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ORIGINAL RESEARCH—CLINICAL

Poor Patient-Reported Outcomes and Impaired Work Productivity in Patients With Inflammatory Bowel Disease in Remission

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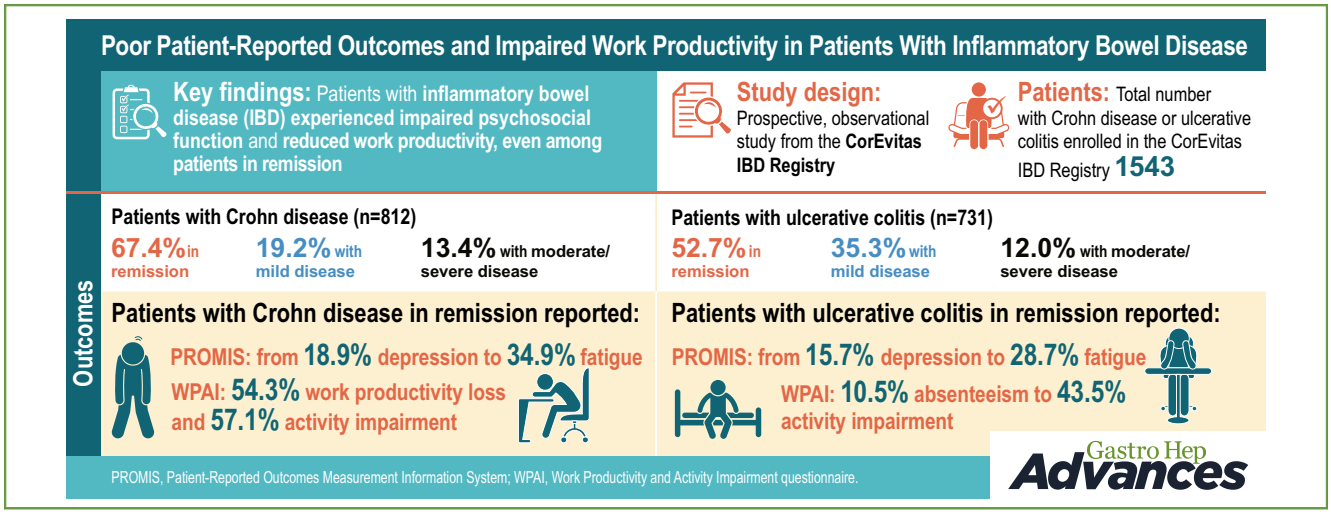

BACKGROUND AND AIMS: This study aimed to evaluate associations between disease severity, patient-reported outcomes (PROs), and work productivity in patients with inflammatory bowel disease (IBD [Crohn's disease (CD) and ulcerative colitis (UC)]). **METHODS:** Patients diagnosed with CD or UC enrolled in CorEvitas' IBD Registry (May 2017 to September 2019) were included (N = 1543; CD, n = 812; UC, n = 731). Disease severity was assessed using the Harvey-Bradshaw Index (CD) and partial Mayo Score (UC); psychosocial PROs (Patient-Reported Outcomes Measurement Information System [PROMIS]) and work productivity (Work Productivity and Activity Impairment [WPAI]) were assessed. Univariable and multivariable regression analyses assessed associations between PROs and disease severity. **RESULTS:** Among CD patients, 67.4% were in remission, 19.2% had mild disease, and 13.4% had moderate/severe disease; among UC patients, 52.7% were in remission, 35.3% had mild disease, and 12.0% had moderate/severe disease. For CD patients in remission, unadjusted percentages of patients with PROMIS scores outside normal limits ranged from 18.9% (depression) to 34.9% (fatigue). For CD patients in remission, 54.3% reported work productivity loss, and 57.1% reported activity impairment. The unadjusted percentage of UC patients in remission with scores outside normal limits ranged from 15.7% (depression) to 28.7% (fatigue) for PROMIS and 10.5% (absenteeism) to 43.5% (activity impairment) for WPAI. Impairment increased with IBD severity. Congruently, adjusted estimates showed significant impairment in PROMIS and WPAI scores for CD and UC patients in

Abbreviations used in this paper: **CD, Crohn's disease; IBD, inflammatory bowel disease; JAK, Janus kinase; OR, odds ratio; PROMIS, Patient-Reported Outcomes Measurement Information System; PROs, patient-reported outcomes; QOL, quality of life; SD, standard deviation; UC, ulcerative colitis; WPAI, Work Productivity and Activity Impairment.**

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remission. **CONCLUSION:** In this real-world analysis, IBD patients across the spectrum of activity, from remission to severe disease, experienced impaired psychosocial function and reduced work productivity. Impairment, even among patients in remission, indicates an unmet need in this patient population.

Keywords: Crohn's Disease; Ulcerative Colitis; Registry; Real-World

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract with periods of exacerbations and remissions. Inflammatory bowel disease (IBD) is characterized by intestinal inflammation, extraintestinal manifestations, and significant morbidity.[1–4] In North America, the estimated incidence is up to 20.2 cases per 100,000 person-years for CD and up to 19.2 cases per 100,000 person-years for UC.[5] In a large IBD epidemiology study based on 12 million US health insurance claims, the prevalence of CD and UC among adults was estimated to be 241 and 263 per 100,000, respectively.[6] IBD treatment strategies seek to induce and maintain remission, promote mucosal healing, prevent complications, minimize the impact of comorbidities, reduce the need for hospitalization and surgery, and enhance the quality of life (QOL).[2,7]

Several physician-reported indices of disease activity or severity have been developed for the clinical assessment of patients with IBD, including the Harvey-Bradshaw Index for patients with CD and the partial Mayo Score for patients with UC.[8] However, elements of a patient's experience may be underrepresented by these indices; specifically, fatigue is highly prevalent in patients with IBD, has a negative impact on other patient-reported outcomes (PROs), and contributes to poor health-related QOL.[9,10] In addition, compared with the general population, patients with IBD have higher rates of psychological comorbidities, such as depression and anxiety,[11,12] reducing patients' QOL. The Patient-Reported Outcomes Measurement Information System (PROMIS) and the Work Productivity and Activity Impairment (WPAI) questionnaires are validated assessments that measure the impact of IBD on other symptoms, work productivity, and activity impairment.[3,13]

There is limited real-world evidence describing the association between remission, disease severity, PROs, and work productivity measures among IBD patients.[13,14] Data from a US internet-based cohort found evidence of elevated depression, anxiety, fatigue, sleep disturbance, and pain interference reported on the PROMIS questionnaire in IBD patients, relative to the general population. Over time, PROMIS scores improved when disease activity improved and worsened when disease activity was exacerbated.[13] Other studies have shown depression and/or anxiety may be associated with clinical recurrence in IBD.[2,11,15] Additional studies have reported that active disease is associated with worse WPAI scores in CD and UC patients.[16–18] To our knowledge, there have been very few studies investigating psychosocial PROs, specifically in patients with IBD in remission, and there are currently limited data quantifying the relationship between disease activity and both the WPAI and PROMIS measures.

The objective of this study was to evaluate the associations between disease severity, psychosocial PROs, and work productivity in patients with IBD from CorEvitas' IBD Registry, which offers a unique source of real-world data for patients with CD and UC.

Materials and Methods

Data Source and Study Design

Launched in May 2017, the IBD registry collects longitudinal follow-up data from gastroenterologists and patients at the time of outpatient clinical encounters using questionnaires. These questionnaires collect data on demographics, disease duration, medical history (including prior and current treatments for IBD), disease activity, and PROs. As of June 2020, the Registry included 62 private and academic clinical sites with 135 gastroenterologists throughout 20 states in the United States.

This large, noninterventional, geographically diverse, cross-sectional study of patients diagnosed with CD or UC who were seen in a clinical practice setting and enrolled in CorEvitas' IBD registry included visits from the IBD registry launch date of May 3, 2017, to September 3, 2019.

Study Population

Registry Patient Selection. Included patients must be aged $\geq$18 years; willing and able to provide written consent for participation in the CorEvitas IBD registry and provide personally identifiable information to include (at a minimum) full name, date of birth, sex, and home address ZIP code; and have been diagnosed with CD or UC by a gastroenterologist. Patients enrolled on or after January 2019 have initiated or switched to an approved biologic or Janus kinase (JAK) inhibitor for the treatment of CD or UC at enrollment or within 12 months before the enrollment visit.

Eligible medications for enrollment include the Food and Drug Administration–approved biologic treatments for IBD (tumor necrosis factor inhibitors: adalimumab and its biosimilar, certolizumab, golimumab, and infliximab and its biosimilar; interleukin-12/23 inhibitor: ustekinumab; integrin $\alpha4\beta7$ inhibitor: vedolizumab; integrin $\alpha4$ inhibitor: natalizumab; JAK inhibitor: tofacitinib).

Effective January 2019, therefore, enrollment of new patients on or initiating or switching to immunosuppressant therapies (methotrexate, 6 mercaptopurine, azathioprine, tacrolimus, cyclosporine, other immunosuppressants), 5-amino salicylic agents, antibiotics, or steroids is on a temporary hold. However, patients previously enrolled will continue to be followed in the IBD registry.

Patients were excluded if they were participating or were planning to participate in an interventional clinical trial with a nonmarketed or marketed investigational drug (ie, phase I–IV drug trial).

All participating investigators were required to obtain full board approval for conducting research involving human

Table 1. Baseline Characteristics Among Patients With Crohn's Disease (CD) or Ulcerative Colitis (UC) Enrolled in the IBD Registry as of September 3, 2019

Variables	Patients with CD (n = 812)	Patients with UC (n = 731)
Age (y), mean (SD)	47.1 (16.8)	47.7 (16.9)
Female, n (%)	n = 809 465 (57.5)	n = 728 391 (53.7)
White race, n (%)	708 (87.2)	608 (83.2)
Disease duration (y), mean (SD)	n = 807 13.7 (12.3)	n = 726 10.1 (9.7)
Private health insurance, n (%)	591 (72.8)	543 (74.3)
Work status, n (%)	n = 811	n = 728
Employed (part time or full time)	527 (65.0)	473 (65.0)
Education, n (%)	n = 810	n = 727
College educated (some or more)	622 (76.8)	558 (76.8)
Geographic region, n (%)	n = 810	n = 729
Northeast	116 (14.3)	111 (15.2)
Central	51 (6.3)	49 (6.7)
South	556 (68.6)	482 (66.1)
West	87 (10.7)	87 (11.9)
Site type, n (%)	n = 812	n = 731
Private	664 (81.8)	667 (91.2)
Academic	148 (18.2)	64 (8.8)
Harvey-Bradshaw index, n (%)		
Remission (0–4)	547 (67.4)	–
Mild disease (5–7)	156 (19.2)	–
Moderate disease (8–16)	103 (12.7)	–
Severe disease (>16)	6 (0.7)	–
Partial Mayo Score, n (%)		
Remission (0–1)	–	385 (52.7)
Mild disease (2–4)	–	258 (35.3)
Moderate disease (5–6)	–	62 (8.5)
Severe disease (7–9)	–	26 (3.6)
History of extraintestinal manifestations, n (%)		
Arthritis	158 (19.5)	71 (9.7)
Skin manifestations	36 (4.4)	8 (1.1)
Eye involvement	23 (2.8)	2 (0.3)
History of comorbidities, n (%)		
Hypertension	158 (19.5)	139 (19.0)
Hyperlipidemia	62 (7.6)	76 (10.4)
Cardiovascular disease	81 (10.0)	73 (10.0)
Diabetes mellitus	44 (5.4)	47 (6.4)
Depression	87 (10.7)	50 (6.8)
Anxiety	104 (12.8)	80 (10.9)
Medication use at enrollment, n (%)		
Biologic or JAK inhibitor	492 (60.6)	291 (39.8)
Immunomodulator	138 (17.0)	86 (11.8)
5-Aminosalicylate	157 (19.3)	396 (54.2)
Corticosteroid	111 (13.7)	102 (14.0)
Antibiotic	15 (1.8)	12 (1.6)
IBD-related surgery, n (%)	–	n = 731
History of proctocolectomy	–	n = 11
J-pouch creation	–	10 (90.9)
End ileostomy	–	1 (9.1)
History of other IBD-related surgery, n (%)	n = 812	n = 731
Resection	256 (31.5)	8 (1.1)
Ostomy	59 (7.3)	12 (1.6)
Lysis of adhesions	0 (0.0)	0 (0.0)
Other	69 (8.5)	12 (1.6)

IBD, inflammatory bowel disease; JAK, Janus kinase; SD, standard deviation.

subjects. Sponsor approval and continuing review were obtained through a central institutional review board (IRB; IntegReview, protocol number is Corrona-PSO-500). For academic investigative sites that did not receive a waiver to use the central IRB, approval was obtained from the respective governing IRBs, and documentation of approval was submitted to the sponsor before initiating any study procedures. All registry subjects were required to provide written informed consent before participating.

Analysis Cohort Patient Selection. Inclusion/exclusion criteria matched those for IBD registry enrollment. Eligible patients were aged ≥18 years, diagnosed with CD or UC, and enrolled in the IBD registry. Patients diagnosed with indeterminate colitis or whose diagnosis changed at subsequent follow-up visits were excluded.

Patients were subsequently classified into 1 of 3 disease severity groups (remission, mild disease, moderate/severe disease) using the Harvey-Bradshaw Index for patients with CD and the partial Mayo Score for patients with UC.

The Harvey-Bradshaw Index calculates single-day scores for general well-being (previous day; 0 = very well to 4 = terrible), abdominal pain (previous day; 0 = none to 3 = severe), the number of liquid or soft stools per day (previous day; open entry with 1–25 possible points), abdominal mass (0 = none to 3 = definite and tender), and complications to assess disease severity (no = none, yes = all complications with 1 point for each [1–8]) in patients with CD.[19] The cutoff scores used were 0–4 for remission, 5–7 for mild disease, and ≥8 for moderate/severe disease.[19,20]

Components of the partial Mayo Score for UC include measures of rectal bleeding (0 = none to 3 = passing blood alone), stool frequency (0 = normal to 3 = 5 or more stools per day than normal), and the Physician's Global Assessment of disease severity (0 = normal [for the patient] to 3 = severe disease) that acknowledges the 3 subscores, the daily record of abdominal discomfort, functional findings, and other observations such as physical findings and patient performance status.[21,22] The cutoff scores used were 0–1 for remission (perfect or very good with minimal symptoms), 2–4 for mild disease, and 5–9 for moderate/severe disease.[21]

Patient-Reported Outcomes

Primary outcomes were collected at the enrollment visit and were compared with disease severity measures. All variables were provider-reported unless indicated otherwise. All covariates, including disease severity measures, were also assessed at the enrollment visit.

PROMIS is a National Institutes of Health–funded instrument that assesses the patient's self-reported health over the past 7 days.[23] Patients report different components of physical, mental, and social health, including anxiety, depression, fatigue, sleep disturbance, and pain interference, and higher scores indicate poorer health. A score of 50 represents the general US population mean, and minimally important differences of 2–6 points have been reported for other disease states, including chronic pain, stroke, osteoarthritis, and cancer.[24,25]

Five WPAI domains measure absenteeism (the percentage of work hours missed due to IBD), presenteeism (the percentage of impairment while working due to IBD), work productivity loss (the overall percentage of work hours affected by IBD), and activity impairment (the overall percentage of daily activities affected by IBD). At enrollment, WPAI scores were dichotomized to assess the proportion of patients who

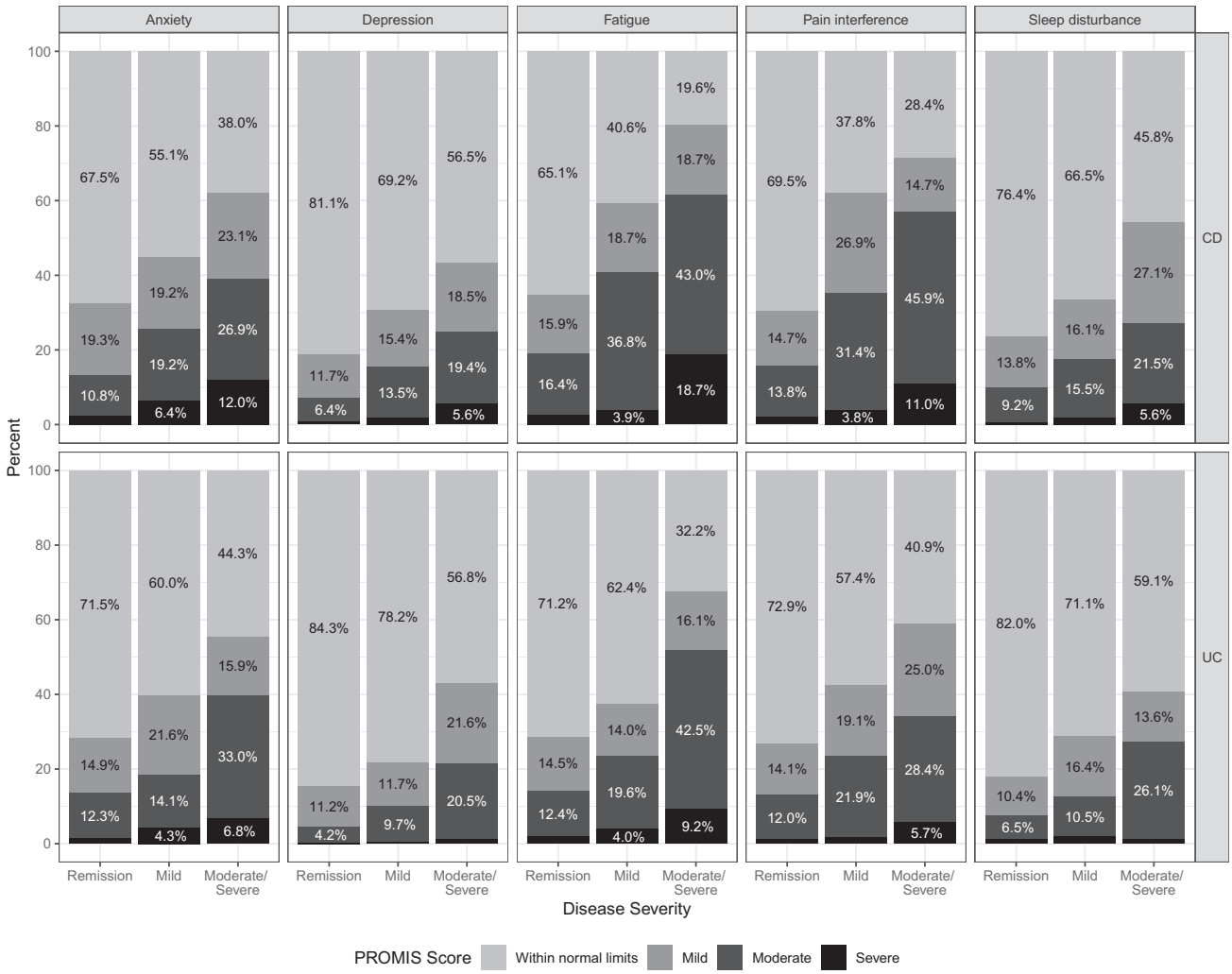

Figure 1. Stacked bar plots of unadjusted percentage reporting impairment in each PROMIS score domain. Kruskal-Wallis and chi-square tests were used to investigate associations between disease severity and PROMIS domains for continuous and categorical variables, respectively. Unadjusted analyses indicate that they were not controlled for age, sex, race (White vs non-White), duration of disease, current treatment, and comorbidities. Patients with missing data were not included in the analysis. "Severe" scores not reported in the figure owing to space (were below 3.5%). All *P* values $<.001$ for CD and UC. CD, Crohn's disease; PROMIS, Patient-Reported Outcomes Measurement Information System; UC, ulcerative colitis.

experienced no (0%) or any (>0%) impairment in the different domains. Absenteeism, presenteeism, and work productivity loss were measured on the subset of patients currently employed.

Statistical Analysis

Descriptive statistics were used to describe patient enrollment characteristics; categorical variables were summarized using frequency counts and percentages; continuous variables were summarized by number of observations, mean, and standard deviation.

Kruskal-Wallis and chi-square tests were used to investigate associations between disease severity and PROMIS domains. The Cochran-Armitage test for trends was used to determine associations between disease severity and WPAI domains. Patients with missing data were not included in the analyses.

We conducted univariable and multivariable linear or logistic regression modeling to evaluate the associations between disease severity groups and (1) the PROMIS domains of anxiety, depression, fatigue, pain interference, and sleep disturbance, as well as (2) the following binary WPAI domains: current employment, absenteeism, presenteeism, work productivity loss, and activity impairment. Models were adjusted a priori for potential confounding variables: age, sex, race, duration of disease, current treatment for IBD (biologics/JAK inhibitors, immunosuppressants, 5-aminosalicylic acid, corticosteroids, and antibiotics), and comorbidities using a modified Charlson Comorbidity Index[26] (see Supplemental Digital Content for the full regression results).

We calculated adjusted means and 95% confidence intervals of PROMIS scores by disease severity among patients with CD and UC, evaluating holding covariates in the regression model at their mean values. Similarly, we calculated adjusted probabilities and 95% confidence intervals of WPAI scores by disease severity, again evaluating holding covariates at their mean values.

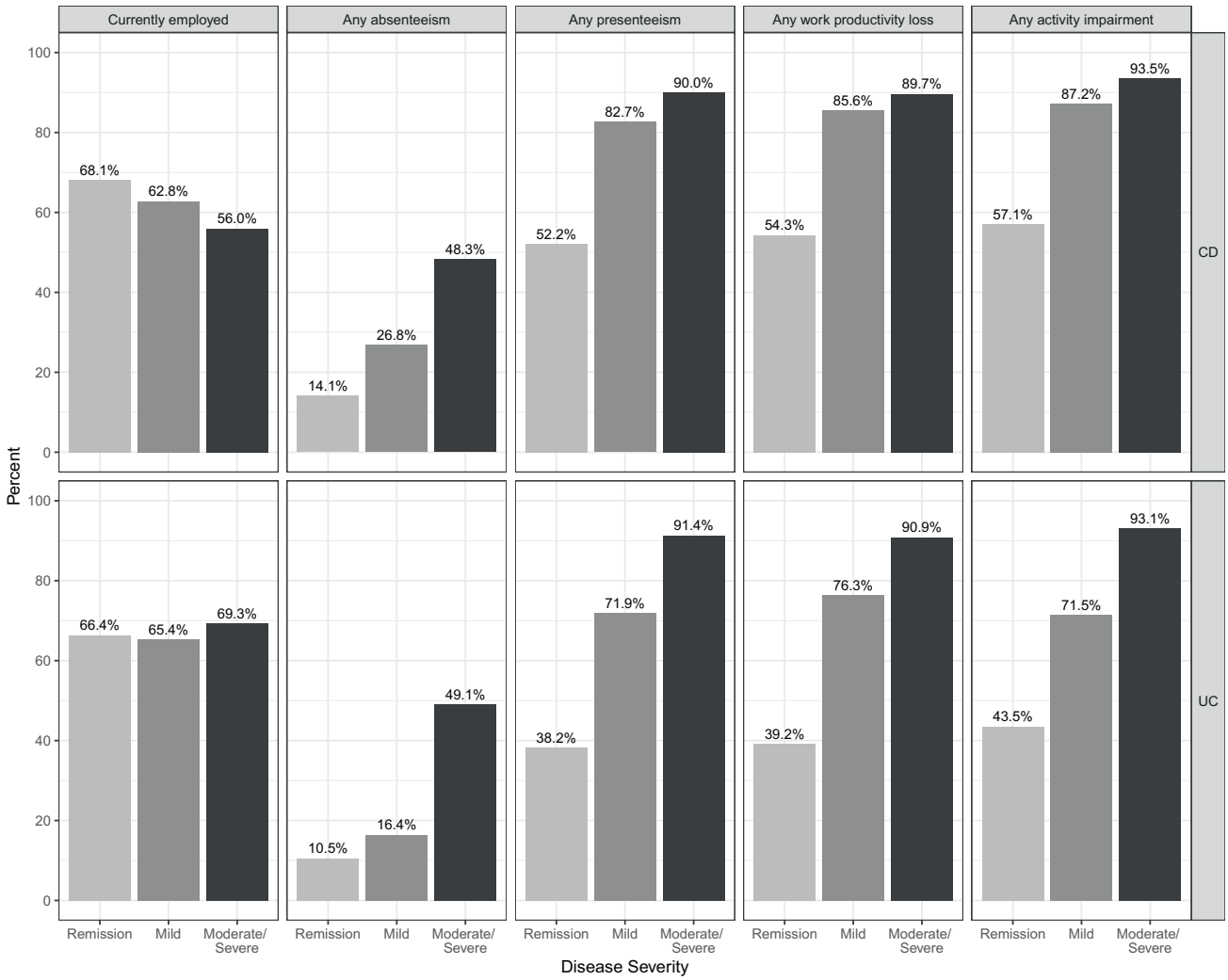

Figure 2. Bar plots of unadjusted percentage reporting impairment in each WPAI domain. The Cochran-Armitage test for trends was used to determine associations between disease severity and WPAI domains. Unadjusted analyses indicate that they were not controlled for age, sex, race (White vs non-White), duration of disease, current treatment, and comorbidities. All P values $<.001$ for CD and UC except for "Currently employed" in CD ($P = .011$) and "Currently employed" in UC ($P = .776$).CD, Crohn's disease; UC, ulcerative colitis; WPAI, Work Productivity and Activity Impairment.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

A total of 1660 patients were enrolled in the IBD registry as of September 3, 2019; of these patients, 1543 were included in this cross-sectional analysis, and 117 were excluded due to a diagnosis of indeterminate colitis, a diagnosis change, or missing disease severity measures.

Crohn's Disease

Our analysis included a total of 812 patients with CD, with 67.4% in remission, 19.2% with mild disease, and 13.4% with moderate/severe disease. The mean age at enrollment was 47.1 years; 57.5% were female and 87.2% were White. The mean disease duration at enrollment was 13.7 years. These and other baseline characteristics are presented in Table 1.

Overall unadjusted PROMIS and WPAI scores indicate a high burden of psychosocial and work impairment in the CD cohort (Figures 1 and 2). Although patients with mild and moderate/severe disease reported more impairment than patients in remission, impaired PROs were commonly reported even among patients with CD in remission. For the patients with CD in remission, the unadjusted percentage of patients with PROMIS scores outside of normal limits ranged from 18.9% (depression) to 34.9% (fatigue). In addition, 54.3% of patients with CD in remission reported work productivity loss, and 57.1% reported activity impairment.

Adjusted estimated means for the PROMIS scores[27,28] for patients with CD exceeded the threshold for "normal" among the general population (ie, estimated mean $\geq$55) for patients with mild disease in the domains of fatigue (55.4) and pain interference (57.4), and for

Table 2. Adjusted Estimated Means of PROMIS Scores[27,28] by Disease Severity Among Patients With Crohn's Disease (N = 812)[a] and Ulcerative Colitis (N = 731)

	Adjusted means for Crohn's disease[b]			Adjusted means for ulcerative colitis[b]		
	Remission	Mild	Moderate/severe	Remission	Mild	Moderate/severe
PROMIS domains[b]	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Anxiety	50.0 (47.1, 52.9)	53.2 (50.1, 56.3)	56.6 (53.3, 59.8)	51.4 (48.3, 54.5)	53.8 (50.7, 56.9)	57.9 (54.7, 61.2)
Depression	46.6 (44.0, 49.3)	49.8 (47.0, 52.6)	52.2 (49.3, 55.1)	49.0 (46.4, 51.5)	50.4 (47.8, 53.0)	54.6 (51.8, 57.3)
Fatigue	49.6 (46.4, 52.7)	55.4 (52.1, 58.7)	59.9 (56.5, 63.3)	49.1 (45.6, 52.7)	52.3 (48.7, 55.8)	58.7 (55.0, 62.4)
Pain interference	51.5 (48.6, 54.3)	57.4 (54.4, 60.5)	61.3 (58.2, 64.5)	51.1 (48.1, 54.1)	54.3 (51.3, 57.4)	58.1 (54.9, 61.3)
Sleep disturbance	50.7 (48.1, 53.2)	54.2 (51.5, 57.0)	57.0 (54.2, 59.8)	48.5 (45.7, 51.3)	51.0 (48.1, 53.8)	54.6 (51.7, 57.6)

A higher score denotes more symptoms on that scale and a minimally important difference for the psychosocial PROMIS domain scales ranges from 2 to 6.[15,24,28]
PROMIS, Patient-Reported Outcomes Measurement Information System.
[a]General population thresholds are the following: within normal limits (<55), mild (55, <60), moderate (60, 65), severe (>65) with an overall average of 50.[27]
[b]Adjusted estimated means from corresponding multivariable regression model adjusted a priori for age, sex, race (White vs non-White), duration of disease, current treatment, and comorbidities; evaluated holding covariates at their mean values.

patients with moderate/severe disease in the domains of anxiety (56.6), fatigue (59.9), pain interference (61.3), and sleep disturbance (57.0; Table 2). Adjusted estimated probabilities for the WPAI scores exceeded 50% for patients with CD in remission for any presenteeism, any work productivity loss, and any activity impairment. Higher probabilities were observed in mild and moderate/severe CD as well (Table 3). In addition, greater disease severity for patients with CD was associated with worse outcomes on both the PROMIS and WPAI measures (see Tables A1[15,24,28] and A2).

Ulcerative Colitis

Our analysis included a total of 731 patients with UC, with 52.7% in remission, 35.3% with mild disease, and 12.0% with moderate/severe disease. The mean age at enrollment was 47.7 years; 53.7% were female and 83.2% were White. The mean disease duration was 10.1 years. These and other demographic details are presented in Table 1.

As seen in the CD cohort, overall unadjusted PROMIS and WPAI scores indicate a high burden of mental and physical distress and work impairment in patients with UC as well (Figures 1 and 2). Impaired PROs were commonly reported in all patients with UC, including those in remission. The unadjusted percentage of patients with UC in remission with scores outside of normal limits ranged from 15.7% (depression) to 28.7% (fatigue) for PROMIS domains and 10.5% (absenteeism) to 43.5% (activity impairment) for WPAI domains.

Adjusted estimated means for the PROMIS scores[27,28] for patients with UC exceeded normal limits among patients with moderate/severe disease in the domains of anxiety (57.9), fatigue (58.7), and pain interference (58.1; Table 2). The adjusted estimated probabilities for the WPAI scores exceeded 50% for patients with UC in remission for any presenteeism. Higher probabilities were observed in mild and moderate/severe UC as well (Table 3). Finally, as seen in the CD cohort, greater disease severity for patients with UC was associated with worse outcomes on both the PROMIS and WPAI measures (see Tables A3[15,24,28] and A4).

In an exploratory regression analysis, disease activity coefficients were only mildly attenuated after adjusting for college education and history of surgery, and no meaningful changes were observed.

Discussion

In our study, patients with IBD, including those in remission, experienced impaired PROMIS outcomes and work productivity. Although patients with greater disease severity reported poorer QOL and work-related outcomes, our observation of significant impairment in psychosocial function and activity for CD and UC patients in remission, which represented about 50%–70% of IBD patients in our study, highlights a critical unmet need in this population.

Our study results are consistent with previous research. A large study using data from the Crohn's and Colitis Foundation Partners internet cohort reported that disease activity was associated with higher PROMIS scores both cross-sectionally and longitudinally.[13] In addition, a substantial proportion of patients with IBD have impaired presenteeism as shown by the percentage of work hours impacted by IBD in a recent study.[29] A previous study of patients with IBD reported significant economic burden associated with work productivity loss and activity impairment.[30] Although studies have shown there is an incremental increase in WPAI scores as CD and UC worsen from remission to severe disease,[18,31] no study to our knowledge has examined PRO impairment in patients in remission.

PRO instruments such as PROMIS and the WPAI questionnaire provide important information about the patient experience that may be underrepresented by physician-

Table 3. Adjusted Estimated Probabilities of WPAI Scores by Disease Severity Among Patients With Crohn's Disease (N = 812)[a] and Ulcerative Colitis (N = 731)

	Adjusted probabilities[b] for Crohn's disease			Adjusted probabilities[b] for ulcerative colitis		
	Remission	Mild	Moderate/severe	Remission	Mild	Moderate/severe
WPAI domains[b]	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Currently employed	69.9 (53.6, 82.4)	65.0 (46.9, 79.6)	57.8 (39.1, 74.6)	81.7 (64.1, 91.7)	79.5 (60.6, 90.7)	78.8 (59.0, 90.6)
Any absenteeism	26.0 (13.0, 45.2)	42.2 (23.0, 64.1)	67.6 (44.5, 84.5)	18.3 (7.7, 37.5)	26.0 (11.6, 48.4)	60.7 (36.8, 80.4)
Any presenteeism	63.1 (35.0, 84.5)	89.0 (70.2, 96.5)	92.6 (75.5, 98.1)	51.1 (27.9, 73.9)	80.6 (59.9, 92.0)	93.8 (80.9, 98.2)
Any work productivity loss	64.1 (35.8, 85.2)	90.8 (73.7, 97.2)	92.1 (74.2, 97.9)	46.9 (24.2, 71.0)	80.8 (59.7, 92.3)	92.3 (76.8, 97.8)
Any activity impairment	62.6 (41.2, 80.0)	89.5 (76.5, 95.7)	94.5 (84.7, 98.1)	46.3 (26.7, 67.1)	72.7 (52.7, 86.4)	92.9 (81.0, 97.5)

WPAI, Work Productivity and Activity Impairment.
[a]All domain scores are expressed as percentages, with lower values indicating less impairment.
[b]Adjusted probabilities from corresponding multivariable logistic regression model; evaluated holding covariates at their mean values.

reported disease activity indices. As in many other chronic illnesses, individuals with IBD may suffer from psychosocial and physical stress (eg, depression, anxiety, fatigue, pain interference, sleep disturbance), which can worsen QOL and/or exacerbate symptoms of disease. Depression and anxiety have been shown to predict clinical reoccurrence, regardless of remission status.[2,11,32] The high burden of psychological distress within our cohorts emphasizes the importance of mental health screening and treatment, irrespective of disease activity.[13]

One symptom of interest was fatigue, which has been associated with poor general and disease-specific health-related QOL, disability, and depression in patients with IBD.[10] Pain, fatigue, and other disease-related symptoms are frequently cited reasons for missed work among patients with IBD.[3] Fatigue has been reported in IBD by up to 48% of patients in remission and 86% of patients with active disease.[33] We also noted persistent fatigue symptoms outside of normal limits in both patients with UC and CD in remission within our study. Fatigue in IBD can be exacerbated by sleep disturbance and associated with physical and mental symptoms that limit the patients' social, physical, and work activities.[34,35] A study of 220 newly diagnosed patients with IBD[10] demonstrated that fatigued patients had more work impairment (difference: CD, 29.5%; UC, 23.8%) and activity impairment (difference: CD, 32.3%; UC, 25.7%) than those without fatigue. After controlling for disease activity, a significant association was found between fatigue and impairment scores.[10]

Our study demonstrates that patients with moderate to severe CD/UC have physical and psychosocial symptoms that further impact work productivity. We observed that a substantial proportion of patients with IBD in remission experienced productivity loss at work (CD, 54%; UC, 39%; Figure 2). It is possible that the symptoms are interrelated, making it difficult to determine what symptom is primarily impacting work productivity impairment. A potential explanation for the impaired PROs in patients in symptomatic remission includes the presence of subclinical inflammation. It is well known that there can be a disconnect between symptoms and inflammation; in a study of 121 patients with CD, only weak correlations were found between the severity of symptoms and the level of inflammation.[36,37] Therefore, patients in remission or with mild symptoms may still have significant inflammation resulting in impaired PROs. This emphasizes the need for gastroenterologists to adopt a treat-to-target approach to verify control of inflammatory activity regardless of symptoms.[38]

Our findings provide additional motivation for examining the relationship between psychosocial factors, such as depression and anxiety, and poor clinical outcomes in patients with IBD. There have been limited studies surrounding QOL and PROs in IBD patients in remission, and our findings help to address this important gap within the literature. The results of our study contrast with one previous study that found the psychological well-being of IBD patients in long-standing remission was similar to that of the general public.[39] Future research should include additional comparisons to the general public to further understand the symptomatic burden that patients with IBD in remission still experience.

The strengths of this study include the sample size, use of validated indices, and geographic distribution of the cohort. Our findings contribute to the currently limited body of knowledge on the relationship between disease activity measures and PROs in patients with IBD.

This study is subject to the limitations of real-world observational studies. It includes health care providers with high proportions of patients with IBD, which may bias the results to a more refractory population not representative of the general US IBD population. In addition, the patient population was predominantly White, privately insured, employed, and highly educated (some college and beyond). This limits the ability to generalize these data across diverse patient populations, including those from lower socioeconomic groups. Recent literature suggests that social determinants (markers of lower socioeconomic status) impact IBD outcomes, thereby warranting further research in a more diverse patient population.[40,41]

As this was a cross-sectional analysis, causal inferences cannot be made regarding disease severity and PROs, and

changes in disease severity and PROs over time were not measured. In addition, there is a lack of objective markers of disease activity such as endoscopy or disease markers using labs/fecal laboratory values.

In this study, patients in remission showed impairment in PROs, highlighting how those in remission may still need active management. Further investigation into the factors that impact persistent PRO impairment is warranted. Even in remission, the prevalence of fatigue, pain, and anxiety/depression is high, which affects QOL and work productivity.

Conclusions

In our study of patients with IBD, psychosocial impairment and decreased work productivity were seen even in patients in remission, who made up approximately 67% and 53% of patients in the CD and UC cohorts, respectively. The prevalence of self-reported fatigue, pain, and anxiety and depression remains high among patients with IBD in remission and indicates that there may be important aspects of disease impacting patients' lives that have not been captured in standard disease activity assessments.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.07.003.

References

1. Dahlhamer JM, Zammitti EP, Ward BW, et al. Prevalence of inflammatory bowel disease among adults aged >/=18 years - United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1166–1169.
2. Gaines LS, Slaughter JC, Horst SN, et al. Association between affective-cognitive symptoms of depression and exacerbation of Crohn's disease. Am J Gastroenterol 2016;111:864–870.
3. Yarlas A, Maher SM, Bayliss MS, et al. Psychometric validation of the work productivity and activity impairment questionnaire in ulcerative colitis: results from a systematic literature review. J Patient Rep Outcomes 2018;2:62.
4. Juillerat P, Manz M, Sauter B, et al. Therapies in inflammatory bowel disease patients with extraintestinal manifestations. Digestion 2020;101(Suppl 1):83–97.
5. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.e42; quiz e30.
6. Kappelman MD, Moore KR, Allen JK, et al. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. Dig Dis Sci 2013;58:519–525.
7. Mao EJ, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalisation and surgery in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2017;45:3–13.
8. de Jong MJ, Huibregtse R, Masclee AAM, et al. Patient-reported outcome measures for use in clinical trials and clinical practice in inflammatory bowel diseases: a systematic review. Clin Gastroenterol Hepatol 2018;16:648–663.e3.
9. Kreijne JE, Lie MR, Vogelaar L, et al. Practical guideline for fatigue management in inflammatory bowel disease. J Crohns Colitis 2016;10:105–111.
10. Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. Aliment Pharmacol Ther 2014;39:811–822.
11. Mikocka-Walus A, Pittet V, Rossel JB, et al. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. Clin Gastroenterol Hepatol 2016;14:829–835.e1.
12. Bernstein CN, Hitchon CA, Walld R, et al. Increased burden of psychiatric disorders in inflammatory bowel disease. Inflamm Bowel Dis 2019;25:360–368.
13. Kappelman MD, Long MD, Martin C, et al. Evaluation of the patient-reported outcomes measurement information system in a large cohort of patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014;12:1315–1323.e2.
14. Thomas PWA, den Broeder N, Derikx M, et al. Impact of biological therapies and tofacitinib on real-world work impairment in inflammatory bowel disease patients: a prospective study. Inflamm Bowel Dis 2022;4Feb;izac002: Online Ahead of Print.
15. Kochar B, Martin CF, Kappelman MD, et al. Evaluation of gastrointestinal patient reported outcomes measurement information system (GI-PROMIS) symptom scales in subjects with inflammatory bowel diseases. Am J Gastroenterol 2018;113:72–79.
16. Armuzzi A, Tarallo M, Lucas J, et al. The association between disease activity and patient-reported outcomes in patients with moderate-to-severe ulcerative colitis in the United States and Europe. BMC Gastroenterol 2020;20:18.
17. Jackson BD, Con D, Gorelik A, et al. Examination of the relationship between disease activity and patient-reported outcome measures in an inflammatory bowel disease cohort. Intern Med J 2018;48:1234–1241.
18. Van Assche G, Peyrin-Biroulet L, Sturm A, et al. Burden of disease and patient-reported outcomes in patients with moderate to severe ulcerative colitis in the last 12 months - multicenter European cohort study. Dig Liver Dis 2016;48:592–600.
19. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514.
20. Peyrin-Biroulet L, Panes J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. Clin Gastroenterol Hepatol 2016;14:348–354.e17.
21. Mayo score for assessment of ulcerative colitis - Updated: partial Mayo score, 2020. Available at: https://globalrph.com/medcalcs/mayo-score-for-assessment-of-ulcerative-colitis-updated/. Accessed November 19, 2020.
22. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–1629.

23. Spiegel BM. Patient-reported outcomes in gastroenterology: clinical and research applications. J Neurogastroenterol Motil 2013;19:137–148.
24. Meaningful change for PROMIS®, 2020. Available at: https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/meaningful-change. Accessed October 1, 2020.
25. PROMIS reference populations, 2020. Available at: https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/reference-populations. Accessed August 30, 2021.
26. Pappas DA, Etzel CJ, Crabtree M, et al. Effectiveness of tocilizumab in patients with rheumatoid arthritis is unaffected by comorbidity burden or obesity: data from a US registry. J Rheumatol 2020;47:1464–1474.
27. PROMIS® score cut points, 2020. Available at: http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points. Accessed March 23, 2020.
28. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six patient-reported outcomes measurement information system-cancer scales in advanced-stage cancer patients. J Clin Epidemiol 2011;64:507–516.
29. Zand A, van Deen WK, Inserra EK, et al. Presenteeism in inflammatory bowel diseases: a hidden problem with significant economic impact. Inflamm Bowel Dis 2015;21:1623–1630.
30. 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.
31. Reilly MC, Gerlier L, Brabant Y, et al. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. Clin Ther 2008;30:393–404.
32. Gracie DJ, Guthrie EA, Hamlin PJ, et al. Bi-directionality of brain-gut interactions in patients with inflammatory bowel disease. Gastroenterology 2018;154:1635–1646, e1633.
33. Radford SJ, McGing J, Czuber-Dochan W, et al. Systematic review: the impact of inflammatory bowel disease-related fatigue on health-related quality of life. Frontline Gastroenterol 2020;12:11–21.
34. van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. Aliment Pharmacol Ther 2010;32:131–143.
35. Beck A, Bager P, Jensen PE, et al. How fatigue is experienced and handled by female outpatients with inflammatory bowel disease. Gastroenterol Res Pract 2013;2013:153818.
36. Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut 2014;63:88–95.
37. Cellier C, Sahmoud T, Froguel E, et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. Gut 1994;35:231–235.
38. 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.
39. Simrén M, Axelsson J, Gillberg R, et al. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. Am J Gastroenterol 2002;97:389–396.
40. Bernstein CN, Walld R, Marrie RA. Social determinants of outcomes in inflammatory bowel disease. Am J Gastroenterol 2020;115:2036–2046.
41. Thakur K, Barrett TA. Social determinants of health in inflammatory bowel diseases: barriers and opportunities. Am J Gastroenterol 2021;116:2146.

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Raymond K. Cross, Jenny S. Sauk, Joe Zhuo, Harris A. Ahmad, Antoine G. Sreih, Joehl Nguyen, Sara N. Horst, and David Hudesman designed the study. Joe Zhuo, Ryan W. Harrison, Samantha J. Kerti, Kelechi Emeanuru, and Jacqueline O'Brien contributed to collection and assembly of data. Ryan W. Harrison and Samantha J. Kerti contributed to data analysis. All authors contributed to data interpretation, article review and revisions, and final approval of the article.

Conflicts of Interest:
These authors disclose the following: R.K.C. is a member of advisory boards at AbbVie, Bristol Myers Squibb, Janssen, Samsung Bioepis, and Takeda; consultant at AbbVie and Eli Lilly and Company. J.S.S. is a consultant for CorEvitas; is a member of speakers' bureau of Pfizer Inc and AbbVie; is a member of advisory board at Prometheus. S.N.H. is a consultant at Janssen, Boehringer Ingelheim, and Gilead. D.H. is a consultant at Bristol Myers Squibb, AbbVie, Janssen, Pfizer Inc, and Takeda; and received research support from Takeda. J.N. was a consultant at Bristol Myers Squibb at the time of the study and is currently employee of GlaxoSmithKline. J.Z., H.A., and A.G.S. are employees and may be shareholders of Bristol Myers Squibb. R.W.H., S.J.K., K.E., and J.O. are employees of CorEvitas LLC.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Bristol Myers Squibb shares data from BMS studies that meet our data sharing criteria with qualified researchers who submit a data sharing proposal at: https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. The website provides additional information on (1) submitting a sharing request for BMS data, (2) criteria for studies "in scope" for data sharing, (3) process for submitting data sharing requests, including review of in-scope proposals by the Independent Review Committee (IRC), and (4) Bristol Myers Squibb's disclosure commitment.