Article:
Fairbrass, KM, Gracie, DJ and Ford, AC orcid.org/0000-0001-6371-4359 (2022) Relative Contribution of Disease Activity and Psychological Health to Prognosis of Inflammatory Bowel Disease During 6.5 Years of Longitudinal Follow-Up. Gastroenterology, 163 (1). pp. 190-203. ISSN 0016-5085

https://doi.org/10.1053/j.gastro.2022.03.014

Accepted for publication 4th March 2022

TITLE PAGE

Title: Relative Contribution of Disease Activity and Psychological Health to Prognosis of Inflammatory Bowel Disease During 6.5 years of Longitudinal Follow-up.

Short Title: Contribution of Disease Activity and Psychological Health to IBD Prognosis.

Authors: Keeley M. Fairbrass[1,2], David J. Gracie*[1,2], Alexander C. Ford*[1,2].

*Denotes joint last author.

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

Grant support: 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.

Abbreviations:

ANOVA	analysis of variance
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
PHQ-15	patient health questionnaire-15
RCT	randomized controlled trial
SCCAI	simple clinical colitis activity index
UC	ulcerative colitis

Correspondence: Professor Alexander C. Ford

Leeds Gastroenterology Institute

Room 125, 4th Floor, Bexley Wing

St. James's University Hospital

Beckett Street, Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +447887603665

Disclosures: Keeley M. Fairbrass: none. David J. Gracie: none. Alexander C. Ford: none.

Writing assistance: None.

Specific author contributions: KMF, DJG, and ACF conceived and drafted the study. DJG and KMF collected all data. KMF and ACF analyzed and interpreted the data. KMF, DJG and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

Guarantor: ACF is guarantor.

Word count: 6574

ABSTRACT

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 (≥250mcg/g used to define biochemical activity). Glucocorticosteroid prescription or flare, escalation, hospitalization, intestinal resection, or death were assessed during 6.5 years follow-up. Occurrence was compared using multivariate Cox regression across four 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.

Key words: IBD; mood; psychology; morbidity; mortality

INTRODUCTION

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, 8, 9, 10, 11, 12, 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 bi-directional 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 over 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, 21, 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 four-fold higher rates of myocardial infarction or cardiovascular death than patients with neither, and three-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 over 700 patients with well-characterized IBD,[2, 24] during an average follow-up of 6.5 years.

METHODS

Participants and Setting

Between November 2012 and June 2015 we recruited patients aged ≥16 years with an established radiological, endoscopic, or histological diagnosis of CD or UC into a cross-sectional study.[2] All participants were recruited from the IBD clinic at St. 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 (REC ref: 12/YH/0443/AM03). Study findings were reported in accordance with the STROBE 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 (PHQ-15).[27] As recommended in the original validation study, a HADS anxiety or depression score of ≥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 <250mcg/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 (e.g., 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 utilization.

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 four 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 ≥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 four groups: biochemical remission (FC <250mcg/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 ≥250mcg/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 <100mcg/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 four 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 PHQ-15. Due to multiple comparisons, a 2-tailed P value of <0.01 was considered statistically significant, and the results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). We compared healthcare utilization between the four groups using one way analysis of variance (ANOVA). All statistical analyses were performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA).

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, to have high levels of somatization, and 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.

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 to 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=0.002) (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 to 2.27) and those with clinical activity and symptoms of a common mental disorder at baseline (HR = 2.36; 95% CI 1.58 to 3.54) (p<0.001 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<0.001). Younger age (HR per year = 0.98; 95% CI 0.97 to 0.99, p<0.001) was associated with a reduced likelihood of need for glucocorticosteroid prescription or flare and UC (HR = 1.69; 95% CI 1.22 to 2.32, p=0.001) 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 to 2.62) and significantly raised in those with biochemical activity and symptoms of a common mental disorder at baseline (HR = 2.48; 95% CI 1.38 to 4.46, p=0.002) (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 to 1.00, p=0.004). Sensitivity analyses using a FC of <100mcg/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 to 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=0.073 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 to 2.40, p=0.008) (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.

Results were similar, though 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 to 5.06, p<0.001) (Table 3 and Supplementary Figure 2). There were no other significant predictors of escalation identified. Again, sensitivity analysis using a FC of <100mcg/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 to 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=0.001 for trend) (Table 2). However, after multivariate Cox regression, rates were not significantly higher in any of the three groups (Table 2). Younger age (HR per year = 0.98; 95% CI 0.96 to 0.99, p<0.001), alcohol use (HR = 0.57; 95% CI 0.41 to 0.79, p<0.001), and 5-ASA use at baseline (HR = 0.53; 95% CI 0.35 to 0.81, p=0.003) were all associated with a reduced likelihood of hospitalization, and need for glucocorticosteroids at baseline (HR = 2.01; 95% CI 1.32 to 3.05, p<0.001) and smoking (HR = 1.70; 95% CI 1.16 to 2.49, p=0.006) an increased likelihood.

When considering biochemical activity, rates of hospitalization were generally higher in all three groups, compared with those in biochemical remission without symptoms of a common mental disorder at baseline (p=0.022 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 to 6.68, p=0.004) (Table 3 and Figure 3), with no other predictors identified. Again, when we performed a sensitivity analysis using a FC of <100mcg/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 to 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 of a common mental disorder (p=0.001 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 to 0.99, p=0.007) was associated with a reduced likelihood of intestinal resection.

When we limited the analysis to those patients providing an FC sample, rates of intestinal resection were significantly higher among all three groups, compared with those in biochemical remission without symptoms of a common mental disorder at baseline (p=0.009 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 to 12.33, p=0.012) (Table 3, Supplementary Figure 3). There were no other significant predictors of intestinal resection identified. Sensitivity analysis using a FC of <100mcg/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 over a mean follow-up period of 6.6 years (range 4 days to 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=0.24 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 to 13.88, p=0.002) (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 to 1.15, $p<0.001$).

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%) ($p=0.001$ 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 to 17.56, $p<0.001$) (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 to 1.15, $p<0.001$). Again, results were similar when we performed a sensitivity analysis using a FC of <100mcg/g and a combined definition of activity or remission that incorporated both clinical and biochemical indices (Supplementary Tables 1 and 2).

Healthcare Utilization 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).

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 utilization. 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 to 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. As 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 fact 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, suggests that our observations are not an epiphenomenon related to poor quality care in this patient group. Finally, we used both clinical and biochemical measures of disease activity, and conducted sensitivity analyses based on an FC of <100mcg/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, as interpretation of some, such as glucocorticosteroid prescription or flare of disease activity, may still be subjective as 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 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 measures 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 prior to a study assessing the performance of various screening measures, versus 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 (PROMIS) 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 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, 16, 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, 38, 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 re-admission, 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 attendances, 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 two to three times higher. Likelihood of intestinal resection was up to four 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.

ACKNOWLEDGEMENTS

We are grateful to the patients who took the time to participate in this study.

REFERENCES

1 Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI*, et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017;**390**:2769-78.

2 Gracie DJ, Williams CJ, Sood R, Mumtaz S, Bholah MH, Hamlin PJ*, et al.* Poor Correlation Between Clinical Disease Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in Inflammatory Bowel Disease. Am J Gastroenterol 2016;**111**:541-51.

3 Barberio B, Zamani M, Black CJ, Savarino EV, Ford AC. Prevalence of symptoms of anxiety and depression in patients with inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021;**6**:359-70.

4 Gracie DJ, Guthrie EA, Hamlin PJ, Ford AC. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. Gastroenterology 2018;**154**:1635-46.e3.

5 Panara AJ, Yarur AJ, Rieders B, Proksell S, Deshpande AR, Abreu MT*, et al.* The incidence and risk factors for developing depression after being diagnosed with inflammatory bowel disease: a cohort study. Aliment Pharmacol Ther 2014;**39**:802-10.

6 Gracie DJ, Hamlin PJ, Ford AC. The influence of the brain-gut axis in inflammatory bowel disease and possible implications for treatment. Lancet Gastroenterol Hepatol 2019;**4**:632-42.

7 Guidi L, Marzo M, Andrisani G, Felice C, Pugliese D, Mocci G*, et al.* Faecal calprotectin assay after induction with anti-Tumour Necrosis Factor α agents in inflammatory bowel disease: Prediction of clinical response and mucosal healing at one year. Dig Liver Dis 2014;**46**:974-9.

8 Kostas A, Siakavellas SI, Kosmidis C, Takou A, Nikou J, Maropoulos G*, et al.* Fecal calprotectin measurement is a marker of short-term clinical outcome and presence of mucosal healing in patients with inflammatory bowel disease. World J Gastroenterol 2017;**23**:7387-96.

9 Plevris N, Fulforth J, Lyons M, Siakavellas SI, Jenkinson PW, Chuah CS*, et al.* Normalization of Fecal Calprotectin Within 12 Months of Diagnosis Is Associated With Reduced Risk of Disease Progression in Patients With Crohn's Disease. Clin Gastroenterol Hepatol 2021;**19**:1835-44.e6.

10 Ferreiro-Iglesias R, Barreiro-de Acosta M, Otero Santiago M, Lorenzo Gonzalez A, Alonso de la Peña C, Benitez Estevez AJ*, et al.* Fecal Calprotectin as Predictor of Relapse in Patients With Inflammatory Bowel Disease Under Maintenance Infliximab Therapy. J Clin Gastroenterol 2016;**50**:147-51.

11 Gisbert JP, Bermejo F, Pérez-Calle JL, Taxonera C, Vera I, McNicholl AG*, et al.* Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis 2009;**15**:1190-8.

12 Tibble JA, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. Gastroenterology 2000;**119**:15-22.

13 Arias MT, Vande Casteele N, Vermeire S, de Buck van Overstraeten A, Billiet T, Baert F*, et al.* A Panel to Predict Long-term Outcome of Infliximab Therapy for Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol 2015;**13**:531-8.

14 Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM*, 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**:1570-83.

15 Marrie RA, Graff LA, Fisk JD, Patten SB, Bernstein CN. The Relationship Between Symptoms of Depression and Anxiety and Disease Activity in IBD Over Time. Inflamm Bowel Dis 2021;**27**:1285-93.

16 Kochar B, Barnes EL, Long MD, Cushing KC, Galanko J, Martin CF*, et al.* Depression Is Associated With More Aggressive Inflammatory Bowel Disease. Am J Gastroenterol 2018;**113**:80-5.

17 Narula N, Pinto-Sanchez MI, Calo NC, Ford AC, Bercik P, Reinisch W*, et al.* Anxiety But Not Depression Predicts Poor Outcomes in Inflammatory Bowel Disease. Inflamm Bowel Dis 2019;**25**:1255-61.

18 Fairbrass KM, Lovatt J, Barberio B, Yuan Y, Gracie DJ, Ford AC. Bidirectional brain-gut axis effects influence mood and prognosis in IBD: a systematic review and meta-analysis. Gut 2021;doi:10.1136/gutjnl-2021-325985.

19 Fairbrass KM, Gracie DJ, Ford AC. Longitudinal follow-up study: effect of psychological co-morbidity on the prognosis of inflammatory bowel disease. Aliment Pharmacol Ther 2021;**54**:441-50.

20 Kampling H, Petrak F, Farin E, Kulzer B, Herpertz S, Mittag O. Trajectories of depression in adults with newly diagnosed type 1 diabetes: results from the German Multicenter Diabetes Cohort Study. Diabetologia 2017;**60**:60-8.

21 Yohannes AM, Müllerová H, Hanania NA, Lavoie K, Tal-Singer R, Vestbo J*, et al.* Long-term Course of Depression Trajectories in Patients With COPD: A 3-Year Follow-up

Analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Cohort. Chest 2016;**149**:916-26.

22 Palacios J, Khondoker M, Mann A, Tylee A, Hotopf M. Depression and anxiety symptom trajectories in coronary heart disease: Associations with measures of disability and impact on 3-year health care costs. J Psychosom Res 2018;**104**:1-8.

23 Vaccarino V, Almuwaqqat Z, Kim JH, Hammadah M, Shah AJ, Ko YA*, et al.* Association of Mental Stress-Induced Myocardial Ischemia With Cardiovascular Events in Patients With Coronary Heart Disease. JAMA 2021;**326**:1818-28.

24 Gracie DJ, Williams CJM, Sood R, Mumtaz S, Bholah MH, Hamlin PJ*, et al.* Negative Effects on Psychological Health and Quality of Life of Genuine Irritable Bowel Syndrome–type Symptoms in Patients With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol 2017;**15**:376-84.e5.

25 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007;**147**:573-7.

26 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;**67**:361-70.

27 Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;**64**:258-66.

28 Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;**1**:514.

29 Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut 1998;**43**:29-32.

30 Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. Clin Gastroenterol Hepatol 2010;**8**:357-63.

31 Jowett SL, Seal CJ, Phillips E, Gregory W, Barton JR, Welfare MR. Defining relapse of ulcerative colitis using a symptom-based activity index. Scand J Gastroenterol 2003;**38**:164-71.

32 Rogler G, Aldeguer X, Kruis W, Lasson A, Mittmann U, Nally K*, et al.* Concept for a rapid point-of-care calprotectin diagnostic test for diagnosis and disease activity monitoring in patients with inflammatory bowel disease: expert clinical opinion. J Crohns Colitis 2013;**7**:670-7.

33 National Institute for Health and Care Excellence. Infliximab and adalimumab for the treatment of Crohn's disease [TA187]. 2010: https://www.nice.org.uk/guidance/ta187/resources/infliximab-and-adalimumab-for-the-treatment-of-crohns-disease-pdf-82598501180869; reviewed 2018. Accessed 2 December 2021.

34 National Institute for Health and Care Excellence. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy [TA329]. 2015: https://www.nice.org.uk/guidance/ta329/resources/infliximab-adalimumab-and-golimumab-for-treating-moderately-to-severely-active-ulcerative-colitis-after-the-failure-of-conventional-therapy-pdf-82602495307717; reviewed 2018. Accessed 2 December 2021.

35 Bernstein CN, Zhang L, Lix LM, Graff LA, Walker JR, Fisk JD*, et al.* The Validity and Reliability of Screening Measures for Depression and Anxiety Disorders in Inflammatory Bowel Disease. Inflamm Bowel Dis 2018;**24**:1867-75.

36 Jordi SBU, Lang BM, Auschra B, von Känel R, Biedermann L, Greuter T*, et al.* Depressive Symptoms Predict Clinical Recurrence of Inflammatory Bowel Disease. Inflamm Bowel Dis 2021;doi:10.1093/ibd/izab136.

37 Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S*, et al.* Predicting relapse in Crohn's disease: a biopsychosocial model. Gut 2008;**57**:1386-92.

38 Langhorst J, Hofstetter A, Wolfe F, Häuser W. Short-term stress, but not mucosal healing nor depression was predictive for the risk of relapse in patients with ulcerative colitis: a prospective 12-month follow-up study. Inflamm Bowel Dis 2013;**19**:2380-6.

39 Levenstein S, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C*, et al.* Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. Am J Gastroenterol 2000;**95**:1213-20.

40 Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L*, et al.* The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment Pharmacol Ther 2005;**22**:101-10.

41 Allegretti JR, Borges L, Lucci M, Chang M, Cao B, Collins E*, et al.* Risk Factors for Rehospitalization Within 90 Days in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2015;**21**:2583-9.

42 Regueiro M, Click B, Anderson A, Shrank W, Kogan J, McAnallen S*, et al.* Reduced Unplanned Care and Disease Activity and Increased Quality of Life After Patient Enrollment in an Inflammatory Bowel Disease Medical Home. Clin Gastroenterol Hepatol 2018;**16**:1777-85.

43 Sehgal P, Ungaro RC, Foltz C, Iacoviello B, Dubinsky MC, Keefer L. High Levels of Psychological Resilience Associated With Less Disease Activity, Better Quality of Life, and Fewer Surgeries in Inflammatory Bowel Disease. Inflamm Bowel Dis 2021;**27**:791-6.

44 Keefer L, Gorbenko K, Siganporia T, Manning L, Tse S, Biello A*, et al.* Resilience-based integrated IBD care is associated with reductions in health care use and opioids. Clin Gastroenterol Hepatol 2021;doi.org/10.1016/j.cgh.2021.11.013.

45 Macer BJ, Prady SL, Mikocka-Walus A. Antidepressants in Inflammatory Bowel Disease: A Systematic Review. Inflamm Bowel Dis 2017;**23**:534-50.

46 Gracie DJ, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;**2**:189-99.

47 Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. Aliment Pharmacol Ther 2013;**38**:761-71.

48 Bennebroek Evertsz F, Sprangers MAG, Sitnikova K, Stokkers PCF, Ponsioen CY, Bartelsman J*, et al.* Effectiveness of cognitive-behavioral therapy on quality of life, anxiety, and depressive symptoms among patients with inflammatory bowel disease: A multicenter randomized controlled trial. J Consult Clin Psychol 2017;**85**:918-25.

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***
Mean age in years at baseline (SD)	45.6 (18.3)	43.5 (15.1)	43.4 (15.7)	40.7 (14.3)	0.13
Female sex (%)	166 (49.1)	48 (56.5)	102 (59.3)	80 (65.0)	0.011
Married or co-habiting (%)	206 (61.3)	50 (60.2)	109 (64.1)	72 (58.5)	0.80
University graduate/professional (%)	107 (32.0)	20 (24.1)	50 (29.2)	24 (19.5)	0.051
Tobacco user (%)	49 (14.5)	10 (12.0)	29 (16.9)	33 (27.0)	0.008
Alcohol user (%)	234 (69.2)	53 (63.1)	118 (69.0)	60 (49.2)	<0.001
CD (%)	183 (54.1)	50 (58.8)	104 (60.5)	75 (61.0)	0.42

CD location (%)					
Ileal	37/183 (20.2)	11/50 (22.0)	20/104 (19.2)	24/75 (32.0)	
Colonic	61/183 (33.3)	16/50 (32.0)	24/104 (23.1)	17/75 (22.7)	
Ileocolonic	85/183 (46.4)	23/50 (46.0)	60/104 (57.7)	34/75 (45.3)	0.14
Non-stricturing, non-penetrating CD (%)	157/183 (85.8)	39/50 (78.0)	86/104 (82.7)	58/75 (77.3)	0.67
Perianal CD (%)	15/183 (8.2)	5/50 (10.0)	14/104 (13.5)	6/75 (8.0)	0.49
UC extent (%)					
Proctitis	36/155 (23.2)	12/35 (34.3)	14/68 (20.6)	11/49 (22.4)	
Left-sided	74/155 (47.7)	13/35 (37.1)	30/68 (44.1)	24/49 (49.0)	
Extensive	45/155 (29.0)	10/35 (28.6)	24/68 (35.3)	14/49 (28.6)	0.74
5-ASA use (%)	169 (50.0)	39 (45.9)	81 (47.1)	53 (43.1)	0.59
Immunomodulator use (%)	121 (35.8)	27 (31.8)	64 (37.2)	42 (34.1)	0.84
Anti-TNFα use (%)	68 (20.1)	18 (21.2)	30 (17.4)	18 (14.6)	0.51
Glucocorticosteroid use (%)	27 (8.0)	9 (10.6)	25 (14.5)	17 (13.8)	0.094
High levels of somatization on PHQ-15 (%)	6 (1.8)	9 (11.5)	15 (9.0)	30 (25.9)	<0.001
FC <250mcg/g	114/182 (62.6)	29/44 (65.9)	40/77 (51.9)	37/62 (59.7)	0.353

*One-way ANOVA for comparison of normally distributed continuous data, χ^2 for comparison of categorical data across all four groups.

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)	0.002*
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)†	<0.001
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)	0.073*
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)†	0.014
Hospitalization due to uncontrolled IBD activity (%)	62/326 (19.0)	25/82 (30.5)	41/169 (24.3)	43/115 (37.4)	0.001*

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)	0.13
Intestinal resection due to uncontrolled IBD activity (%)	26/326 (8.0)	12/82 (14.6)	21/170 (12.4)	26/118 (22.0)	0.001*
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)	0.18
Death (%)	25/331 (7.6)	5/82 (6.1)	5/170 (2.9)	7/120 (5.8)	0.24*
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)†	0.007

*For comparison across all four groups.

†$p<0.01$ versus reference category.

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)	0.022*
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)†	0.009
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)	0.014*
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)†	0.001

Hospitalization due to uncontrolled IBD activity (%)	21/154 (13.6)	15/65 (23.1)	20/107 (18.7)	14/41 (34.1)	0.022*
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)†	0.030
Intestinal resection due to uncontrolled IBD activity (%)	8/154 (5.2)	6/65 (9.2)	8/107 (7.5)	9/42 (21.4)	0.009*
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)	0.049
Death (%)	13/156 (8.3)	1/66 (1.5)	9/109 (8.3)	10/42 (23.8)	0.001*
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)†	0.003

*χ^2 for comparison across all four groups.

†p<0.01 versus 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.

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.

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.

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.