46.1%)	68 (46.9%)	14 (42.4%)	-4.5% (-14.2 to 22.4%)	0.642
Treatment satisfaction	n=227	n=188	n=39		
Yes, n (%)[¥]	138 (60.8%)	110 (58.5%)	28 (71.8%)	-13.3% (-27.9 to 3.3%)	0.122
Treatment adherence	n=222	n=183	n=39		
Yes, n (%)[§]	200 (90.1%)	174 (95.1%)	26 (66.7%)	28.4% (13.9 to 43.8%)	<0.001

[¥]Responses for "very/extremely satisfied"
[§]Responses for "I follow my treatment regularly"
[a]Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors
[b]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics
[c]Unadjusted mean difference (95%CI) between groups for continuous variables and difference in percentage points (95%CI) between groups for categorical variables
[d]Pearson's χ2 test or Mann–Whitney test
PHQ-9, Patient Health Questionnaire-9; PROs, Patient-Reported Outcomes; SD, standard deviation; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; WPAI, Work Productivity and Activity Impairment

Table 3 Factors associated with moderately to severely (SIBDQ <60) impaired QoL: univariate and multivariate logistic regression analyses

SIBDQ	Univariate analysis		Multivariate analysis	
	OR [95%CI]	P-value	OR [95%CI]	P-value
Sex				
Male	Ref	0.005	Ref	
Female	2.54 [1.32-4.9]		1.23 [0.49-3.09]	0.658
Age				
<50 years	Ref			
50 years or more	1.18 [0.57-2.45]	0.655		
Employment status				
In paid employment	Ref		Ref	
Without paid employment	3.22 [1.54-6.71]	0.002	5.07 [1.74-14.79]	0.003
BMI				
Underweight and normal	Ref			
Overweight and obese	1.32 [0.69-2.51]	0.403		
Smoking status				
Never smoker	Ref		Ref	
Former smoker	1.53 [0.67-3.48]	0.313	2.37 [0.72-7.82]	0.157
Current smoker	1.94 [0.89-4.22]	0.095	1.98 [0.66-5.94]	0.225
Disease activity*				
Inactive	Ref		Ref	
Active	19.07 [7.05-51.55]	<0.001	19.71 [5.99-64.81]	<0.001
Age at diagnosis				
0-30 years	Ref			
>30 years	1.33 [0.69-2.54]	0.39		
Disease duration				
<10 years	Ref			
10-19 years	1.08 [0.5-2.28]	0.849		
20 years or more	0.66 [0.29-1.5]	0.321		
Surgery				
No	Ref			
Yes	1.12 [0.57-2.2]	0.75		
Hospitalization in the past 12 months				
No	Ref			
Yes	1.21 [0.45-3.26]	0.704		
Ongoing treatments[ł]		0.041		0.933
Non-advanced	Ref		Ref	
Advanced	2.26 [1.03-4.94]		1.05 [0.39-3.26]	
Comorbidities				
None	Ref		Ref	
One or more	4.06 [2.04-8.08]	<0.001	2.65 [0.98-7.16]	0.055

*Inactive: Patients in remission. Active: Patients with mild, moderate or severe disease activity

[ł]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics. Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors

CI, confidence interval; BMI, body mass index; OR, odds ratio; ref, reference value; SIBDQ, Short Inflammatory Bowel Disease Questionnaire

Multivariate analysis also confirmed that smoking, disease activity and the presence of comorbidities were significantly associated with depression. In particular, participants who were current smokers (OR 2.67, 95%CI 1.02-7.03; P=0.047), those with active disease (OR 8.93, 95%CI 3.94-20.27; P<0.001), and patients with 1 or more comorbidities (OR 2.84, 95%CI 1.16-6.94; P=0.022) were more likely to report moderate-to-severe depressive symptoms.

Active disease was also found to be associated with lower odds of treatment satisfaction, indicating a 70% reduction compared to patients in remission (OR 0.30, 95%CI 0.14-0.65; P=0.002) (Supplementary Table 4). Additionally, patients without paid employment had 53% lower odds of being satisfied with their treatment, compared to patients with paid employment (OR 0.47, 95%CI 0.22-0.98; P=0.045). Regarding treatment adherence, current smokers were less likely to adhere to their treatment compared to never smokers (OR 0.17, 95%CI 0.03-0.86; P=0.032), whereas patients receiving advanced treatment were much more likely to adhere to treatment, compared to those on non-

Table 4 Factors associated with moderate-to-severe overall work impairment (WPAI ≥20%): univariate and multivariate logistic regression analyses

WPAI	Univariate analysis		Multivariate analysis	
	OR [95%CI]	P-value	OR [95%CI]	P-value
Sex				
Male	Ref		Ref	
Female	2.55 [1.13-5.75]	0.024	3.30 [1.06-10.27]	0.04
Age				
<50 years	Ref			
50 years or more	1.43 [0.54-3.79]	0.47		
BMI				
Underweight and normal	Ref			
Overweight and obese	1.11 [0.49-2.49]	0.802		
Smoking status				
Never smoker	Ref		Ref	
Former smoker	1.08 [0.38-3.09]	0.881	0.61 [0.15-2.46]	0.485
Current smoker	2.17 [0.8-5.89]	0.13	1.46 [0.39-5.41]	0.58
Disease activity*				
Inactive	Ref		Ref	
Active	8.75 [3.37-22.72]	<0.001	11.16 [3.14-39.74]	<0.001
Age at diagnosis				
0-30 years	Ref		Ref	
>30 years	1.93 [0.86-4.34]	0.11	0.70 [0.15-3.20]	0.644
Disease duration				
<10 years	Ref			
10-19 years	0.56 [0.23-1.36]	0.203		
20 years or more	0.48 [0.16-1.42]	0.185		
Surgery				
No	Ref		Ref	
Yes	1.26 [0.55-2.9]	0.145	3.13 [0.95-10.29]	0.06
Hospitalization in the past 12 months				
No	Ref			
Yes	1.25 [0.38-4.16]	0.713		
Ongoing treatments[ł]				
Non-advanced	Ref			
Advanced	0.8 [0.29-2.18]	0.662		
Comorbidities				
None	Ref			
One or more	1.68 [0.75-3.8]	0.211		

*Inactive: Patients in remission. Active: Patients with mild, moderate or severe disease activity

[ł]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics. Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors

BMI, body mass index; CI, confidence interval; OR, odds ratio; ref, reference value; WPAI, Work Productivity and Activity Impairment

advanced treatment (OR 22.39, 95%CI 4.34-115.61; P<0.001) (Supplementary Table 5).

Correlations between PROs and disease activity

All the SCCs revealed statistically significant (P<0.001) associations between PROs and disease activity, with the exception of treatment adherence (Table 6). The strongest correlations were observed between presenteeism and work productivity loss (SCC 0.97, 95%CI 0.96-0.98), and between QoL and both psychological burden (SCC -0.82, 95%CI -0.86 to -0.76), and activity impairment (SCC -0.79, 95%CI -0.84 to -0.72).

Disease activity (HBI) was very strongly and inversely associated with QoL (SCC -0.79, 95%CI -0.84 to -0.73) and was positively correlated with greater work and activity impairment: absenteeism (SCC 0.57, 95%CI 0.41-0.69), presenteeism (SCC 0.52, 95%CI 0.34-0.65), work productivity loss (SCC 0.58, 95%CI 0.42-0.70), and activity impairment (SCC 0.72, 95%CI 0.64-0.79). A strong positive correlation was also found between disease activity and psychological burden (SCC 0.63, 95%CI 0.53-0.71).

Table 5 Factors associated with moderate-to-severe depressive symptoms (PHQ-9 ≥10): univariate and multivariate logistic regression analyses

PHQ-9	Univariate analysis		Multivariate analysis	
	OR [95%CI]	Pvalue	OR [95%CI]	P-value
Sex				
Male	Ref		Ref	
Female	2.50 [1.37-4.58]	0.003	1.31 [0.60-2.89]	0.497
Age				
<50 years	Ref	0.754		
50 years or more	1.11 [0.58-2.1]			
Employment status				
In paid employment	Ref		Ref	
Without paid employment	1.65 [0.91-2.99]	0.101	1.71 [0.77-3.78]	0.188
BMI				
Underweight and normal	Ref			
Overweight and obese	1.42 [0.79-2.56]	0.237		
Smoking status				
Never smoker	Ref		Ref	
Former smoker	1.57 [0.71-3.46]	0.265	1.95 [0.69-5.51]	0.205
Current smoker	2.18 [1.05-4.53]	0.037	2.67 [1.02-7.03]	0.047
Disease activity*				
Inactive	Ref		Ref	
Active	8.83 [4.43-17.60]	<0.001	8.93 [3.94-20.27]	<0.001
Age at diagnosis				
0-30 years	Ref			
>30 years	1.11 [0.62-1.99]	0.715		
Disease duration				
<10 years	Ref			
10-19 years	0.86 [0.45-1.66]	0.659		
20 years or more	1.06 [0.48-2.31]	0.89		
Surgery				
No	Ref			
Yes	0.76 [0.41-1.41]	0.386		
Hospitalization in the past 12 months				
No	Ref			
Yes	1.70 [0.71-4.07]	0.236		
Ongoing treatments[ł]				
Non-advanced	Ref			
Advanced	1.2 [0.56-2.57]	0.642		
Comorbidities				
None	Ref		Ref	
One or more	3.97 [2.03-7.75]	<0.001	2.84 [1.16-6.94]	0.022

*Inactive: Patients in remission. Active: Patients with mild, moderate or severe disease activity

[ł]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics. Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors

BMI, body mass index; CI, confidence interval; OR, odds ratio; ref, reference value; PHQ-9, Patient Health Questionnaire

Impaired QoL was strongly and inversely correlated with absenteeism (SCC -0.53, 95%CI -0.66 to -0.36), presenteeism (SCC -0.65, 95%CI -0.76 to -0.51), and work productivity loss (SCC -0.68, 95%CI -0.78 to -0.55). In addition, activity impairment was also very strongly associated with presenteeism (SCC 0.75, 95%CI 0.64-0.83) and work productivity loss (SCC 0.73, 95%CI 0.62-0.82).

Psychological burden was positively correlated with all WPAI domains, including absenteeism (SCC 0.41, 95%CI 0.22-0.56), presenteeism (SCC 0.51, 95%CI 0.34-0.65), work productivity loss (SCC 0.53, 95%CI 0.37-0.68), and activity impairment (SCC 0.67, 95%CI 0.58-0.75).

The weakest, though still significant, correlations were associated with treatment satisfaction and both activity impairment (SCC -0.32, 95%CI -0.45 to -0.18) and psychological burden (SCC -0.28, 95%CI -0.42 to -0.14). Correlations between treatment satisfaction on the one hand, and disease activity, QoL, absenteeism, presenteeism and work productivity on the other, were moderate. Absenteeism was moderately correlated with presenteeism (SCC 0.43,

Table 6 Spearman's correlation coefficient (SCC) for patient-reported outcomes and disease activity

Outcomes		Disease Activity (HBI)	Quality of life (SIBDQ)	Work Productivity and Activity Impairment (WPAI)				Psychological burden (PHQ-9)	Treatment satisfaction	Treatment adherence
				Absenteeism	Presenteeism	Work productivity loss	Activity Impairment			
Disease Activity (HBI)		--								
Quality of life (SIBDQ)		-0.79**	--							
Work Productivity and Activity Impairment (WPAI)	Absenteeism	0.57**	-0.53**	--						
	Presenteeism	0.52**	-0.65**	0.43**	--					
	Work productivity loss	0.58**	-0.68**	0.57**	0.97**	--				
	Activity Impairment	0.72**	-0.79**	0.40**	0.75**	0.73**	--			
Psychological burden (PHQ-9)		0.63**	-0.82**	0.41**	0.51**	0.53**	0.67**	--		
Treatment satisfaction		-0.38**	0.45**	-0.36**	-0.46**	-0.43**	-0.32**	-0.28**	--	
Treatment adherence		0.01	-0.06	0.06	0.14	0.17	0.01	0.13	-0.05	--

SCC: 0.00-0.29
SCC: 0.30-0.49
SCC: 0.50-0.69
SCC: >0.70

*Correlation is significant at the 0.001 level (2-tailed)

HBI, Harvey–Bradshaw Index; PHQ-9, Patient Health Questionnaire-9; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; WPAI, Work Productivity and Activity Impairment Questionnaire

95%CI 0.25-0.59), activity impairment (SCC 0.40, 95%CI 0.21-0.56), and psychological burden (SCC 0.41, 95%CI 0.22-0.56). No correlations were observed between treatment adherence and other PROs or disease activity.

Discussion

CD significantly affects patients' lives, extending beyond gastrointestinal symptoms to impair HRQoL, mental health and work performance. Despite therapeutic advances, many patients continue to experience physical and psychological challenges. Consequently, PROs have emerged as critical tools for the comprehensive assessment of disease burden [9]. Understanding PROs is crucial for optimizing care and aligning treatment strategies with patients' experiences. This survey assessed the impact of CD as reflected by PROs, and evaluated the unmet medical needs of CD patients in a Greek real-world setting, where existing knowledge is limited.

In this study, nearly 3 of 4 (73%) patients reported moderately to severely impaired QoL, reflecting the chronic and relapsing nature of CD, where uncomfortable symptoms and treatment side-effects often reduce QoL [2,28-30]. Interestingly, patients on advanced therapies reported moderately to severely impaired QoL more frequently (76.3% vs. 58.8%, P=0.038), consistent with the report by Kalafateli *et al* [31]. In addition, unemployment and disease activity were significantly associated with lower QoL, in line with previous studies [12,31-33].

Work-related impact was substantial, with moderate-to-severe absenteeism, presenteeism and overall work productivity loss reported by 17.5%, 53.2% and 55.7% of patients, respectively. These findings align with prior research in inflammatory bowel disease (IBD), where fatigue was a major driver of both absenteeism and presenteeism, regardless of disease activity [34]. In a previous Greek study, 40% of IBD patients also reported disease-related work-limitations, particularly among those aged 18-29 and 40-49 years [35]. More than half of the patients (57%) required time off work due to symptoms or clinic visits, with annual sick leave ranging from 1-20 days [35]. Female sex and disease activity were associated with a greater risk of moderate-to-severe productivity loss, as found in earlier studies [2,16,36].

Patients with CD experience a great psychological burden, which is reflected in anxiety and depression. Feelings of shame, isolation and body dissatisfaction are frequently reported and significantly compromise their psychosocial functioning [37]. The present survey identified that moderate-to-severe depressive symptoms were highly prevalent (approximately half of participants), and were significantly associated with smoking, active disease and comorbidities. Smoking increases the risk of complications, recurrences and surgeries, with smokers being over twice as likely to experience a flare-up compared to non-smokers [38,39]. Furthermore, the presence of comorbidities has been earlier associated

with depressive symptoms in IBD [40]. A separate study in CD patients has also demonstrated that major depressive disorder was significantly more common in those with active disease (OR 796.0, 95%CI 133.7-4738.8), suggesting a strong association between disease activity and psychological burden [19]. These findings highlight the need for integrated care strategies addressing mental health in CD, including the development of structured psychological interventions. Recent evidence suggests that group cognitive behavioral therapy may effectively improve both disease outcomes and psychosocial functioning in this population [41].

Nearly 40% of patients expressed dissatisfaction with their treatment, citing increasing fatigue as the primary reason. Despite the availability of advanced therapies, chronic fatigue remains a significant challenge in CD [42]. Dissatisfaction was reported by 42% of patients on advanced therapies, aligning with meta-analyses showing modest fatigue reduction [43]. Patients with active disease had 70% lower odds of satisfaction compared to those in remission, highlighting the burden of ongoing symptoms on treatment perceptions. Similarly, Burisch *et al* estimated that 27.9% of CD patients in remission were dissatisfied with their treatment, compared to 65.4% of those with active disease [30]. Patients without paid employment were less likely to be satisfied with their treatment, consistent with Ding *et al*, who found higher satisfaction among working CD patients (72.8%) compared to non-working patients (58.5%) [36]. These findings highlight the importance of patient-centered care and shared decision-making to optimize therapeutic outcomes.

Treatment non-adherence was reported by only one tenth of participants, suggesting that the reported dissatisfaction was not primarily due to poor adherence. Instead, it may reflect persistent unmet therapeutic needs despite ongoing treatment. Moreover, adherence was higher among advanced therapy recipients, possibly reflecting greater engagement. The primary reason for non-adherence in the non-advanced recipients was the belief that "my symptoms are under control". This mirrors findings by Brady *et al*, where non-adherent patients on similar therapies expressed confidence in self-management, concern about the risks of medications and a general ambivalence to treatment [44]. At a multivariate level, current smokers were less likely to adhere to their prescribed therapies, consistently with previous findings [45].

The correlations between PROs and disease activity revealed the following links: i) poor QoL is associated with great work productivity loss, high activity impairment and increased depression; ii) high disease activity is associated with decreased QoL, great work productivity loss, high activity impairment and high levels of depression; iii) increased depression levels are associated with high work productivity loss and activity impairment; and iv) low treatment satisfaction is associated with poor QoL and higher work productivity and activity impairment. These findings are consistent with those of Williet *et al*, who demonstrated strong associations between poor QoL, productivity loss, and depression in a large French IBD cohort [2]. In addition, a meta-analysis confirmed a significant inverse correlation between disease activity and QoL (r=-0.61) [46]. In a real-world study, CD patients experienced greater absenteeism (0.95-14.6%), presenteeism (11.7-44.9%), and work impairment (12.4-51.0%) with increasing disease activity, resulting in higher indirect costs [36]. Beck *et al* also demonstrated that even mild depressive symptoms are associated with decrements in work function [47]. To the best of our knowledge, this is the first Greek study to investigate the correlations between PROs in CD.

This study presents several key strengths. First, it evaluated multiple dimensions of PROs in CD patients, offering valuable insights into the disease burden among the Greek population. Both validated and study-specific tools were used. Additionally, the inclusion of real-world patient experiences provides evidence that are directly relevant to clinical practice and support a more patient-centered approach to care. Disease activity was identified as the main factor associated with almost all PROs. Notably, a substantial proportion of CD patients receiving advanced therapies continued to report a high disease burden, characterized by poor QoL (even in remission), with greater work productivity loss, depressive symptoms and ongoing disease activity. These findings underscore a persistent unmet need in this population.

Our study had some limitations. First, the cross-sectional design limits any causal inference between PROs and associated factors. Second, the study sample consisted of adult CD patients affiliated with the HELLESCC, which may not fully represent the broader Greek CD population and may introduce selection bias. However, it is important to note that the HELLESCC is the only national IBD patient association and is a member of the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA). Third, as data were self-reported, there was a potential for interpretation bias. Objective measures of disease activity (e.g., endoscopy, biomarkers) were not considered. Potential recall or reporting biases may also have affected the accuracy of responses. Furthermore, the relatively small sample size of the non-advanced treatment group limits the generalizability of the findings to this patient population. Lastly, treatment satisfaction and adherence were assessed using study-specific, non-validated tools; however, despite their limitations, these effectively captured patient perspectives [48-50]. Despite these constraints, the study provides important real-world insights into the patient experience, which are critical for informing patient-centered care and evidence-based clinical decision-making.

In conclusion, this real-world study highlights the residual disease burden and persistent unmet needs in CD management in Greece. Impaired QoL, reduced work productivity, and significant psychological distress were consistently observed. These findings, combined with low treatment satisfaction, underscore the need for greater emphasis on patient-centered care and shared decision-making to ensure that treatment strategies align with patients' lived experiences and evolving needs.

Acknowledgment

The authors would like to express their sincere gratitude to the members of the Hellenic Society of Crohn's Disease and Ulcerative Colitis Patients (HELLESCC).

Summary Box

What is already known:

- Crohn's disease (CD) imposes a substantial clinical burden, with symptoms such as diarrhea, abdominal pain and fatigue progressing to bowel damage, and disability
- Beyond the clinical burden, CD severely affects patients' daily lives, impairing work productivity, social participation and overall quality of life
- Patient-reported outcomes highlight the real-world impact of CD, offering essential insights into unmet needs, and guiding more patient-centered, value-based care—particularly important in Greece, where such data are currently limited

What the new findings are:

- Around 73% of patients, and 76% of those on advanced therapies (of whom 31% were in remission), reported moderately to severely impaired quality of life
- A significant functional and psychological burden was observed, with one third of patients reporting work productivity loss and activity impairment, and nearly half experiencing moderate-to-severe depressive symptoms
- Interestingly, 39% of patients were "not at all", "not very" or "quite" satisfied with their treatment, with the main reason for dissatisfaction being increasing fatigue
- The results emphasize the residual disease burden and persistent unmet needs in CD management, underscoring the importance of patient-centered care and comprehensive strategies to improve overall outcomes

References

1. Cockburn E, Kamal S, Chan A, et al. Crohn's disease: an update. *Clin Med (Lond)* 2023;**23**:549-557.
2. Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. *J Crohns Colitis* 2017;**11**:165-174.
3. Bernstein CN, Hitchon CA, Walld R, et al; CIHR Team in defining the burden and managing the effects of psychiatric comorbidity in chronic immunoinflammatory disease. Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflamm Bowel Dis* 2019;**25**:360-368.
4. Tse CS, Van Citters AD, Ricci B, et al; IBD Qorus. Identifying and predicting the goals and concerns prioritised by individuals with inflammatory bowel disease. *J Crohns Colitis* 2022;**16**:379-388.
5. Rubin DT, Hart A, Panaccione R, et al. Ulcerative colitis narrative global survey findings: communication gaps and agreements between patients and physicians. *Inflamm Bowel Dis* 2021;**27**:1096-1106.
6. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nat Rev Gastroenterol Hepatol* 2019;**16**:247-259.
7. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021;**160**:1570-1583.
8. Fiorino G, Lytras T, Younge L, et al. Quality of care standards in inflammatory bowel diseases: a European Crohn's and Colitis Organisation [ECCO] position paper. *J Crohns Colitis* 2020;**14**:1037-1048.
9. Horrigan JM, Louis E, Spinelli A, et al. The real-world global use of patient-reported outcomes for the care of patients with inflammatory bowel disease. *Crohns Colitis 360* 2023;**5**:otad006.
10. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2014;**12**:1246-1256.e6.
11. Sloan JA, Halyard MY, Frost MH, Dueck AC, Teschendorf B, Rothman ML; Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group. The Mayo Clinic manuscript series relative to the discussion, dissemination, and operationalization of the Food and Drug Administration guidance on patient-reported outcomes. *Value Health* 2007;**10**(Suppl 2):S59-S63.
12. Christiansen LK, Lo B, Bendtsen F, Vind I, Vester-Andersen MK, Burisch J. Health-related quality of life in inflammatory bowel disease in a Danish population-based inception cohort. *United European Gastroenterol J* 2019;**7**:942-954.
13. Irvine EJ, Zhou Q, Thompson AK. The short inflammatory bowel disease questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol* 1996;**91**:1571-1578.
14. Keller R, Mazurak N, Fantasia L, et al. Quality of life in inflammatory bowel diseases: it is not all about the bowel. *Intest Res* 2021;**19**:45-52.
15. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;**4**:353-365.
16. Cross RK, Sauk JS, Zhuo J, et al. Poor patient-reported outcomes and impaired work productivity in patients with inflammatory bowel disease in remission. *Gastro Hep Adv* 2022;**1**:927-935.
17. Youssef M, Hossein-Javaheri N, Hoxha T, Mallouk C, Tandon P. Work productivity impairment in persons with inflammatory bowel diseases: a systematic review and meta-analysis. *J Crohns Colitis* 2024;**18**:1486-1504.
18. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen lntern Med* 2001;**16**:606-613.
19. Facanali CBG, Sobrado Junior CW, Fraguas Junior R, et al. The relationship of major depressive disorder with Crohn's disease activity. *Clinics (Sao Paulo)* 2023;**78**:100188.
20. Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of anxiety and depression in patients with inflammatory bowel disease. *Can J Gastroenterol Hepatol* 2017;**2017**:6496727.
21. Best WR. Predicting the Crohn's disease activity index from the Harvey-Bradshaw Index. *Inflamm Bowel Dis* 2006;**12**:304-310.
22. Gourzoulidis G, Vakouftsi VR, Mavridoglou G, Psarra M, Tzanetakos C. Disease burden and unmet medical needs in patients with ulcerative colitis in Greece: a cross-sectional patient survey. *Med Sci (Basel)* 2025;**13**:117.
23. Hellenic Group for the Study of Inflammatory Bowel Diseases (EOMIFNE), member of European Crohn´s and Colitis Organisation (ECCO). Official website. Available from: https://eomifne.gr/[Accessed 19 September 2025].

24. Reilly Associates official website. Available from: http://www.reillyassociates.net/[Accessed 19 September 2025].
25. The Patient Health Questionnaire (PHQ) Screeners. Instruction manual. Available from: https://www.phqscreeners.com/images/sites/g/files/g10016261/f/201412/instructions.pdf [Accessed 19 September 2025].
26. The Patient Health Questionnaire (PHQ) Screeners. Greek version of PHQ-9. Available from: https://www.phqscreeners.com/images/sites/g/files/g10060481/f/201412/PHQ9_Greek%20for%20Greece.pdf [Accessed 19 September 2025].
27. du Prel JB, Hommel G, Röhrig B, Blettner M. Confidence interval or p-value?: part 4 of a series on evaluation of scientific publications. *Dtsch Arztebl Int* 2009;**106**:335-339.
28. Benjamin J, Makharia GK, Kalaivani M, Joshi YK. Nutritional status of patients with Crohn's disease. *Indian J Gastroenterol* 2008;**27**:195-200.
29. Mitropoulou MA, Fradelos EC, Lee KY, et al. Quality of life in patients with inflammatory bowel disease: importance of psychological symptoms. *Cureus* 2022;**14**:e28502.
30. Burisch J, Hart A, Sturm A, et al. Residual disease burden among European patients with inflammatory bowel disease: a real-world survey. *Inflamm Bowel Dis* 2025;**31**:411-424.
31. Kalafateli M, Triantos C, Theocharis G, et al. Health-related quality of life in patients with inflammatory bowel disease: a single-center experience. *Ann Gastroenterol* 2013;**26**:243-248.
32. Parra RS, Chebli JMF, Amarante HMBS, et al. Quality of life, work productivity impairment and healthcare resources in inflammatory bowel diseases in Brazil. *World J Gastroenterol* 2019;**25**:5862-5882.
33. Holko P, Kawalec P, Mossakowska M, Pilc A. Health-related quality of life impairment and indirect cost of Crohn's disease: a self-report study in Poland. *PLoS One* 2016;**11**:e0168586.
34. van Gennep S, Evers SW, Rietdijk ST, et al. High disease burden drives indirect costs in employed inflammatory bowel disease patients: the WORK-IBD study. *Inflamm Bowel Dis* 2021;**27**:352-363.
35. Viazis N, Mantzaris G, Karmiris K, et al; Hellenic Foundation of Gastroenterology and Nutrition. Inflammatory bowel disease: Greek patients' perspective on quality of life, information on the disease, work productivity and family support. *Ann Gastroenterol* 2013;**26**:52-58.
36. Ding Z, Muser E, Izanec J, Lukanova R, Kershaw J, Roughley A. Work-related productivity loss and associated indirect costs in patients with Crohn's disease or ulcerative colitis in the United States. *Crohns Colitis 360* 2022;**4**:otac023.
37. Eugenicos MP, Ferreira NB. Psychological factors associated with inflammatory bowel disease. *Br Medl Bull* 2021;**138**:16-28.
38. Underner M, Perriot J, Cosnes J, Beau P, Peiffer G, Meurice JC. [Smoking, smoking cessation and Crohn's disease]. *Presse Med* 2016;**45**:390-402.
39. IBD clinic. University of Alberta. How does smoking affect Crohn's Disease? 2024. Available from: https://ibdclinic.ca/resources/smoking-and-crohns-disease/[Accessed 19 September 2025].
40. Bernabeu P, Belén-Galipienso O, van-der Hofstadt C, et al. Psychological burden and quality of life in newly diagnosed inflammatory bowel disease patients. *Front Psychol* 2024;**15**:1334308.
41. Kalogeropoulou M, Karaivazoglou K, Konstantopoulou G, et al. The impact of group cognitive behavioral psychotherapy on disease severity and psychosocial functioning in patients with inflammatory bowel disease: a randomized controlled study. *J Crohns Colitis* 2025;**19**:jjae144.
42. Włodarczyk M, Makaro A, Prusisz M, et al. The role of chronic fatigue in patients with Crohn's disease. *Life (Basel)* 2023;**13**:1692.
43. Skjellerudsveen BM, Skoie IM, Dalen I, Grimstad T, Omdal R. The effect of biological treatment on fatigue in inflammatory bowel disease: a systematic review and meta-analysis. *Drugs* 2023;**83**:909-921.
44. Brady RE, Salwen-Deremer JK, Tunnell NC, Winter MW. Understanding medication nonadherence in Crohn's disease patients: a qualitative evaluation. *Inflamm Bowel Dis* 2024;**30**:2046-2056.
45. Shah NB, Haydek J, Slaughter J, et al. Risk factors for medication nonadherence to self-injectable biologic therapy in adult patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2020;**26**:314-320.
46. van der Have M, van der Aalst KS, Kaptein AA, et al. Determinants of health-related quality of life in Crohn's disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014;**8**:93-106.
47. Beck A, Crain AL, Solberg LI, et al. Severity of depression and magnitude of productivity loss. *Ann Fam Med* 2011;**9**:305-311.
48. de Castro ML, Sanromán L, Martín A, et al. Assessing medication adherence in inflammatory bowel diseases. A comparison between a self-administered scale and a pharmacy refill index. *Rev Esp Enferm Dig* 2017;**109**:542-551.
49. King K, Norton C, Chalder T, Czuber-Dochan W. N17 Exploration of medication non-adherence in inflammatory bowel disease patients: a systematic review. *J Crohns Colitis* 2024;**18**:i2207.
50. Hubscher E, Vurgun N. PCR152 Underutilization of a validated treatment satisfaction instrument in inflammatory bowel disease. *Value Health* 2022;**25**:S420.

Supplemental material

Supplementary Table 1 Comorbidities stratified by treatment type

Comorbidities	Total (N=108)	Advanced therapies[a] (N=91)	Non-advanced therapies[b] (N=17)
COPD	4 (3.7%)	3 (3.3%)	1 (5.9%)
Arthritis	42 (38.9%)	36 (39.6%)	6 (35.3%)
Iron deficiency anemia	23 (21.3%)	22 (24.2%)	1 (5.9%)
Hypothyroidism	21 (19.4%)	16 (17.6%)	5 (29.4%)
Skin allergies or other skin conditions	34 (31.5%)	29 (31.9%)	5 (29.4%)
Cancer	2 (1.8%)	2 (2.2%)	0 (0%)
Depression	29 (26.8%)	25 (27.5%)	4 (23.5%)
Diabetes	12 (11.1%)	11 (12.1%)	1 (5.9%)
Hypertension	15 (13.9%)	13 (14.3%)	2 (11.8%)
Cardiovascular disease	4 (3.7%)	2 (2.2%)	2 (11.8%)
Coronary artery disease	0 (0%)	0 (0%)	0 (0%)
Osteoporosis	10 (9.2%)	8 (8.8%)	2 (11.8%)
Migraine or severe headache	14 (13%)	8 (8.8%)	6 (35.3%)
Other	28 (25.9%)	24 (26.4%)	4 (23.5%)

[a]Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors
[b]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics
COPD, chronic obstructive pulmonary disease

Supplementary Table 2 Treatment satisfaction and reasons of dissatisfaction stratified by treatment type

Variable	Total (N=227)	Advanced therapies[a] (N=188)	Non-advanced therapies[b] (N=39)
Treatment satisfaction, n (%)			
Extremely	70 (30.8%)	52 (27.7%)	18 (46.2%)
Very	68 (30%)	58 (30.9%)	10 (25.6%)
Quite	65 (28.6%)	55 (29.3%)	10 (25.6%)
Not very	16 (7%)	16 (8.5%)	0 (0%)
Not at all	8 (3.5%)	7 (3.7%)	1 (2.6%)
Reasons for dissatisfaction, n (%)			
Side effects	21 (9.3%)	19 (10.1%)	2 (5.1%)
I have frequent stools	26 (11.5%)	24 (12.8%)	2 (5.1%)
I have frequent flares	21 (9.3%)	19 (10.1%)	2 (5.1%)
The frequency of doses	10 (4.4%)	9 (4.8%)	1 (2.6%)
The cost of medications	3 (1.3%)	3 (1.6%)	0 (0%)
I experience more abdominal pain	7 (3.1%)	6 (3.2%)	1 (2.6%)
Fatigue is increasing	37 (16.3%)	32 (17%)	5 (12.8%)
I do not like the mode of administration	13 (5.7%)	13 (6.9%)	0 (0%)
I experience more urgency to go to the bathroom	12 (5.3%)	11 (5.9%)	1 (2.6%)
Other reason	20 (8.8%)	19 (10.1%)	1 (2.6%)

[a]Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors
[b]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics

Supplementary Table 3 Treatment adherence and reasons of non-adherence stratified by treatment type

Variable	Total (N=222)	Advanced therapies[a] (N=183)	Non-advanced therapies[b] (N=39)
Treatment adherence, n (%)			
I follow my treatment regularly	200 (90.1%)	174 (95.1%)	26 (66.7%)
Occasionally I forget to/do not take my treatment	16 (7.2%)	6 (3.3%)	10 (25.6%)
Sometimes I forget to/do not take my treatment	3 (1.4%)	1 (0.5%)	2 (5.1%)
Often, I forget to/do not take my treatment	3 (1.4%)	2 (1.1%)	1 (2.6%)
Reasons for non-adherence, n (%)			
I feel that my symptoms are under control	9 (4.1%)	4 (2.2%)	5 (12.8%)
Mode of administration	1 (0.5%)	1 (0.5%)	0 (0%)
Frequent drug doses	5 (2.3%)	3 (1.6%)	2 (5.1%)
The drug is not effective	0 (0%)	0 (0%)	0 (0%)
Fear of side effects	6 (2.7%)	4 (2.2%)	2 (5.1%)
Other reason	6 (2.7%)	1 (0.5%)	5 (12.8%)

[a]Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors
[b]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics

Supplementary Table 4 Factors associated with treatment satisfaction[†]: univariate and multivariate logistic regressions analyses

Satisfaction	Univariate analysis		Multivariate analysis	
	OR [95%CI]	P-value	OR [95%CI]	P-value
Sex				
Male	Ref			
Female	0.87 [0.52-1.46]	0.593		
Age				
<50 years	Ref			
50 years or more	1.23 [0.67-2.24]	0.508		
Employment status		0.017		
In paid employment	Ref		Ref	
Without paid employment	0.47 [0.26-0.87]		0.47 [0.22-0.98]	0.045
BMI	Ref	0.226		
Underweight and normal	0.72 [0.43-1.22]			
Overweight and obese				
Smoking status				
Never smoker	Ref		Ref	
Former smoker	0.99 [0.5-1.96]	0.971	1.30 [0.49-3.41]	0.598
Current smoker	0.58 [0.32-1.08]	0.085	0.75 [0.31-1.82]	0.53
Disease activity*				
Inactive	Ref		Ref	
Active	0.25 [0.14-0.44]	<0.001	0.30 [0.14-0.65]	0.002
Age at diagnosis				
0-30 years	Ref			
>30 years	0.76 [0.46-1.27]	0.298		
Disease duration				
<10 years	Ref			
10-19 years	0.99 [0.56-1.75]	0.97		
20 years or more	1.17 [0.58-2.38]	0.659		
Surgery				
No	Ref			
Yes	0.74 [0.39-1.37]	0.334		
Hospitalization in the past 12 months				
No	Ref		Ref	
Yes	0.43 [0.18-1.02]	0.056	0.56 [0.1-1.52]	0.255
Ongoing treatments[ł]	Ref	0.125	Ref	0.703
Non-advanced	0.55 [0.26-1.18]		1.21 [0.45-3.26]	
Advanced				
Comorbidities				
None	Ref		Ref	
One or more	0.48 [0.25-0.94]	0.033	0.69 [0.30-1.60]	0.385

[†]Logistic regression: the dependent variable of satisfaction was categorized as 0: "not at all/not very/quite satisfied" and 1: "very/extremely satisfied"
[*]Inactive: Patients in remission. Active: Patients with mild, moderate or severe disease activity
[ł]Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics. Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors
BMI, body mass index; CI, confidence interval; OR, odds ratio; ref, reference value

Supplementary Table 5 Factors associated with treatment adherence†: univariate and multivariate logistic regressions analyses

Adherence	Univariate analysis		Multivariate analysis	
	OR [95%CI]	P-value	OR [95%CI]	P-value
Sex				
Male	Ref			
Female	1.12 [0.51-2.44]	0.781		
Age				
<50 years	Ref		Ref	
50 years or more	0.57 [0.25-1.3]	0.15	0.21 [0.04-1.19]	0.078
Employment status				
In paid employment	Ref			
Without paid employment	1.88 [0.69-5.15]	0.218		
BMI				
Underweight and normal	Ref			
Overweight and obese	1.42 [0.65-3.09]	0.381		
Smoking status				
Never smoker	Ref		Ref	
Former smoker	0.95 [0.26-3.46]	0.943	4.62 [0.36-59.20]	0.240
Current smoker	0.33 [0.12-0.94]	0.037	0.17 [0.03-0.86]	0.032
Disease activity*				
Inactive	Ref			
Active	0.92 [0.38-2.33]	0.855		
Age at diagnosis				
0-30 years	Ref			
>30 years	0.76 [0.35-1.66]	0.49		
Disease duration				
<10 years	Ref			
10-19 years	1.74 [0.67-4.47]	0.253		
20 years or more	0.83 [0.32-2.21]	0.716		
Surgery				
No	Ref			
Yes	1.15 [0.43-3.04]	0.78		
Hospitalization in the past 12 months				
No	Ref			
Yes	0.80 [0.21-3.01]	0.743		
Ongoing treatments‡				
Non-advanced	Ref		Ref	
Advanced	9.67 [3.76-24.86]	<0.001	16.37 [3.63-73.18]	<0.001
Comorbidities				
None	Ref			
One or more	1.5 [0.59-3.85]	0.396		

†Logistic regression: the dependent variable of adherence was categorized as 0: "I forget to/do not take my treatment (occasionally/sometimes/often/always)" and 1: "I follow my treatment regularly"

*Inactive: Patients in remission. Active: Patients with mild, moderate or severe disease activity

‡Non-advanced therapies: 5-aminosalicylic acids, corticosteroids, immunosuppressants, and antibiotics. Advanced therapies: tumor necrosis factor inhibitors, integrin α4 inhibitors, interleukin-12/23 inhibitors, and Janus kinase inhibitors

BMI, body mass index; CI, confidence interval; OR, odds ratio; ref, reference value