Gastroenterology 2022;163:190–203

Relative Contribution of Disease Activity and Psychological Health to Prognosis of Inflammatory Bowel Disease During 6.5 Years of Longitudinal Follow-Up

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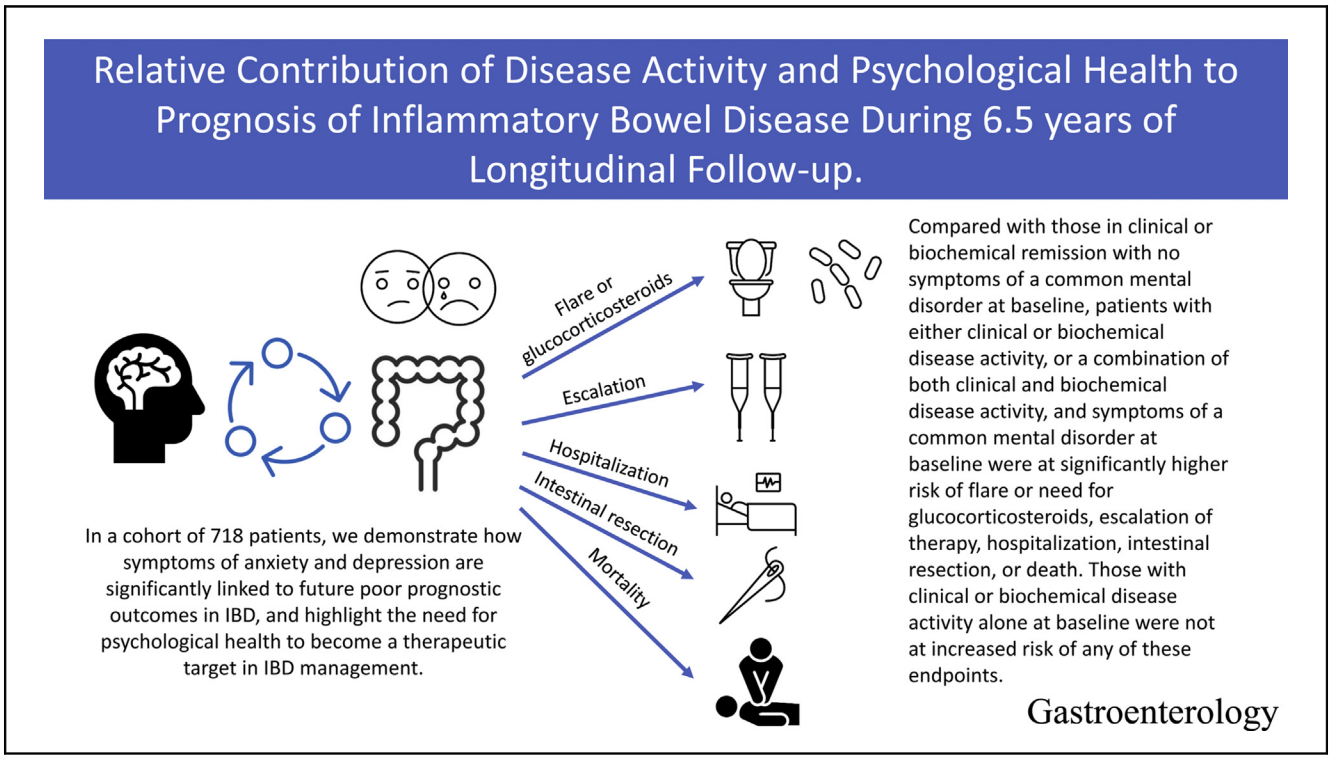

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BACKGROUND & AIMS: Symptoms of common mental disorders, such as anxiety or depression, are common in inflammatory bowel disease (IBD) and may affect prognosis. However, unlike clinical or biochemical markers of disease activity, psychological health is not a recommended therapeutic target. We assessed relative contribution of poor psychological health and clinical or biochemical activity to prognosis. **METHODS:** Demographic features, IBD subtype, treatments, and anxiety and depression scores were recorded at baseline for 760 adults, with clinical activity determined using validated scoring systems. Fecal calprotectin was analyzed in 379 (49.9%) patients ($\geq$250 μg/g used to define biochemical activity). Glucocorticosteroid prescription or flare, escalation, hospitalization, intestinal resection, or death were assessed during 6.5 years of follow-up. Occurrence was compared using multivariate Cox regression across 4 patient groups according to presence of disease remission or activity, with or without symptoms of a common mental disorder, at baseline. **RESULTS:** In total, 718 (94.5%) participants provided data. Compared with clinical remission without symptoms of a common mental disorder at baseline, need for glucocorticosteroid prescription or flare (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.58–3.54), escalation (HR, 1.65; 95% CI, 1.14–-2.40), and death (HR, 4.99; 95% CI, 1.80–13.88) were significantly higher in those with clinical activity and symptoms of a common mental disorder. Rates in those with clinical remission and symptoms of a common mental disorder at baseline or those with clinical activity without symptoms of a common mental disorder were not significantly higher. Similarly, with biochemical activity and symptoms of a common mental disorder, rates of glucocorticosteroid prescription or flare (HR, 2.48; 95% CI, 1.38–4.46), escalation (HR, 2.97; 95% CI, 1.74–5.06), hospitalization (HR, 3.10; 95% CI, 1.43–6.68), and death (HR, 6.26; 95% CI, 2.23–17.56) were significantly higher. **CONCLUSIONS:** Psychological factors are important determinants of poor prognostic outcomes in IBD and should be considered as a therapeutic target.

Keywords: IBD; Mood; Psychology; Morbidity; Mortality.

Inflammatory bowel disease (IBD), which incorporates both Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition of the gastrointestinal tract with increasing prevalence across North America and Europe.[1] The clinical course typically fluctuates through periods of disease activity or remission, with patients experiencing symptoms including abdominal pain, diarrhea, and rectal bleeding during flares of activity. These manifestations of disease impact negatively on social functioning and quality of life.[2] The chronic and unpredictable nature of IBD has been linked to an increased prevalence of symptoms of common mental disorders, such as anxiety or depression, which affect more than 30% and 25% of patients with IBD, respectively.[3] Studies have shown that patients with active disease at baseline, without prior history of a common mental disorder, are also more likely to develop symptoms of anxiety or depression in the future,[4,5] suggesting gut-brain axis effects.[6]

Conventionally, uncontrolled symptoms or biochemical activity of disease, as evidenced by raised C-reactive protein or fecal calprotectin (FC), may be adverse prognostic factors in IBD.[7–13] As such, these are recommended therapeutic targets according to the International Organization for the Study of IBD.[14] However, there is also evidence that gut-brain axis effects are bidirectional in IBD, with the presence of common mental disorders appearing to influence future clinical course. In some studies, symptoms of anxiety or depression have been associated with increased rates of flare of disease activity or escalation of medical therapy,[4,15] and depression with higher rates of hospitalization or intestinal surgery.[16,17] A recent meta-analysis of more than 9000 patients confirmed that symptoms of both anxiety and depression were significantly associated with such adverse disease outcomes.[18] There also appears to be a cumulative impact of these symptoms. In one study, those displaying symptoms of more than one common mental disorder were at higher risk of adverse outcomes including flare of disease activity, escalation of therapy, hospitalization, or intestinal resection, compared with those with no such symptoms, despite being in biochemical remission at baseline.[19]

A negative impact of common mental disorders on prognosis in other chronic medical conditions, including diabetes mellitus, coronary heart disease, and chronic obstructive pulmonary disorder, has been reported previously.[20–22] In a recent study, rates of cardiovascular death or myocardial infarction during longitudinal follow-up were examined in patients with coronary heart disease according to the presence or absence of myocardial ischemia induced by psychological stress or conventional exercise-induced myocardial ischemia at baseline.[23] Compared with patients with neither psychological stress-induced nor conventional exercise-induced ischemia, rates of death or myocardial infarction were significantly higher among those with psychological stress-induced, but not exercise-induced, ischemia. In addition, there was a cumulative impact, with patients with both psychological stress-induced and exercise-induced myocardial ischemia having almost 4-fold higher rates of myocardial infarction or cardiovascular death than patients with neither, and 3-fold higher rates compared with those with exercise-induced myocardial ischemia alone. This suggests that psychological factors may be more important than physiological factors in determining outcomes in chronic disease.

To our knowledge, the influence of psychological factors in addition to proposed therapeutic targets, such as the gastrointestinal symptoms incorporated into clinical disease activity indices or biochemical markers of disease activity, on the prognosis of IBD has not been studied. We examined this issue in a longitudinal follow-up study of more than 700 patients with well-characterized IBD,[2,24] during an average follow-up of 6.5 years.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Common mental disorders are common in inflammatory bowel disease and are associated with adverse outcomes, but relative contribution of symptoms of a common mental disorder, vs disease activity, on prognosis is unknown.

NEW FINDINGS

Need for glucocorticosteroids or flare, escalation, and death were significantly higher with clinical activity and symptoms of a common mental disorder at baseline compared with clinical remission without such symptoms.

LIMITATIONS

Some endpoints depend on the physician's interpretation of patient-reported symptoms, and assessment of the presence of common mental disorders was based on the Hospital Anxiety and Depression Scale, not a physician's diagnosis.

IMPACT

There is a cumulative effect of poor psychological health and inflammatory bowel disease activity on prognosis; poor psychological health should be screened for and, if present, considered as a therapeutic target.

Methods

Participants and Setting

Between November 2012 and June 2015 we recruited patients aged ≥16 years with an established radiological, endoscopic, or histologic diagnosis of CD or UC into a cross-sectional study.[2] All participants were recruited from the IBD Clinic at St.

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Abbreviations used in this paper: **CD, Crohn's disease; CI, confidence interval; FC, fecal calprotectin; HADS, Hospital Anxiety and Depression Scale; HBI, Harvey-Bradshaw Index; HR, hazard ratio; IBD, inflammatory bowel disease; RCT, randomized controlled trial; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis.**


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0016-5085
https://doi.org/10.1053/j.gastro.2022.03.014

James's University Hospital, Leeds, United Kingdom, which is the sole provider of IBD care to these patients. Patients with IBD-unclassified, end ileostomy, or colostomy were excluded due to potential inaccuracies in assessing clinical disease activity. Inability to understand written English was also an exclusion criterion. Prospective longitudinal follow-up was conducted between September 2014 and November 2021 (Research Ethics Committee reference: 12/YH/0443/AM03). Study findings were reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[25]

Data Collection and Synthesis

The date of original recruitment, type of IBD, IBD-related medications, and demographic data, including age, sex, and lifestyle factors, were recorded at baseline. We also collected data concerning symptoms of a common mental disorder (anxiety or depression) using the Hospital Anxiety and Depression Scale (HADS)[26] and somatization via the Patient Health Questionnaire-15.[27] As recommended in the original validation study, a HADS anxiety or depression score of $\geq$11 was classified as abnormal.[26]

We measured clinical disease activity using the Harvey-Bradshaw index (HBI) for CD[28] and the Simple Clinical Colitis Activity Index (SCCAI) for UC.[29] We used a score of <5 to define clinical remission in both, as recommended previously.[30,31] We also asked patients to provide a FC sample for analysis (Immundiagnostik, Blensheim, Germany). We defined biochemical remission using a FC threshold of <250 μg/g of stool, as supported by international consensus.[32]

A sole investigator (KMF), blinded to the baseline questionnaire data, reviewed each participant's medical records during longitudinal follow-up to make an objective assessment of disease activity. We extracted the following end points, along with the date of their occurrence: glucocorticosteroid prescription or flare of disease activity based on a physician's global assessment, escalation of medical therapy due to uncontrolled IBD activity, hospitalization due to uncontrolled IBD activity, intestinal resection due to uncontrolled IBD activity, and death. Changes to medication without evidence of uncontrolled IBD activity (eg, based on the results of therapeutic drug monitoring) or surgery for isolated perianal CD were not included as endpoints. We also recorded the number of each of these events of interest, the number of IBD-related clinic appointments, and the number of radiological and endoscopic investigations performed for assessment of disease activity to examine healthcare use.

Statistical Analysis

We classified all individuals at baseline according to presence or absence of either clinical disease activity (clinical remission or clinical activity) as well as presence or absence of symptoms of a common mental disorder at baseline. This led to all individuals being categorized into 4 groups: clinical remission (HBI or SCCAI <5) with no evidence of symptoms of a common mental disorder at baseline, clinical remission with evidence of symptoms of a common mental disorder at baseline, clinical activity (HBI or SCCAI $\geq$5) with no evidence of symptoms of a common mental disorder at baseline, and clinical activity with evidence of symptoms of a common mental disorder at baseline. We repeated this exercise for the subgroup of individuals who provided a FC sample, creating a further 4 groups: biochemical remission (FC <250 μg/g) with no evidence of symptoms of a common mental disorder at baseline, biochemical remission with evidence of symptoms of a common mental disorder at baseline, biochemical activity (FC $\geq$250 μg/g) with no evidence of symptoms of a common mental disorder at baseline, and biochemical activity with evidence of symptoms of a common mental disorder at baseline. We also performed sensitivity analyses using a FC of <100 μg/g to define biochemical remission and a combined definition of activity or remission that incorporated both clinical and biochemical indices (clinical and biochemical remission or clinical and biochemical activity).

To assess the impact of both clinical and biochemical activity and symptoms of a common mental disorder at baseline on each of the disease activity outcomes of interest (glucocorticosteroid prescription or flare of disease activity, escalation of therapy, hospitalization, intestinal resection, or death) during longitudinal follow-up we compared their rates in each of the 4 groups using a χ^2 test. Independent predictors of the development of each of these outcomes were determined by performing multivariate Cox regression analysis to control for baseline characteristics including age, sex, marital status, tobacco and alcohol intake, educational level, type of IBD, IBD-related medications at baseline, and level of somatization according to the Patient Health Questionnaire-15. Due to multiple comparisons, a 2-tailed P value of <.01 was considered statistically significant, and the results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). We compared healthcare use between the 4 groups using one-way analysis of variance. All statistical analyses were performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL).

Results

In total, 760 individuals were recruited, with 718 (94.5%) providing complete clinical activity data at baseline (396 [55.2%] female, mean age at baseline 44.0 years, 412 [57.4%] CD), and 379 (49.9%) providing a FC sample at baseline. Among the 718 providing clinical activity data at baseline, the number of individuals who provided longitudinal follow-up data varied between 572 (79.7%; flare of disease activity or need for glucocorticosteroids) and 703 (97.9%; death) with a mean duration of follow-up of 6.5 years. Among the 379 who provided a FC sample at baseline, the number of individuals who provided longitudinal follow-up data varied between 323 (85.2%; flare of disease activity or need for glucocorticosteroids) and 373 (98.4%; death) with mean follow-up 6.7 years. When comparing patient characteristics according to clinical disease activity and presence or absence of symptoms of a common mental disorder at baseline, those with clinical activity and symptoms of a common mental disorder were significantly more likely to smoke and to have high levels of somatization and were significantly less likely to drink alcohol (Table 1). There were no other significant differences according to other baseline characteristics including sex, IBD-related medications at baseline, type of IBD, or disease location, behavior, or extent.

Table 1. Baseline Characteristics of Patients According to Clinical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Clinical remission, no symptoms of a common mental disorder (n = 338)	Clinical remission, symptoms of a common mental disorder (n = 85)	Clinical activity, no symptoms of a common mental disorder (n = 172)	Clinical activity, symptoms of a common mental disorder (n = 123)	*P* value[a]
Mean age (*y*) at baseline (SD)	45.6 (18.3)	43.5 (15.1)	43.4 (15.7)	40.7 (14.3)	.13
Female sex (%)	166 (49.1)	48 (56.5)	102 (59.3)	80 (65.0)	.011
Married or cohabiting (%)	206 (61.3)	50 (60.2)	109 (64.1)	72 (58.5)	.80
University graduate/professional (%)	107 (32.0)	20 (24.1)	50 (29.2)	24 (19.5)	.051
Tobacco user (%)	49 (14.5)	10 (12.0)	29 (16.9)	33 (27.0)	.008
Alcohol user (%)	234 (69.2)	53 (63.1)	118 (69.0)	60 (49.2)	<.001
CD (%)	183 (54.1)	50 (58.8)	104 (60.5)	75 (61.0)	.42
CD location (%) Ileal Colonic Ileocolonic	37/183 (20.2) 61/183 (33.3) 85/183 (46.4)	11/50 (22.0) 16/50 (32.0) 23/50 (46.0)	20/104 (19.2) 24/104 (23.1) 60/104 (57.7)	24/75 (32.0) 17/75 (22.7) 34/75 (45.3)	.14
Nonstricturing, nonpenetrating CD (%)	157/183 (85.8)	39/50 (78.0)	86/104 (82.7)	58/75 (77.3)	.67
Perianal CD (%)	15/183 (8.2)	5/50 (10.0)	14/104 (13.5)	6/75 (8.0)	.49
UC extent (%) Proctitis Left-sided Extensive	36/155 (23.2) 74/155 (47.7) 45/155 (29.0)	12/35 (34.3) 13/35 (37.1) 10/35 (28.6)	14/68 (20.6) 30/68 (44.1) 24/68 (35.3)	11/49 (22.4) 24/49 (49.0) 14/49 (28.6)	.74
5-aminosalicyate use (%)	169 (50.0)	39 (45.9)	81 (47.1)	53 (43.1)	.59
Immunomodulator use (%)	121 (35.8)	27 (31.8)	64 (37.2)	42 (34.1)	.84
Anti-TNFα use (%)	68 (20.1)	18 (21.2)	30 (17.4)	18 (14.6)	.51
Glucocorticosteroid use (%)	27 (8.0)	9 (10.6)	25 (14.5)	17 (13.8)	.094
High levels of somatization on Patient Health Questionnaire-15 (%)	6 (1.8)	9 (11.5)	15 (9.0)	30 (25.9)	<.001
FC <250 μg/g	114/182 (62.6)	29/44 (65.9)	40/77 (51.9)	37/62 (59.7)	.353

TNF, tumor necrosis factor.
[a]One-way analysis of variance for comparison of normally distributed continuous data; χ^2 for comparison of categorical data across all 4 groups.

Need for Glucocorticosteroid Prescription or Flare of Disease Activity

In total, 308 (53.8%) of 572 patients needed a prescription for glucocorticosteroids or had a flare of disease activity during a mean duration of follow-up of 4.0 years (range, 7 days–8.7 years). Rates were highest in those with symptoms of a common mental disorder at baseline, irrespective of clinical disease activity, with 60.5% of those in clinical remission with symptoms of a common mental disorder and 70.2% of those with clinical activity and symptoms of a common mental disorder reaching this endpoint, compared with 48.0% of those in clinical remission without symptoms of a common mental disorder ($P = .002$; Table 2). After multivariate Cox regression analysis, rates remained highest in those with clinical remission with symptoms of a common mental disorder at baseline (HR, 1.57; 95% CI, 1.08–2.27) and those with clinical activity and symptoms of a common mental disorder at baseline (HR, 2.36; 95% CI, 1.58–3.54; $P < .001$ for trend; Table 2 and Figure 1), although only rates among those with clinical activity and symptoms of a common mental disorder were statistically higher ($P < .001$). Younger age (HR per year, 0.98; 95% CI, 0.97–0.99; $P < .001$) was associated with a reduced likelihood of need for glucocorticosteroid prescription or flare and UC (HR, 1.69; 95% CI, 1.22–2.32; $P = .001$) an increased likelihood.

When we performed multivariate Cox regression analysis according to biochemical activity at baseline in those providing a sample for FC, rates of glucorticosteroid prescription or flare were higher among those with biochemical remission and symptoms of a common mental disorder at baseline (HR, 1.67; 95% CI, 1.07–2.62) and significantly increased in those with biochemical activity and symptoms of a common mental disorder at baseline (HR, 2.48; 95% CI, 1.38–4.46; $P = .002$; Table 3 and Supplementary Figure 1). Again, younger age was associated with a reduced likelihood of need for glucocorticosteroid prescription or flare (HR per year, 0.98; 95% CI, 0.97–1.00; $P = .004$). Sensitivity analyses using a FC of <100 μg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices yielded similar results (Supplementary Tables 1 and 2).

Escalation of Medical Therapy Due to Uncontrolled IBD Activity

Of 631 patients with complete data, 345 (54.7%) required escalation of medical therapy due to uncontrolled IBD activity over a mean follow-up period of 3.8 years (range, 4 days–8.7 years). Rates of escalation of therapy were highest in patients with symptoms of a common mental disorder at baseline for both those in clinical remission (61.3%) and those with clinically active disease (62.6%), although this failed to reach statistical significance ($P = .073$ for trend; Table 2). After multivariate Cox regression, escalation rates were significantly higher in those with clinically active disease and symptoms of a common mental disorder at baseline (HR, 1.65; 95% CI, 1.14–2.40; $P = .008$; Table 2 and Figure 2). Younger age (HR per year = 0.98; 95% CI, 0.97 to 0.99; $P < 0.001$) was associated with a reduced likelihood of escalation of medical therapy and need for glucocorticosteroids at baseline (HR = 1.73; 95% CI, 1.22 to 2.45; $P = 0.002$) an increased likelihood of escalation of medical therapy.

Results were similar, although more pronounced, according to biochemical activity at baseline (Table 3). On multivariate analysis, rates of escalation were significantly higher for patients with biochemical activity and symptoms of a common mental disorder at baseline (HR, 2.97; 95% CI, 1.74–5.06; $P < .001$; Table 3 and Supplementary Figure 2). There were no other significant predictors of escalation identified. Again, sensitivity analysis using a FC of <100 μg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices yielded similar results (Supplementary Tables 1 and 2).

Hospitalization Due to Uncontrolled IBD Activity

In total, 171 (24.7%) of 692 patients required hospitalization over a mean follow-up period of 5.4 years (range, 2 days–8.7 years). Again, hospitalization rates were significantly higher among those with symptoms of a common mental disorder at baseline, irrespective of clinical activity ($P = .001$ for trend; Table 2). However, after multivariate Cox regression, rates were not significantly higher in any of the 3 groups (Table 2). Younger age (HR per year, 0.98; 95% CI, 0.96–0.99; $P < .001$), alcohol use (HR, 0.57; 95% CI, 0.41–0.79; $P < .001$), and 5-aminosalicylate use at baseline (HR, 0.53; 95% CI, 0.35–0.81; $P = .003$) were all associated with a reduced likelihood of hospitalization; need for glucocorticosteroids at baseline (HR, 2.01; 95% CI, 1.32–3.05; $P < .001$) and smoking (HR, 1.70; 95% CI, 1.16–2.49; $P = .006$) were associated with an increased likelihood of hospitalization.

When considering biochemical activity, rates of hospitalization were generally higher in all 3 groups, compared with those in biochemical remission without symptoms of a common mental disorder at baseline ($P = .022$ for trend; Table 3). On multivariate analysis, hospitalization due to uncontrolled IBD activity was significantly more likely among those with biochemical activity and symptoms of a common mental disorder at baseline (HR, 3.10; 95% CI, 1.43–6.68; $P = .004$; Table 3 and Figure 3), with no other predictors identified. Again, when we performed a sensitivity analysis using a FC of <100 μg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices, results were similar (Supplementary Tables 1 and 2).

Intestinal Resection Due to Uncontrolled IBD Activity

Of 696 patients, 85 (12.2%) underwent intestinal resection for uncontrolled IBD activity, during a mean follow-up of 6.0 years (range, 4 days–8.7 years). Progression to intestinal resection was greatest in those reporting symptoms of a common mental disorder at baseline in those with clinical activity (22.0%) and in those in clinical remission (14.6%), compared with those without symptoms

Table 2. Clinical Outcomes of Patients According to Clinical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Clinical remission, no symptoms of a common mental disorder	Clinical remission, symptoms of a common mental disorder	Clinical activity, no symptoms of a common mental disorder	Clinical activity, symptoms of a common mental disorder	*P* value
Glucorticosteroid prescription or flare of disease activity (%)	144/300 (48.0)	46/76 (60.5)	59/112 (52.7)	59/84 (70.2)	.002[a]
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.57 (1.08–2.27)	1.50 (1.09–2.07)	2.36 (1.58–3.54)[b]	<.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	155/311 (49.8)	49/80 (61.3)	79/141 (56.0)	62/99 (62.6)	.073[a]
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.47 (1.03–2.09)	1.43 (1.07–1.92)	1.65 (1.14–2.40)[b]	.014
Hospitalization due to uncontrolled IBD activity (%)	62/326 (19.0)	25/82 (30.5)	41/169 (24.3)	43/115 (37.4)	.001[a]
Multivariate HR for hospitalization due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.51 (0.89–2.56)	1.37 (0.90–2.08)	1.71 (1.06–2.75)	.13
Intestinal resection due to uncontrolled IBD activity (%)	26/326 (8.0)	12/82 (14.6)	21/170 (12.4)	26/118 (22.0)	.001[a]
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.22 (0.52–2.87)	1.57 (0.84–2.92)	2.09 (1.06–4.13)	.18
Death (%)	25/331 (7.6)	5/82 (6.1)	5/170 (2.9)	7/120 (5.8)	.24[a]
Multivariate HR for death (95% CI)	1.00 (reference)	1.68 (0.55–5.13)	0.65 (0.22–1.98)	4.99 (1.80–13.88)[b]	.007

[a]For comparison across all 4 groups.
[b]$P < .01$ vs reference category.

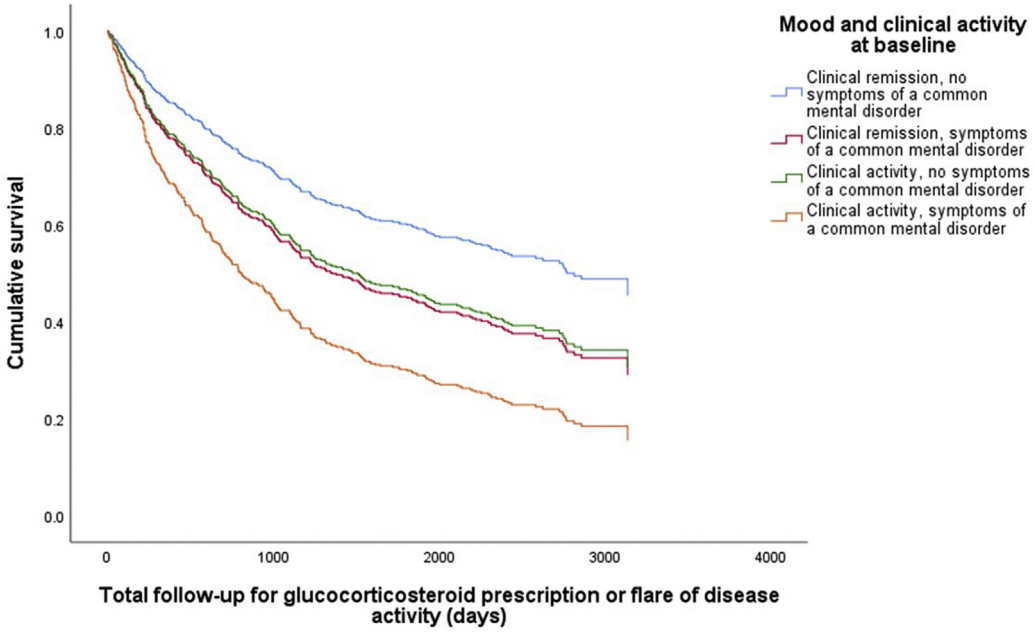

Figure 1. Survival analysis for occurrence of glucocorticosteroid prescription or flare of disease activity according to clinical activity and presence or absence of symptoms of a common mental disorder at baseline.

of a common mental disorder ($P = .001$ for trend; Table 2). However, after multivariate Cox regression, these differences were not statistically significant (Table 2). Again, younger age (HR per year, 0.98; 95% CI, 0.96–0.99; $P = .007$) was associated with a reduced likelihood of intestinal resection.

When we limited the analysis to those patients providing a FC sample, rates of intestinal resection were significantly higher among all 3 groups, compared with those in biochemical remission without symptoms of a common mental disorder at baseline ($P = .009$ for trend; Table 3). However, on multivariate Cox regression analysis, this trend failed to reach significance, although for those with biochemical activity with symptoms of a common mental disorder at baseline this approached statistical significance (HR, 4.11; 95% CI, 1.37–12.33; $P = .012$; Table 3, Supplementary Figure 3). There were no other significant predictors of intestinal resection identified. Sensitivity analysis using a FC of <100 μg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices yielded similar results (Supplementary Tables 1 and 2).

Mortality

In total, 42 (6.0%) of 703 patients died during a mean follow-up period of 6.6 years (range, 4 days–8.8 years). There was no significant difference in mortality rates between those with symptoms of a common mental disorder and clinical activity (5.8%) or clinical remission (6.1%), compared with those in clinical remission without symptoms of a common mental disorder at baseline (7.6%; $P = .24$ for trend; Table 2). However, after multivariate Cox regression analysis, mortality rates were significantly higher in those with clinical activity and symptoms of a common mental disorder at baseline (HR, 4.99; 95% CI, 1.80–13.88; $P = .002$; Table 2 and Figure 4). Older age was also associated with an increased risk of death (HR per year, 1.12; 95% CI, 1.09–1.15; $P < .001$).

According to biochemical activity at baseline, mortality was significantly higher in those with biochemical activity and symptoms of a common mental disorder at baseline (23.8%), compared with those in remission without symptoms of a common mental disorder (8.3%; $P = .001$ for trend; Table 3). Again, after multivariate Cox regression analysis, mortality rates were significantly higher in those with biochemical activity and symptoms of a common mental disorder (HR, 6.26; 95% CI, 2.23–17.56; $P < .001$; Table 3 and Supplementary Figure 4). Older age was again associated with an increased risk of death (HR per year, 1.11; 95% CI, 1.07–1.15; $P < .001$). Again, results were similar when we performed a sensitivity analysis using a FC of <100 μg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices (Supplementary Tables 1 and 2).

Healthcare Use During Longitudinal Follow-Up

The mean number of flares of disease activity, glucocorticosteroid prescriptions, hospitalizations, intestinal resections, outpatient appointments, and investigations were all significantly higher among those with clinical activity and symptoms of a common mental disorder at baseline (Supplementary Table 3). The mean number of these events was also generally higher among those with biochemical activity and symptoms of a common mental disorder at baseline, although these differences did not reach statistical significance (Supplementary Table 4).

Table 3. Clinical Outcomes of Patients According to Biochemical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Biochemical remission, no symptoms of a common mental disorder	Biochemical remission, symptoms of a common mental disorder	Biochemical activity, no symptoms of a common mental disorder	Biochemical activity, symptoms of a common mental disorder	*P* value
Glucorticosteroid prescription or flare of disease activity (%)	71/153 (46.4)	43/64 (67.2)	37/76 (48.7)	19/30 (63.3)	.022[a]
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.67 (1.07–2.62)	1.09 (0.71–1.66)	2.48 (1.38–4.46)[b]	.009
Escalation of medical therapy due to uncontrolled IBD activity (%)	67/154 (43.5)	40/65 (61.5)	48/91 (52.7)	24/35 (68.6)	.014[a]
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.58 (1.02–2.44)	1.40 (0.94–2.08)	2.97 (1.74–5.06)[b]	.001
Hospitalization due to uncontrolled IBD activity (%)	21/154 (13.6)	15/65 (23.1)	20/107 (18.7)	14/41 (34.1)	.022[a]
Multivariate HR for hospitalization due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.76 (0.84–3.71)	1.22 (0.63–2.37)	3.10 (1.43–6.68)[b]	.030
Intestinal resection due to uncontrolled IBD activity (%)	8/154 (5.2)	6/65 (9.2)	8/107 (7.5)	9/42 (21.4)	.009[a]
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.25 (0.38–4.13)	1.12 (0.38–3.30)	4.11 (1.37–12.33)	.049
Death (%)	13/156 (8.3)	1/66 (1.5)	9/109 (8.3)	10/42 (23.8)	.001[a]
Multivariate HR for death (95% CI)	1.00 (reference)	0.64 (0.08–5.45)	0.98 (0.40–2.39)	6.26 (2.23–17.56)[b]	.003

[a] χ^2 for comparison across all 4 groups.
[b] $P < .01$ vs reference category.

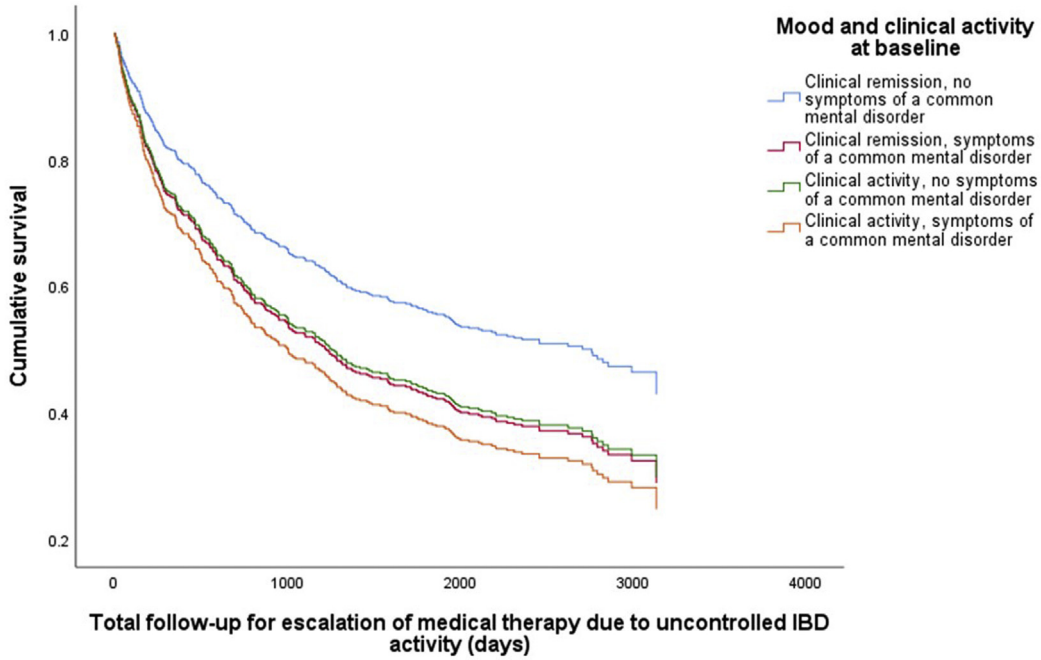

Figure 2. Survival analysis for occurrence of escalation of medical therapy due to uncontrolled IBD activity according to clinical activity and presence or absence of symptoms of a common mental disorder at baseline.

Discussion

We present data from a large, well-characterized cohort of 760 participants, with longitudinal follow-up over a mean of 6.5 years. To our knowledge, this is the first study to examine the relative contribution of psychological health and clinical or biochemical activity on adverse disease outcomes in IBD, as well as to assess whether there is a cumulative impact of poor psychological health and disease activity. Our study demonstrates that symptoms of common mental disorders influence IBD prognosis independently. Patients with disease activity reporting symptoms of a common mental disorder at baseline were at significantly higher risk of need for glucocorticosteroid therapy or flare of disease activity, escalation of therapy, hospitalization for uncontrolled IBD activity, or death. Rates of intestinal resection were also higher in this patient group, although this difference did not reach statistical significance. In contrast, these endpoints were not significantly more common in those with clinical or biochemical activity without symptoms of a common mental disorder, or in patients with clinical or biochemical remission with symptoms of a common mental disorder. Mean numbers of each of these events of interest were also higher in those with clinical activity and symptoms of a common mental disorder at baseline, as were other markers of healthcare use. Our results suggest that aiming for clinical or biochemical remission alone is an inadequate therapeutic target in IBD. Psychological health is also an important driver of disease activity and may even be more important than clinical or biochemical disease activity in determining outcomes. Unless this is assessed and addressed, prognosis is likely to be worse. Our results underline the need to provide a service for patients with IBD that incorporates psychological support alongside medical management, particularly during periods of disease activity.

The long duration of follow-up allowed more time for rarer events, such as hospitalization, intestinal resection, or death, to occur, which previous studies examining the impact of psychological health on prognosis of IBD may have been underpowered to assess.[4] Data collection via the patients' electronic medical records is likely to have increased reliability and accuracy of the endpoints recorded, and collection of these events was carried out by an assessor blinded to all baseline data to reduce the risk of potential bias. Because the hospital is the sole provider of IBD care to all participants, it is unlikely that occurrence of any of the endpoints of interest has been missed. We used multivariate Cox regression controlling for demographic and disease characteristics, including somatoform-type behavior, which may be an important confounder, to assess whether our observations on univariate analysis were likely to be independent predictors of adverse outcomes. Very few other patient characteristics, including sex, marital status, tobacco and alcohol intake, educational level, type of IBD, IBD-related medications at baseline, or somatoform-type behavior, were associated with our endpoints of interest. Several of the endpoints we examined were objective, such as hospitalization, intestinal resection, or death, which means our findings are unlikely to be driven by patients with poor psychological health being more likely to report gastrointestinal symptoms.[2] The facts that rates of outpatient consultation were, if anything, higher among those with the worst outcomes and that glucocorticosteroid prescriptions, although higher, were not unreasonably so given the duration of the study suggest that our observations are not an epiphenomenon related to poor quality care

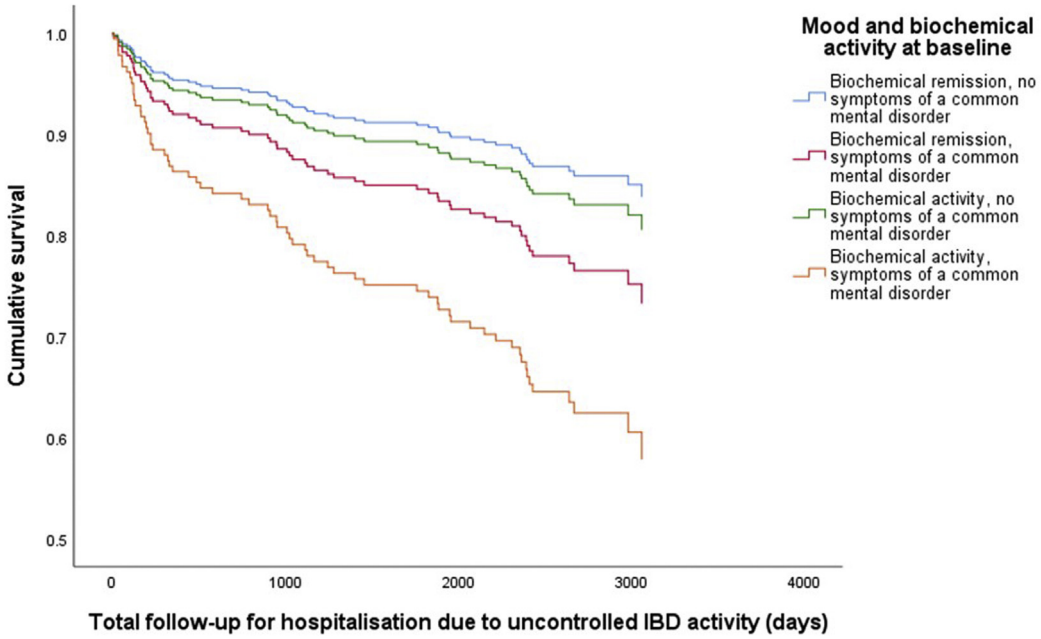

Figure 3. Survival analysis for occurrence of hospitalization due to uncontrolled IBD activity according to biochemical activity and presence or absence of symptoms of a common mental disorder at baseline.

in this patient group. Finally, we used both clinical and biochemical measures of disease activity, and conducted sensitivity analyses based on a FC of <100 μg/g and a combined definition of disease activity or remission that incorporated both clinical and biochemical indices. Our results in these analyses were virtually unchanged, and in some cases the magnitude and significance of the difference in these endpoints seen in the group with disease activity and symptoms of a common mental disorder at baseline increased further.

With approximately half of patients providing FC samples for analysis at baseline, analyses in this group may be less robust, particularly for some of the rarer outcomes, although direction and magnitude of effects were similar for all analyses. Review of electronic medical records, rather than real-time assessment of endpoints of interest, is also a limitation because interpretation of some, such as glucocorticosteroid prescription or flare of disease activity, may still be subjective because they depend on the physician's interpretation of patient-reported symptoms. Escalation of therapy may also be at risk of subjective influence, although in our center we adhere to the National Institute for Health and Care Excellence guidelines,[33,34] which state that there must be definitive evidence of disease activity before escalating medical therapy. Although the patients' electronic medical records were reviewed by one individual, blinded to

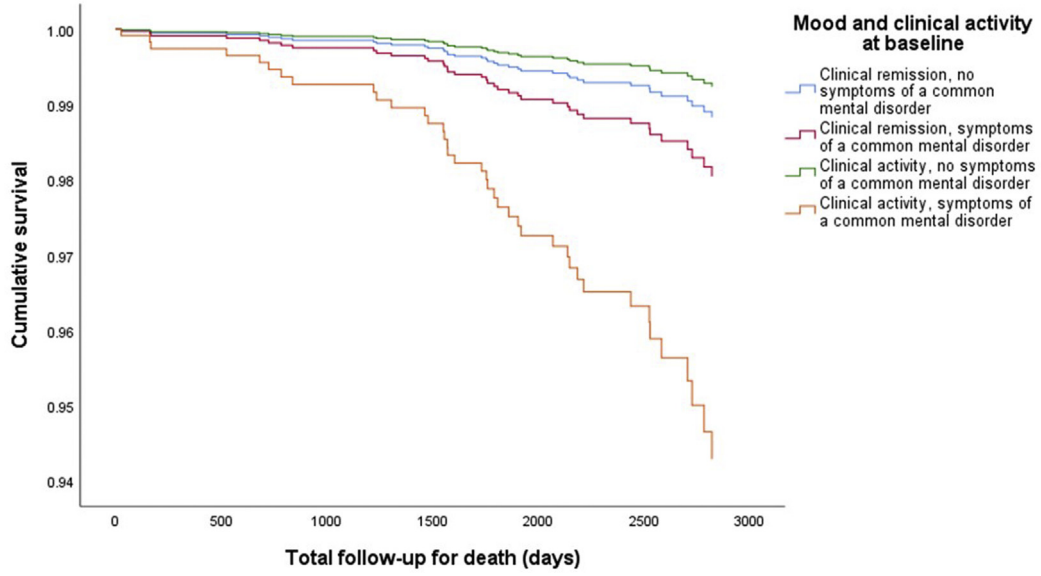

Figure 4. Survival analysis for occurrence of death according to clinical activity and presence or absence of symptoms of a common mental disorder at baseline.

the baseline questionnaire data, there is the possibility that a diagnosis of a common mental disorder was recorded within them, which may have introduced bias in assessing endpoints. The assessment of presence or absence of common mental disorders was based on the HADS, which is used to measure symptoms of depression and anxiety at one point in time, rather than being based on a physician's diagnosis of anxiety or depression. Our choice of the HADS was made before a study assessing the performance of various screening measures, vs a structured clinical interview, for common mental disorders in patients with IBD.[35] This study reported that the Patient Health Questionnaire-9 had the highest sensitivity for detecting depression and the Anxiety Short Form 8a for anxiety, although all symptom scales performed similarly. In addition, the HADS does not collect data concerning somatic depressive symptoms, such as anhedonia, change in appetite, or irritability, so it may underestimate the prevalence of depression. We acknowledge that a structured clinical interview to assess for presence of a common mental disorder would be preferable but, with almost 800 participants, this was not feasible.

Whether common mental disorders have a negative impact on the prognosis of IBD has been examined previously. However, many of these studies have not characterized patients based on presence or absence of disease activity at baseline.[15–17,36] In one study that restricted recruitment to patients with IBD in remission, a significant increase in risk of flare of disease activity and escalation was seen in those with symptoms of common mental disorders at baseline.[4] In other studies of similar design, stress also appears to be a predictor of relapse.[37–39] Patients with active disease with a history of major depressive disorder or symptoms of anxiety at baseline appear less likely to achieve remission, despite an escalation in therapy.[40] In addition, those with symptoms of depression and a recent flare of disease activity requiring hospitalization were more likely to require readmission, compared with those without an underlying common mental disorder.[41] Our results, demonstrating a cumulative impact of common mental disorders and disease activity on IBD-related outcomes and mortality, mirror recent findings from a study conducted in patients with coronary heart disease, in which psychological stress-induced myocardial ischemia increased risk of future myocardial infarction or cardiovascular death significantly, compared with conventional exercise-induced ischemia alone.[23] This effect was cumulative; those with both psychological stress-induced and conventional ischemia were at greatest risk of myocardial infarction or cardiovascular death. We are not aware of any similar studies in the IBD literature, to date.

The possibility that psychological health may have a greater impact on IBD prognosis than disease activity raises important questions as to how patients are managed. We have identified a cohort of patients with a high psychological and disease burden, who are more likely to require investigation, escalation, and intervention over time, and who are likely to be long-term high utilizers of health care. Where psychological support has been enlisted alongside physician input for patients, there is evidence of improved outcomes and reduced service need, with fewer unplanned admissions.[42] Higher levels of psychological resilience, the innate ability of the individual to overcome psychological and physical adversity, are also associated with fewer flares, lower rates of IBD-related surgery, and better quality of life.[43] Preliminary results in the field of resilience training appear promising. A recent study recruiting patients with IBD with low resilience demonstrated that an integrated program of resilience-based management reduced emergency department visits, unplanned hospitalizations, and glucorticosteroid use.[44] Our study results also suggest that clinicians need to target more than just clinical or mucosal remission when treating patients with IBD. There is a need to incorporate psychological health as an independent therapeutic target in updates to current guidelines,[14] for both long-term prognostic benefits, as well as a likely reduction in the economic burden of IBD.

With limited randomized controlled trials (RCTs) of antidepressants or anxiolytics in patients with IBD, their role remains unclear.[45] There have been more RCTs of psychological therapies, summarized in a prior meta-analysis[46]; in one trial hypnotherapy led to a significant reduction in likelihood of relapse in UC.[47] A subsequent RCT of cognitive behavioral therapy demonstrated beneficial effects on health-related quality of life, anxiety, and depression.[48] However, most trials have recruited unselected groups of patients. Another consideration is that psychological health may fluctuate, and there may be a subset of patients who are at even higher risk of poor prognostic outcomes. There is supportive evidence of this from other chronic diseases. For example, in a 3-year longitudinal follow-up study in chronic obstructive pulmonary disease, persistent depression was associated with increased morbidity and mortality, whereas those whose depression remitted were comparable with those who were never depressed, showing improved walking distance and reduced frequency of exacerbations.[21] There remains a need for further RCTs of psychological therapies and antidepressants in more selected groups of patients with IBD, after appropriate screening for common mental disorders and objective quantification of inflammatory burden, as well as studies examining the trajectories of common mental disorders in IBD, and whether this influences prognosis. Replication of our results by studies recruiting patients subjected to a structured interview to assess formally for presence of common mental disorders would also be important.

In summary, patients with IBD with symptoms of a common mental disorder at baseline as well as clinical or biochemical evidence of disease activity were more likely to experience adverse disease outcomes. Rates of glucocorticosteroid prescription or flare, escalation, and hospitalization were 2 to 3 times higher. Likelihood of intestinal resection was up to 4 times higher, although this did not reach statistical significance in our primary analysis. Finally, mortality rates were significantly higher in this patient group. Rates of these endpoints were not significantly higher in patients with active disease without symptoms of a common mental disorder. These data suggest that common mental disorders are a risk factor for a poor prognosis

in IBD. Their presence should be screened for routinely and, if present, considered as a therapeutic target.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2022.03.014.

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Received December 7, 2021. Accepted March 4, 2022.

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Acknowledgments
The authors are grateful to the patients who took the time to participate in this study.

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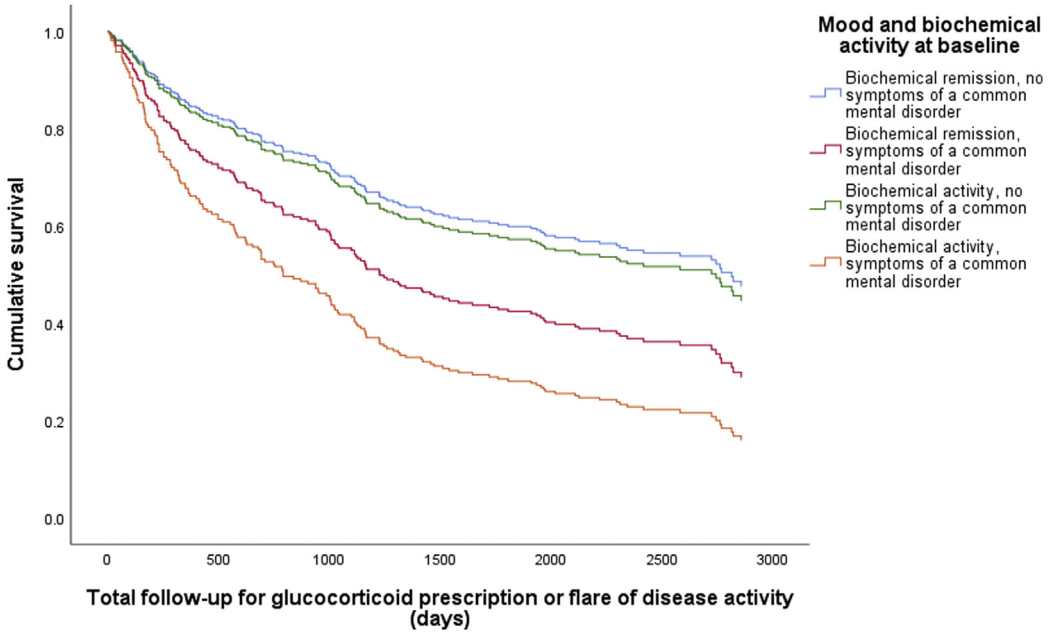
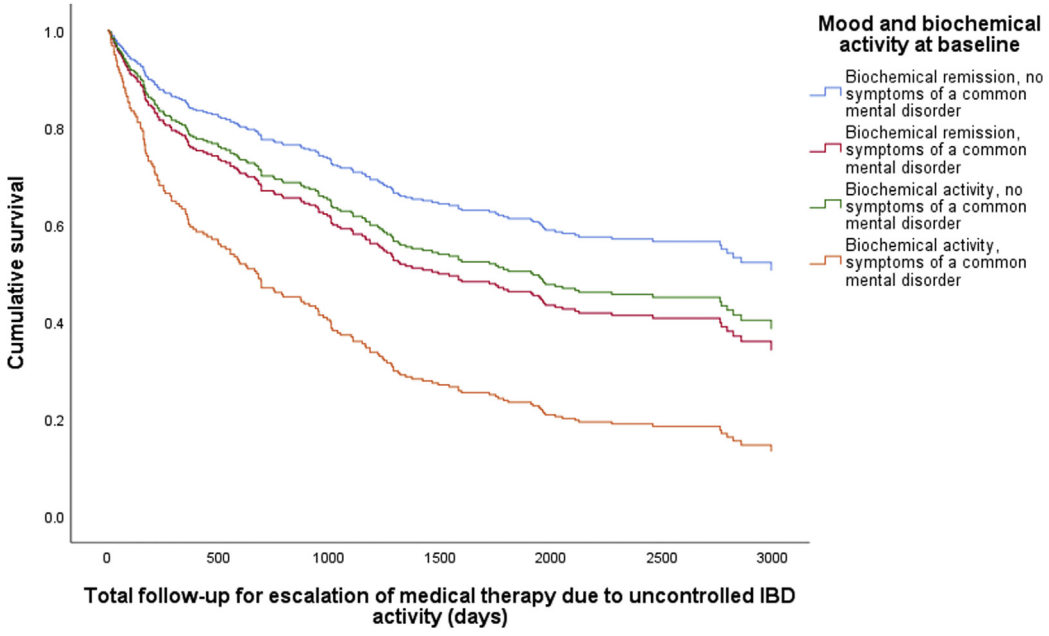
original draft: Lead; Writing – review & editing: Equal). David J. Gracie, PhD (Conceptualization: Equal; Formal analysis: Supporting; Funding acquisition: Supporting; Investigation: Equal; Methodology: Equal; Project administration: Equal; Supervision: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal). Alexander C. Ford, MD (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Lead; Investigation: Equal; Methodology: Equal; Project administration: Equal; Supervision: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal).

Conflicts of interest
The authors disclose no conflicts.

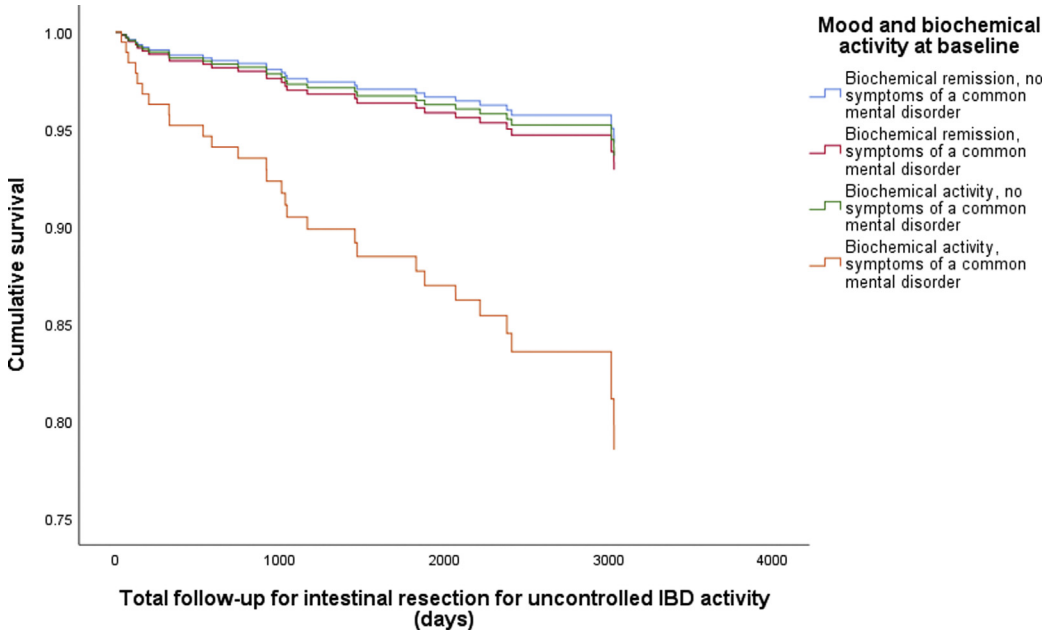
Funding
This work was supported by the Leeds Teaching Hospitals Charitable Foundation (9R11/14-02). Unrestricted research monies were also provided by Tillotts Pharma UK Ltd.. The study sponsor had no input into the concept, design, analysis, or reporting of the study.



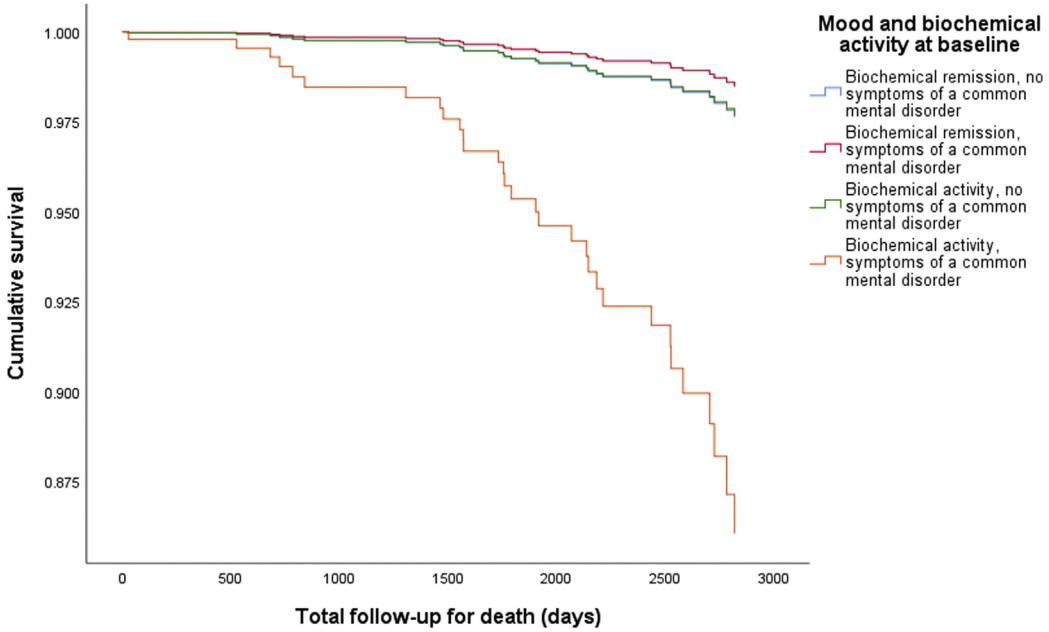
Supplementary Figure 1. Survival analysis for occurrence of glucocorticosteroid prescription or flare of disease activity according to biochemical activity and presence or absence of symptoms of a common mental disorder at baseline.



Supplementary Figure 2. Survival analysis for occurrence of escalation of medical therapy due to uncontrolled IBD activity according to biochemical activity and presence or absence of symptoms of a common mental disorder at baseline.



Supplementary Figure 3. Survival analysis for occurrence of intestinal resection due to uncontrolled IBD activity according to biochemical activity and presence or absence of symptoms of a common mental disorder at baseline.



Supplementary Figure 4. Survival analysis for occurrence of death according to biochemical activity and presence or absence of symptoms of a common mental disorder at baseline.

Supplementary Table 1. Clinical Outcomes of Patients According to Biochemical Disease Activity (FC <100 μg/g) and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Biochemical remission, no symptoms of a common mental disorder	Biochemical remission, symptoms of a common mental disorder	Biochemical activity, no symptoms of a common mental disorder	Biochemical activity, symptoms of a common mental disorder	*P* value
Glucorticosteroid prescription or flare of disease activity (%)	52/114 (45.6)	26/35 (74.3)	56/115 (48.7)	36/59 (61.0)	.011[a]
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.99 (1.16–3.39)	1.14 (0.77–1.70)	1.92 (1.18–3.12)[b]	.020
Escalation of medical therapy due to uncontrolled IBD activity (%)	48/115 (41.7)	24/36 (66.7)	67/130 (51.5)	40/64 (62.5)	.013[a]
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.72 (0.99–2.97)	1.39 (0.94–2.05)	2.22 (1.39–3.53)[b]	.009
Hospitalization due to uncontrolled IBD activity (%)	14/115 (12.2)	6/36 (16.7)	27/146 (18.5)	23/70 (32.9)	.006[a]
Multivariate HR for hospitalization due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.22 (0.41–3.57)	1.40 (0.71–2.76)	3.24 (1.57–6.67)[b]	.007
Intestinal resection due to uncontrolled IBD activity (%)	4/115 (3.5)	3/36 (8.3)	12/146 (8.2)	12/71 (16.9)	.016[a]
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.48 (0.25–8.88)	2.04 (0.63–6.63)	4.35 (1.28–14.86)	.088
Death (%)	8/116 (6.9)	0/37 (0.0)	14/149 (9.4)	11/71 (15.5)	.044[a]
Multivariate HR for death (95% CI)	1.00 (reference)	n/a	1.58 (0.64–3.88)	5.81 (2.04–16.52)[b]	.009

n/a, not applicable.
[a] χ^2 for comparison across all 4 groups.
[b] $P < .01$ vs reference category.

Supplementary Table 2. Clinical Outcomes of Patients According to Combined Clinical and Biochemical Disease Activity (FC <250 μg/g) and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Combined clinical and biochemical remission, no symptoms of a common mental disorder	Combined clinical and biochemical remission, symptoms of a common mental disorder	Combined clinical and biochemical activity, no symptoms of a common mental disorder	Combined clinical and biochemical activity, symptoms of a common mental disorder	*P* value
Glucorticosteroid prescription or flare of disease activity (%)	48/109 (44.0)	18/29 (62.1)	12/16 (75.0)	12/14 (85.7)	.004[a]
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.73 (0.93–3.21)	4.12 (1.95–8.68)[b]	5.58 (2.30–13.6)[b]	<.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	48/109 (44.0)	18/29 (62.1)	19/24 (79.2)	15/18 (83.3)	.001[a]
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.86 (1.02–3.38)	3.79 (2.06–6.97)[b]	4.37 (2.02–9.46)[b]	<.001
Hospitalization due to uncontrolled IBD activity (%)	15/109 (13.8)	6/29 (20.7)	9/37 (24.3)	9/24 (37.5)	.051[a]
Multivariate HR for hospitalization due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.60 (0.58–4.45)	1.55 (0.62–3.85)	5.94 (2.20–16.1)[b]	.006
Intestinal resection due to uncontrolled IBD activity (%)	4/109 (3.7)	2/29 (6.9)	4/37 (10.8)	7/25 (28.0)	.001[a]
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.55 (0.25–9.45)	2.42 (0.51–11.4)	13.8 (3.17–60.2)[b]	.004
Death (%)	10/111 (9.0)	1/29 (3.4)	0/37 (0.0)	6/25 (24.0)	.007[a]
Multivariate HR for death (95% CI)	1.00 (reference)	1.20 (0.13–10.9)	n/a	17.8 (4.00–78.8)[b]	.002

[a] χ^2 for comparison across all 4 groups.
[b] $P < .01$ vs reference category.

Supplementary Table 3. Healthcare Use According to Clinical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Clinical remission, no symptoms of a common mental disorder	Clinical remission, symptoms of a common mental disorder	Clinical activity, no symptoms of a common mental disorder	Clinical activity, symptoms of a common mental disorder	*P* value[a]
Mean number of flares of disease activity (SD)	1.2 (1.6)	1.4 (1.6)	1.8 (1.8)	2.0 (1.9)	<.001
Mean number of glucocorticosteroid prescriptions (SD)	0.6 (1.2)	0.7 (1.1)	1.0 (1.3)	1.1 (1.3)	.001
Mean number of escalations (SD)	0.9 (1.2)	1.1 (1.2)	1.3 (1.3)	1.3 (1.3)	.015
Mean number of hospitalizations (SD)	0.3 (0.7)	0.4 (0.7)	0.4 (0.8)	0.6 (1.0)	.001
Mean number of intestinal resections (SD)	0.1 (0.3)	0.2 (0.4)	0.1 (0.4)	0.2 (0.4)	.005
Mean number of outpatient appointments (SD)	8.1 (6.2)	9.1 (6.5)	10.5 (6.1)	11.7 (6.3)	<.001
Mean number of radiological investigations (SD)	0.7 (1.3)	0.8 (1.5)	1.0 (1.4)	1.5 (1.9)	<.001
Mean number of endoscopic investigations (SD)	0.7 (1.0)	0.9 (1.0)	1.1 (1.1)	1.2 (1.3)	<.001

[a]*P* value for 1-way analysis of variance.

Supplementary Table 4. Healthcare Use According to Biochemical Disease Activity and Presence or Absence of Symptoms of a Common Mental Disorder at Baseline

	Biochemical remission, no symptoms of a common mental disorder	Biochemical remission, symptoms of a common mental disorder	Biochemical activity, no symptoms of a common mental disorder	Biochemical activity, symptoms of a common mental disorder	*P* value[a]
Mean number of flares of disease activity (SD)	1.1 (1.9)	1.4 (1.5)	1.6 (1.8)	1.9 (2.0)	.057
Mean number of glucocorticosteroid prescriptions (SD)	0.6 (1.4)	0.7 (1.1)	0.9 (1.3)	1.1 (1.5)	.15
Mean number of escalations (SD)	0.8 (1.3)	1.0 (1.1)	1.1 (1.2)	1.5 (1.5)	.012
Mean number of hospitalizations (SD)	0.2 (0.7)	0.3 (0.5)	0.2 (0.6)	0.5 (0.8)	.082
Mean number of intestinal resections (SD)	0.1 (0.2)	0.1 (0.4)	0.1 (0.3)	0.2 (0.4)	.013
Mean number of outpatient appointments (SD)	8.4 (6.6)	10.1 (5.4)	9.2 (6.7)	10.9 (7.1)	.087
Mean number of radiological investigations (SD)	0.6 (1.1)	0.8 (1.2)	0.9 (1.4)	1.4 (2.0)	.006
Mean number of endoscopic investigations (SD)	0.9 (1.3)	1.2 (1.1)	0.8 (0.9)	0.9 (1.3)	.15

[a]*P* value for 1-way analysis of variance.