

# Similar Risk of Depression and Anxiety Following Surgery or Hospitalization for Crohn's Disease and Ulcerative Colitis

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- OBJECTIVES:** Psychiatric comorbidity is common in Crohn's disease (CD) and ulcerative colitis (UC). Inflammatory bowel disease (IBD)-related surgery or hospitalizations represent major events in the natural history of the disease. The objective of this study is to examine whether there is a difference in the risk of psychiatric comorbidity following surgery in CD and UC.
- METHODS:** We used a multi-institution cohort of IBD patients without a diagnosis code for anxiety or depression preceding their IBD-related surgery or hospitalization. Demographic-, disease-, and treatment-related variables were retrieved. Multivariate logistic regression analysis was performed to individually identify risk factors for depression and anxiety.
- RESULTS:** Our study included a total of 707 CD and 530 UC patients who underwent bowel resection surgery and did not have depression before surgery. The risk of depression 5 years after surgery was 16% and 11% in CD and UC patients, respectively. We found no difference in the risk of depression following surgery in the CD and UC patients (adjusted odds ratio, 1.11; 95% confidence interval, 0.84–1.47). Female gender, comorbidity, immunosuppressant use, perianal disease, stoma surgery, and early surgery within 3 years of care predicted depression after CD surgery; only the female gender and comorbidity predicted depression in UC patients. Only 12% of the CD cohort had  $\geq 4$  risk factors for depression, but among them nearly 44% subsequently received a diagnosis code for depression.
- CONCLUSIONS:** IBD-related surgery or hospitalization is associated with a significant risk for depression and anxiety, with a similar magnitude of risk in both diseases.

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at <http://www.nature.com/ajg>

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## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract affecting over 1.4 million Americans and accounting for an estimated \$6 billion in direct healthcare costs (1–3). They are associated with

considerable indirect costs in lost productivity and days absent from work. Nearly two-thirds of the patients with CD require at least one surgery during the course of their disease (4,5), and a significant proportion requires hospitalization (4). Up to a third of the patients with UC may require surgical treatment of their

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disease, either for refractoriness to medical therapy or cancer (6–8). Although recurrence of disease is common after surgery for CD, colectomy is considered curative for UC, even though subsequent ileo-anal pouch-related issues including single or recurrent episodes of pouchitis, or other pouch-related complications occur frequently (9).

Psychiatric comorbidity, in particular depression and anxiety, are common in patients with inflammatory bowel disease (IBD). Lifetime prevalence of major depression may approach 30% and anxiety may occur even more commonly (10–13). Although many cross-sectional or prospective studies have examined the frequency of occurrence of such comorbidity (14–16), fewer have examined risk factors (12). Intuitively, disease severity and activity are important determinants of psychological effects of an underlying bowel disease (11,17–19). Nevertheless, no prior studies have specifically addressed the frequency of occurrence of or risk factors for depression or anxiety following an IBD-related surgery or hospitalization, which represent major events in the natural history of disease. Identifying such subgroups may identify a high-risk cohort of patients who could be targeted for screening for such comorbidity and may also identify early interventions to improve outcomes. Furthermore, no studies have specifically compared the occurrence of such psychiatric comorbidity following surgery or hospitalization between CD and UC.

We performed this study with the aims of (1) examining the risk of depression and anxiety following an IBD-related surgery or hospitalization in a large multi-institution cohort; (2) identifying the risk factors for such psychiatric comorbidity following surgery or hospitalization in IBD patients; and (3) comparing the occurrence of such psychiatric comorbidity in those patients with CD with that of UC patients undergoing interventions.

## METHODS

### Study cohort

This study included a cohort of patients with CD or UC seen at two large tertiary referral hospitals (Massachusetts General Hospital, and Brigham and Women's Hospital) in Boston, serving over four million people. Prior work has described the creation of this cohort in detail (20). In brief, we first extracted all patients with  $\geq 1$  International Classification of Diseases, 9th Edition (ICD-9) code for CD (555;  $n = 14,288$ ) or UC (556;  $n = 14,355$ ). Subsequently, using an algorithm developed using clinical, laboratory, endoscopy, and pathology data, refined using ICD-9 codes and free-text natural language-processing concepts, we identified a cohort of 5,506 CD and 5,522 UC patients with a positive predictive value of 97%, with validation of the algorithm through additional chart review by a board-certified gastroenterologist (20).

### Variables

Information was obtained on age, age at the time of the first diagnosis code of CD or UC, gender, and modified Charlson comorbidity index (21) (excluding variables related to anxiety or depression), using the ICD-9 codes. We identified the cohort of patients who underwent a bowel resection through the use of

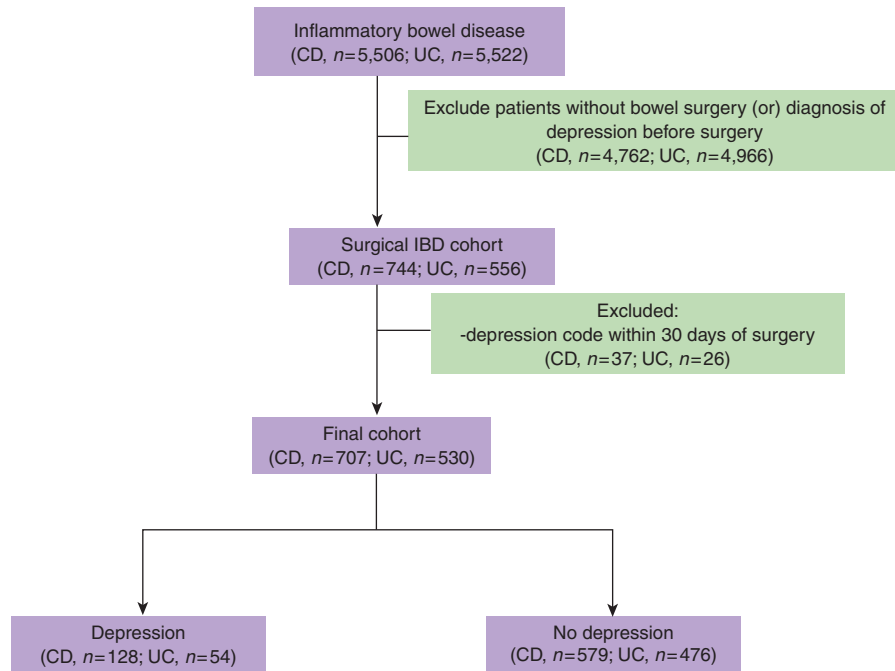
ICD-9 codes for abdominal surgery (**Supplementary Table 1**), and extracted the date of the occurrence of such procedures. Information was also obtained on disease-related complications, including fistulizing or stricturing disease, and perianal disease for CD patients, using the ICD-9 codes (**Supplementary Table 1**). Use of medications, including immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), antitumor necrosis factor- $\alpha$  therapies (infliximab, adalimumab), and corticosteroids (prednisone, budesonide), were ascertained as codified data using the electronic prescription function of our electronic medical record. The IBD-related hospitalizations were identified as those with a primary diagnosis of CD or UC upon discharge from the hospital. We also identified patients who had undergone at least one stoma surgery (ICD-9 46.1, 46.2) and those who had undergone more than one surgery. To adjust for intensity of healthcare utilization, we included a variable—"number of facts"—which included the total number of distinct medical encounters, including office visits, laboratory tests, radiological studies, and inpatient or outpatient procedures. This, divided by the duration of follow-up, yielded a "fact density," which was a measure of healthcare utilization per unit time of follow-up.

### Outcomes

Our primary outcome of the study was the development of anxiety and depression defined as in previous studies, using the ICD-9 codes for depressive disorders (296.2, 296.3, 298.0, 311) or generalized anxiety (293.84, 300.0, 313.0) (13,22). To validate the accuracy of the ICD-9 codes for depression and anxiety, we selected a random subset of 100 patients from both hospitals with each of these codes, reviewed their medical records, and found a positive predictive value for a diagnosis of depression or anxiety to be 92% and 90%, respectively. The predictive value was similar from both major hospitals (Massachusetts General Hospital and Brigham and Women's Hospital). Patients who had a diagnosis code for depression or anxiety before or on their first date of surgery, or within 30 days after the date of surgery were excluded from this study, to reduce likelihood of identifying prevalent cases (**Figure 1**). Similarly, in the analysis of hospitalizations, those with psychiatric comorbidity (major depression or anxiety) at the time of or before an IBD-related hospitalization, or within 30 days of such a hospitalization, were excluded.

### Statistical analysis

All data were analyzed using Stata 11.0. (StataCorp, College Station, TX, USA). Continuous variables were summarized using means and s.d. and compared using Student's *t*-tests. Categorical variables were expressed as proportions and compared using the  $\chi^2$ -test. Multivariate logistic regression analysis adjusting for potential confounders formed our main analysis examining predictors of depression or anxiety following surgery or hospitalization. Variables were selected for entry into the multivariate model based on significance at  $P < 0.1$  on univariate analysis. The multivariate analysis was carried out using the forward stepwise procedure, retaining variables with  $P < 0.05$ . To account for secular trends in coding, year of surgery was included as a separate variable in all our multivariate models. We examined the occurrence



**Figure 1.** Flowchart demonstrating development of Crohn's disease (CD) and ulcerative colitis (UC) cohorts.

of such psychiatric comorbidity in the entire CD/UC cohort, as well as each disease subgroup individually, comparing the rates across CD and UC. The predictors of depression and anxiety were also examined in the overall cohort, as well as CD and UC separately. We performed sensitivity analyses to examine if having the diagnosis code for post-surgery depression or anxiety was a reflection of frequency of healthcare utilization by adjusting for fact density as described above, and for frequency of outpatient visits. The study was approved by the Institutional Review Board of Partners Healthcare.

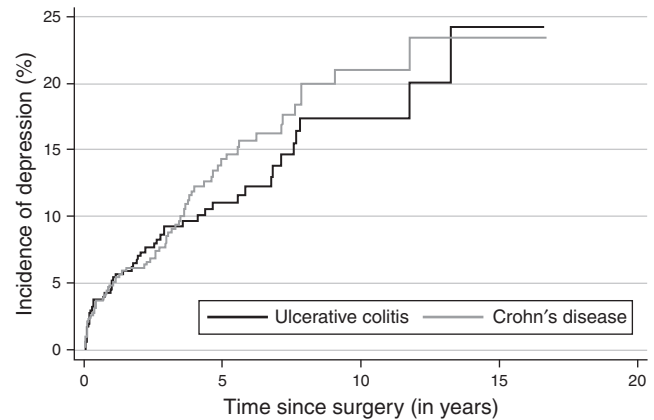
## RESULTS

### Study population

There were a total of 744 CD and 556 UC patients in our cohort, who underwent  $\geq 1$  bowel resection surgery and did not have a diagnosis of depression before surgery. Among these, 63 patients had their first diagnosis code for depression within 30 days of the surgery (median 1 day) and were excluded, resulting in 707 CD and 530 UC patients who were included in the analysis of post-surgery depression (**Figure 1**). The mean age of the cohort was 48 years, with a mean age at surgery of 42 years. Just under half the cohort were women (47%). The cohort for analysis of anxiety following an IBD-related surgery comprised 1,183 patients.

### Risk of depression and anxiety following IBD-related surgery or hospitalization

A total of 128 CD patients subsequently were given a diagnosis code for depression at a median of 2.2 years. Among those who required surgery, the risk of depression at 1, 2, and 5 years after surgery was 6%, 8%, and 16%, respectively (**Figure 2**). Similarly,



**Figure 2.** Risk of depression following inflammatory bowel disease (IBD)-related surgery in Crohn's disease and ulcerative colitis.

54 UC patients were given a diagnosis of depression at a median of 2.5 years. Interestingly, the risk of depression at 1, 2, and 5 years after surgery for UC was similar to the CD cohort at 5%, 7% and 11%, respectively (**Figure 2**). The crude overall frequency of depression was higher than what we found for those undergoing surgery for diverticulitis (9%) or inguinal hernia (7%,  $P < 0.05$ ). On multivariate logistic regression, adjusting for age, gender, and comorbidity, there was no difference in the risk of depression among the post-surgery CD and UC patients (adjusted odds ratio (OR), 1.11; 95% confidence interval (CI), 0.84–1.47), suggesting a similar risk of post-surgery depression in both diseases. Among the entire CD cohort, 4,762 patients never required surgery. Compared with such patients, we observed a significantly elevated risk of depression in patients who required surgery (adjusted OR,

**Table 1.** Characteristics of the study cohort of patients with Crohn's disease and ulcerative colitis undergoing surgery

Characteristic	Crohn's disease		Ulcerative colitis	
	No depression (n=574) %	Depression (n=128) %	No depression (n=476)	Depression (n=54)
Age in years (mean (s.d.))	48 (17)	51 (17)*	47 (19)	49 (18)
Age at first diagnosis code for IBD (mean (s.d.))	39 (17)	41 (19)	39 (18)	39 (17)
Female	49	63*	41	68*
Charlson score $\geq 3$	23	58*	23	54*
<i>Disease complications</i>				
Fistulizing disease	44	38		
Stricturing disease	68	70		
Perianal involvement	17	30*		
<i>Surgery characteristics</i>				
Early surgery (<3 years)	32	49*	24	39*
Surgery at age <35 years	59	67*	58	58
Stoma surgery	14	27*	62	55
$\geq 2$ surgeries	15	27*	22	29
<i>Ever medication use</i>				
Aminosalicylates	44	51	42	54*
Steroids	55	70*	66	75
Immunomodulators	41	52*	25	32
Anti-TNF biological use	23	34*	15	24*

Anti-TNF, anti-tumor-necrosis factor- $\alpha$ ; IBD, inflammatory bowel diseases.  
Immunomodulators include azathioprine, 6-mercaptopurine, or methotrexate; anti-TNF agents include infliximab or adalimumab.  
\* $P < 0.05$ .

1.34; 95% CI, 1.01–1.77). Compared with UC patients who never required surgery ( $n=4,928$ ), those who did undergo surgery did not demonstrate this increase in risk for depression following surgery (OR, 1.21; 95% CI, 0.93–1.58).

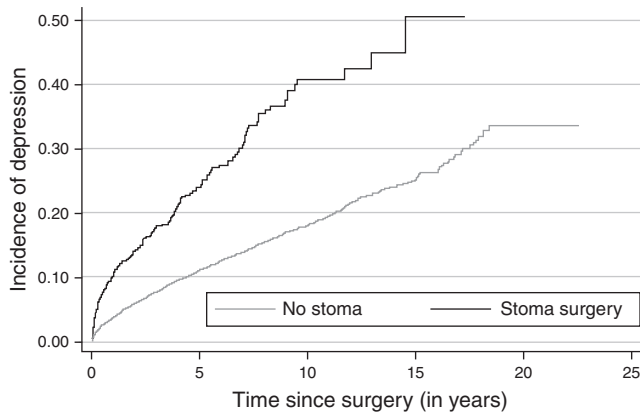
The risk of anxiety following IBD-related surgery at 1, 2, and 5 years was 7%, 9%, and 14%, respectively, in CD patients and 7%, 10%, and 12%, respectively, in UC patients. There was no difference in the likelihood of anxiety based on IBD type (OR for CD vs. UC, 1.09; 95% CI, 0.82–1.44). Unlike what we identified for depression, the likelihood of anxiety following an IBD-related surgery was only mildly elevated compared with those who never underwent surgery for either CD (OR, 1.20; 95% CI, 0.93–1.55) or UC (OR, 1.26; 95% CI, 0.96–1.65).

A total of 2,062 CD patients and 1,345 UC patients required at least one IBD-related hospitalization, among whom 33 and 41% subsequently required surgery. An IBD-related hospitalization itself was associated with a significant risk of depression. Even excluding those who subsequently underwent surgery, the risk of depression 5 years after a CD-related hospitalization was 17%, with a corresponding risk of anxiety of 12%. This was nearly two-fold the risk of depression in those who never required hospitalization (OR, 1.91; 95% CI, 1.60–2.77). Similarly for UC patients, a disease-related hospitalization was associated with an increase in risk for depression (OR, 1.28; 95% CI, 1.06–1.54) and anxiety

(OR, 1.32; 95% CI, 1.09–1.59) compared to those who were never hospitalized.

#### Predictors of depression and anxiety following IBD-related surgery

**Table 1** presents the characteristics of the patients, stratified by disease type and depression status. Both UC and CD patients who developed depression following surgery were more likely to be female and had greater comorbidity. However, there were also differences between the two diseases. In CD, depressed patients were also more likely to be younger than 35 years at the time of surgery, or had surgery within 3 years of first diagnosis code for CD. The only disease phenotype associated with depression was the presence of perianal disease, which was nearly twice as common in those with depression as those without. Those who developed depression were significantly more likely to have required a stoma than those without (27% vs. 15%). The risk of depression 5 years after stoma surgery was 31% compared with 19% in those who never underwent stoma surgery (**Figure 3**). In UC patients, early surgery within 3 years was associated with an increased risk for depression similar to that seen for CD. However, there was no difference by age at surgery. Interestingly, there was also difference in risk of depression by requirement of a stoma in UC patients, likely because of the high frequency of requiring a stoma (temporary or



**Figure 3.** Risk of depression following surgery in Crohn's disease, stratified by requirement for a stoma.

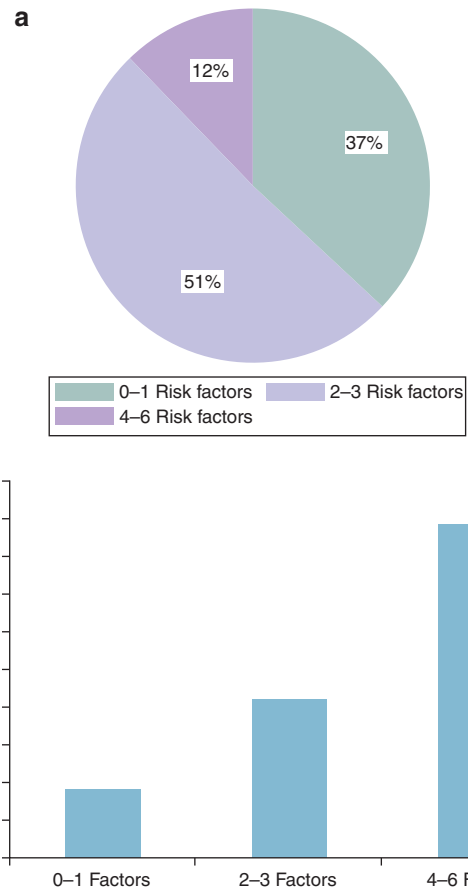
**Table 2.** Multivariate analysis of risk factors for depression following surgery in Crohn's disease and ulcerative colitis

Characteristic	Adjusted odds ratio	95% Confidence interval
<i>Crohn's disease</i>		
Female gender	1.77	1.16–2.71
Charlson score $\geq 3$	4.31	2.82–6.57
Surgery within 3 years	1.54	1.01–2.37
Immunomodulator use	1.56	1.03–2.38
Stoma surgery	1.90	1.15–3.13
Perianal disease	1.64	1.01–2.69
<i>Ulcerative colitis</i>		
Female gender	2.92	1.80–4.76
Charlson score $\geq 3$	3.73	2.33–5.97

All risk factors retained in the multivariate analysis by stepwise regression are described in the table.

permanent) as part of a two- or three-stage total colectomy with ileo-anal pouch reconstruction.

As there were differences in risk factors, we performed separate stepwise multivariate logistic regression analyses for both diseases. In CD, the strongest predictor was non-IBD medical comorbidity (Table 2). Having a stoma was the next strongest predictor with an OR of 1.90 (95% CI, 1.15–3.13). Female gender, perianal disease, need for immunomodulator therapy, and early surgery within 3 years also moderately increased the risk of depression following surgery. The risk of depression increased with the number of risk factors; only 8% of those with 0 or 1 risk factor subsequently developed depression compared with 20% of those with 2 or 3 risk factors, and 44% of those with 4 or more risk factors (Figure 4). However, the distribution of risk factors was also not uniform between the risk strata; only 2% of those in the lowest risk category had a stoma surgery compared with 46% of the highest risk stratum. On the other hand, for UC, only female gender (OR, 2.92) and Charlson score  $\geq 3$  (OR, 3.73) were associated with increased risk of depression (Table 2).



**Figure 4.** Frequency of depression following surgery in Crohn's disease (CD), stratified by the number of risk factors. (a) Distribution of risk factors for depression following CD-related surgery. (b) Frequency of depression stratified by presence of risk factors.

Multivariate analysis for predictors of anxiety revealed a significant overlap with the risk factors for depression, with similar effect sizes for nearly all parameters for both CD and UC (Table 3).

### Sensitivity analysis

We performed a variety of sensitivity analysis to examine the robustness of our findings. Primarily, to determine if the increased risk of anxiety or depression following surgery was solely a reflection of increased healthcare utilization (and consequently, increase in the number of diagnosis codes) in such patients, we adjusted for the number of outpatient gastroenterology office visit, all outpatient visits with a diagnosis of CD or UC, and number of inpatient hospitalizations, and found no attenuation of our effect sizes. Similarly, our OR estimates were rendered larger, adjusting for density of healthcare utilization.

### DISCUSSION

There is an increased risk of depression and anxiety in patients with CD or UC (10–13). The extent to which this increased risk is determined by severity of disease is unclear. Furthermore, there



**Table 3.** Multivariate analysis of risk factors for anxiety following surgery in Crohn's disease and ulcerative colitis

Characteristic	Adjusted odds ratio	95% Confidence interval
<i>Crohn's disease</i>		
Female gender	2.07	1.35–3.19
Charlson score $\geq 3$	1.84	1.19–2.84
Surgery within 3 years	2.19	1.44–3.33
Stoma surgery	1.73	1.05–2.85
$\geq 2$ surgeries	1.79	1.09–2.93
<i>Ulcerative colitis</i>		
Age (per 1 year)	0.98	0.97–1.00
Female gender	1.84	1.18–2.87
Charlson score $\geq 3$	3.26	1.98–5.38

All risk factors retained in the multivariate analysis by stepwise regression are described in the table.

have been no prior studies that have quantified the risk of such psychiatric comorbidity after the IBD-related surgery or hospitalization, which represent major events in the natural history of IBD. Using a multi-institutional cohort, we demonstrate that even after excluding those who received a diagnosis of depression before surgery, CD and UC patients who underwent an IBD-related surgery had a 16% and 11% risk of receiving a diagnosis of depression at 5 years, with a similar substantial risk of anxiety. Furthermore, despite surgery for UC being considered curative, we observed a similar risk between both diseases. We also identified several subgroups of patients at higher risk of such comorbidity, which may facilitate targeted screening and early intervention.

Several studies have examined the co-occurrence of psychiatric comorbidity in patients with IBD (13–16,23). However, there is limited literature examining risk factors for psychological distress in patients with IBD. Nahon *et al.* (12) administered a questionnaire to 1,663 patients with IBD and identified 11% of the patients to be depressed and 41% to be anxious. On multivariate analysis, severity of disease defined as requiring two or more courses of steroids, hospitalization, and need for immunosuppressive therapy or intestinal resection was an independent risk factor for anxiety but not depression. However, this broad definition of severe disease resulted in nearly 90% of their cohort, irrespective of psychiatric comorbidity, being classified as having severe disease, limiting the utility of such composite definitions. Indeed when restricting their analysis to individual components of disease severity, they found that past history of surgery was associated with a lower risk of anxiety and had no effect on risk of depression. Our study differs from the prior studies in that we specifically focused on a relatively homogenous cohort of CD or UC patients who had all undergone surgery or required hospitalization. By specifically excluding those who received a diagnosis of depression or anxiety before surgery, we attempted to minimize the number of prevalent cases and the possibility of reverse causation or confounding, where disease activity predicts both surgery as well as occurrence of psychiatric comorbidity.

A key and interesting finding from our study is that the risk of depression or anxiety following IBD-related surgery or hospitalization was similar in CD and UC. Although surgery for CD is usually not curative, is followed by nearly universal disease recurrence with only mild attenuation of this risk with existing medical therapies, a total colectomy for UC is considered curative. There are a few possible reasons for persistence of the risk for depression and anxiety in UC patients following surgery, similar to that for CD. First, even after an ileal-pouch, patients can continue to have frequency of bowel movements, including need for nocturnal bowel movements, which could affect health-related quality of life, which could in-turn lead to depressive symptoms (24). Second, up to half of the patients may have at least one episode of pouchitis, whereas one-quarter may have recurrent episodes (9). Such fluctuations in disease activity could also influence risk of depression or anxiety. This is consistent with the findings from a small study by Hauser *et al.* (25) that patients with an ileal pouch-anal anastomosis did not differ in their risk of depression compared with UC patients without ileal pouch-anal anastomosis, but were more likely to be depressed than the general population. Other studies have similarly shown that patients with an ileal pouch-anal anastomosis continue to have impairment in quality of life compared with the general population (26,27), although the literature in this area has yielded conflicting results (28).

We also identified common and distinct risk factors for depression following IBD-related surgery. Female gender was common across both diseases, consistent with prior studies examining health-related quality of life and psychiatric comorbidity in IBD (29–32). In a prospective study, Beaugerie *et al.* (33) demonstrated that perianal disease was associated with a disabling course of CD. A high proportion of patients with perianal CD have depressive symptoms (34) and demonstrate long-term impairment of quality of life (35). In addition, early surgery defined as undergoing a resection within 3 years of first CD diagnosis code in our health system also increased the risk of depression post-operatively, consistent with the hypothesis associating aggressive disease behavior with psychological comorbidity.

Requiring an ostomy bag is one of the highest rated concerns among CD and UC patients (36–38). In the present study, among CD patients the risk of depression or anxiety was influenced quite strongly by having an ostomy, which was the strongest risk factor after non-IBD comorbidity. However, we found no such effect on UC patients, which could be due to the high frequency of stoma procedures (as part of two- or three-stage colectomy surgeries in UC patients). The literature on the effect of stoma on risk of subsequent psychological comorbidity has been inconsistent. After surgery for colorectal cancer, having a stoma is associated with worse body image (39) and increases risk for anxiety or depression. However, in CD, where surgery may not represent a permanent cure from disease, and patients may continue to experience symptoms related to ongoing bowel or perianal disease, having a stoma has not been consistently associated with worse quality of life when compared with other CD controls (35,40). However, no prior studies have specifically examined the effect of stoma or multiple surgeries on post-operative anxiety or depression in an IBD cohort.

In addition, the association with non-IBD comorbidity suggests that such patients may be more susceptible to functional impairment and consequences of IBD-related surgery or hospitalization. The association between comorbidity and increased healthcare utilization post-operatively has also been demonstrated in other cohorts (41,42), suggesting management of IBD patients with such comorbidity, particularly in the setting of severe disease requiring surgery remains challenging.

Finally, another important finding from our study was that an IBD-related hospitalization, even in the absence of subsequent surgery, was associated with a significant risk for depression and anxiety. This demonstrates that in addition to their effect on healthcare costs, hospitalizations remain an important event in disease course of both CD and UC. As demonstrated by prior studies, those requiring hospitalization form a high-risk cohort for subsequent surgery (4,43,44), but even in the absence of such an eventuality, they remain at risk for psychological comorbidity associated with their disease. Consideration must be given for routine screening for depression and anxiety in this cohort as well.

Our study has several implications. To our knowledge, ours is the first study specifically examining the overall occurrence of depression and anxiety following IBD-related surgery or hospitalization, as well as the comparative incidence between both diseases. Our examination of predictors of depression or anxiety suggest that there are strong demographic-, disease-, or surgery-related characteristics that place a patient at a substantially elevated risk of psychological comorbidity even among a cohort with relative homogeneity in their disease severity. We suggest the need to routinely screen such patients for depression and anxiety as part of standard care in the immediate and late post-operative period, as well as after an IBD-related hospitalization. Given the significant morbidity and healthcare utilization associated with psychiatric comorbidity, there is need for continued research into effective interventions to identify and treat such patients, and whether preventive interventions may be warranted in high-risk patients.

There are a few limitations to our study. First, we relied on administrative coding to identify the presence and date of diagnosis of depression or anxiety in the post-operative setting, as well as predictors, which may result in misclassification. However, misclassification is unlikely to be differential between the various risk factors, and we performed a validation of the ICD-9 codes used. Recognizing the increased risk for depression and anxiety, future prospective studies are necessary with structured evaluation of mood and other psychiatric comorbidity following IBD-related surgery or hospitalization. Second, we did not have accurate and comprehensive information on the use of antidepressant or anti-anxiety medications in our cohort. Third, owing to the referral nature of our institutions, further studies examining our hypothesis in a population-based cohort will help confirm the generalizability of our results. Given the linear increase in depression and anxiety diagnosis over time, it is unlikely that our findings are solely due to increased frequency of healthcare utilization and, thus, the number of diagnosis codes, in the immediate perioperative period. We also did not have information on smoking status, which could influence risk of surgery in CD.

In conclusion, we demonstrate that IBD-related surgery or hospitalization is associated with a significant risk for depression and anxiety in both CD and UC patients with similar magnitudes of risk across both diseases. Female gender and non-IBD comorbidity were common risk factors for depression or anxiety in both CD and UC. Requirement for a stoma was a strong risk factor for depression following surgery in CD patients, but not UC patients. Continued screening for psychiatric comorbidity following IBD-related surgery or hospitalization should be part of comprehensive IBD care, particularly for high-risk patients. There is need for ongoing research into effective modalities to improve health-related quality of life and other outcomes in such patients.

## CONFLICT OF INTEREST

**Guarantor of the article:** Ashwin N. Ananthakrishnan, MD, MPH.

**Specific author contributions:** Study concept, Ananthakrishnan; study design, Ananthakrishnan, Cai, Karlson, and Liao; data collection, Ananthakrishnan, Gainer, Guzman Perez, Cai, Cheng, Savova, Chen, Churchill, Kohane, Shaw, Xia, De Jager, Plenge, Liao, Szolovits, and Murphy; analysis, Ananthakrishnan, Cai, Cheng, and Perlis; preliminary draft of the manuscript, Ananthakrishnan; approval of final version of the manuscript, Ananthakrishnan, Gainer, Cai, Guzman Perez, Cheng, Savova, Chen, Xia, De Jager, Shaw, Churchill, Karlson, Kohane, Perlis, Plenge, Murphy, and Liao. All authors approved the final version of the manuscript.

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**Potential competing interests:** None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Anxiety and depression are common in patients with Crohn's disease (CD) and ulcerative colitis (UC).
- ✓ Severity of disease may be associated with risk of psychiatric comorbidity.
- ✓ The incidence of depression or anxiety after an IBD-related surgery or hospitalization, or the risk factors for such psychiatric comorbidity, is unknown.

### WHAT IS NEW HERE

- ✓ Approximately 16% of CD patients and 11% of UC patients develop depression at 5 years after undergoing IBD-related surgery, with a similar risk between CD and UC patients.
- ✓ Female gender, younger age at surgery, undergoing surgery soon after a diagnosis of CD, or requirement for a stoma, were associated with increased risk of depression in CD patients, whereas only female gender and comorbidity predicted depression in UC.

## REFERENCES

- Kappelman MD, Rifas-Shiman SL, Porter CQ *et al.* Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. *Gastroenterology* 2008;135:1907–13.
- Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009;361:2066–78.
- Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;474:307–17.
- Bernstein CN, Loftus Jr EV, Ng SC *et al.* Hospitalisations and surgery in Crohn's disease. *Gut* 2012;61:622–9.
- Cosnes J, Gower-Rousseau C, Seksik P *et al.* Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140:1785–94.
- Lakatos L, Kiss LS, David G *et al.* Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002–2006. *Inflamm Bowel Dis* 2011;17:2558–65.
- Solberg IC, Lygren I, Jahnsen J *et al.* Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009;44:431–40.
- Targownik LE, Singh H, Nugent Z *et al.* The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. *Am J Gastroenterol* 2012;107:1228–35.
- Li Y, Shen B. Evaluating pouch problems. *Gastroenterol Clin North Am* 2012;41:355–78.
- Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis* 2009;15:1105–18.
- Graff LA, Walker JR, Lix L *et al.* The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. *Clin Gastroenterol Hepatol* 2006;4:1491–501.
- Nahon S, Lahmek P, Durance C *et al.* Risk factors of anxiety and depression in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;18:2086–91.
- Loftus Jr EV, Guerin A, Yu AP *et al.* Increased risks of developing anxiety and depression in young patients with Crohn's disease. *Am J Gastroenterol* 2011;106:1670–7.
- Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. *Inflamm Bowel Dis* 2006;12:697–707.
- Kurina LM, Goldacre MJ, Yeates D *et al.* Depression and anxiety in people with inflammatory bowel disease. *J Epidemiol Community Health* 2001;55:716–20.
- Walker JR, Ediger JP, Graff LA *et al.* The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol* 2008;103:1989–97.
- Lerebours E, Gower-Rousseau C, Merle V *et al.* Stressful life events as a risk factor for inflammatory bowel disease onset: A population-based case-control study. *Am J Gastroenterol* 2007;102:122–31.
- Levenstein S, Prantera C, Varvo V *et al.* Psychological stress and disease activity in ulcerative colitis: a multidimensional cross-sectional study. *Am J Gastroenterol* 1994;89:1219–25.
- Maunder RG. Evidence that stress contributes to inflammatory bowel disease: evaluation, synthesis, and future directions. *Inflamm Bowel Dis* 2005;11:600–8.
- Ananthakrishnan AN, Cai T, Savova G *et al.* Improving case definition of Crohn's disease and ulcerative colitis in electronic medical records using natural language processing: a novel informatics approach. *Inflamm Bowel Dis* 2013 (in press).
- Charlson ME, Pompei P, Ales KL *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- Castro VM, Gallagher PJ, Clements CC *et al.* Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants. *BMJ Open* 2012;2:e000544.
- Wells KB, Golding JM, Burnam MA. Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am J Psychiatry* 1988;145:976–81.
- Ko CY, Rusin LC, Schoetz Jr DJ *et al.* Long-term outcomes of the ileal pouch anal anastomosis: the association of bowel function and quality of life 5 years after surgery. *J Surg Res* 2001;98:102–7.
- Hauser W, Janke KH, Stallmach A. Mental disorder and psychologic distress in patients with ulcerative colitis after ileal pouch-anal anastomosis. *Dis Colon Rectum* 2005;48:952–62.
- Andersson T, Lunde OC, Johnson E *et al.* Long-term functional outcome and quality of life after restorative proctocolectomy with ileo-anal anastomosis for colitis. *Colorectal Dis* 2011;13:431–7.
- Hauser W, Dietz N, Steder-Neukamm U *et al.* Biopsychosocial determinants of health-related quality of life after ileal pouch anal anastomosis for ulcerative colitis. *Inflamm Bowel Dis* 2004;10:399–407.
- Robb B, Pritts T, Gang G *et al.* Quality of life in patients undergoing ileal pouch-anal anastomosis at the University of Cincinnati. *Am J Surg* 2002;183:353–60.
- Hauser G, Tkalcic M, Stimac D *et al.* Gender related differences in quality of life and affective status in patients with inflammatory bowel disease. *Coll Antropol* 2011;35 (Suppl 2): 203–7.
- Stjernman H, Tysk C, Almer S *et al.* Unfavourable outcome for women in a study of health-related quality of life, social factors and work disability in Crohn's disease. *Eur J Gastroenterol Hepatol* 2011;23:671–9.
- Casellas F, Arenas JJ, Baudet JS *et al.* Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. *Inflamm Bowel Dis* 2005;11:488–96.
- Saibeni S, Cortinovis I, Beretta L *et al.* Gender and disease activity influence health-related quality of life in inflammatory bowel diseases. *Hepatogastroenterology* 2005;52:509–15.
- Beaugerie L, Seksik P, Nion-Larmurier I *et al.* Predictors of Crohn's disease. *Gastroenterology* 2006;130:650–6.
- Mahadev S, Young JM, Selby W *et al.* Self-reported depressive symptoms and suicidal feelings in perianal Crohn's disease. *Colorectal Dis* 2012;14:331–5.
- Kasperek MS, Glatzle J, Temeltcheva T *et al.* Long-term quality of life in patients with Crohn's disease and perianal fistulas: influence of fecal diversion. *Dis Colon Rectum* 2007;50:2067–74.
- Drossman DA, Leserman J, Li ZM *et al.* The rating form of IBD patient concerns: a new measure of health status. *Psychosom Med* 1991;53:701–12.
- Jelsness-Jorgensen LP, Moum B, Bernklev T. Worries and Concerns among Inflammatory Bowel Disease Patients Followed Prospectively over One Year. *Gastroenterol Res Pract* 2011;2011:492034.
- Moser G, Tillinger W, Sachs G *et al.* Disease-related worries and concerns: a study on out-patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1995;7:853–8.
- Sharpe L, Patel D, Clarke S. The relationship between body image disturbance and distress in colorectal cancer patients with and without stomas. *J Psychosom Res* 2011;70:395–402.
- Lask B, Jenkins J, Nabarro L *et al.* Psychosocial sequelae of stoma surgery for inflammatory bowel disease in childhood. *Gut* 1987;28:1257–60.
- Bokemeyer B, Hardt J, Huppe D *et al.* Clinical status, psychosocial impairments, medical treatment and health care costs for patients with inflammatory bowel disease (IBD) in Germany: an online IBD registry. *J Crohns Colitis* 2012.
- Nguyen GC, Saibil F, Steinhart AH *et al.* Postoperative health-care utilization in Crohn's disease: the impact of specialist care. *Am J Gastroenterol* 2012.
- Ananthakrishnan AN, Issa M, Beaulieu DB *et al.* History of medical hospitalization predicts future need for colectomy in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009;15:176–81.
- Dinesen LC, Walsh AJ, Protic MN *et al.* The pattern and outcome of acute severe colitis. *J Crohns Colitis* 2010;4:431–7.