JGH Open An open access journal of gastroenterology and hepatology
Open Access
JGHF Journal of Gastroenterology and Hepatology Foundation
doi:10.1002/jgh3.12836

ORIGINAL ARTICLE

Depression is associated with increased disease activity in patients with ulcerative colitis: A propensity score-matched analysis using a nationwide database in Japan

Hideaki Oyama,* Rintaro Moroi,* Kunio Tarasawa,† Yusuke Shimoyama,* Takeo Naito,* Atsushi Sakuma,‡ Hisashi Shiga,* Yoichi Kakuta,* Kiyohide Fushimi,§ Kenji Fujimori,† Yoshitaka Kinouchi* and Atsushi Masamune*

*Division of Gastroenterology, †Department of Health Administration and Policy, Tohoku University Graduate School of Medicine, ‡Department of Psychiatry, Tohoku University Hospital, Sendai and §Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Bunkyo City, Japan

Key words
Crohn's disease, depression, inflammatory bowel disease, ulcerative colitis.

Accepted for publication 15 October 2022.

Correspondence
Rintaro Moroi, Division of Gastroenterology, Tohoku University Hospital, 1-1, Seiryo, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
Email: rinta@med.tohoku.ac.jp

Financial support: This study was self-funded by the authors.
Declaration of conflict of interest: The authors declare that they have no conflict of interest.

Abstract

Background and Aim: The incidence and prevalence of psychiatric disorders are elevated in patients with inflammatory bowel disease (IBD). Whether psychiatric disorders could affect the clinical course of IBD is uncertain and controversial. We aimed to evaluate the impact of psychiatric disorders, particularly depression, on the clinical course of IBD using a nationwide database in Japan.
Methods: We collected data on admissions with IBD using the Diagnosis Procedure Combination database system introduced in Japan. We divided eligible admissions into IBD with and without depression groups using propensity score matching and compared the rates of surgery, use of molecular targeted drugs and biologics, systemic steroid administrations, and in-hospital death. We also conducted a logistic regression analysis to identify clinical factors affecting surgery, the use of molecular targeted drugs and biologics, and systemic steroid administrations.
Results: The rates of surgery, use of two or more molecular targeted drugs, systemic steroid administrations, and in-hospital deaths in the ulcerative colitis (UC) with depression group were higher than in the UC without depression group. Multivariate analysis of UC showed that depression increased the odds of systemic steroid administrations, use of two or more molecular targeted drugs, and surgery. However, analysis of Crohn's disease showed that only steroid administrations were associated with depression.
Conclusion: Our study demonstrated an association between a worse clinical course of UC and depression. Although this result indicates that depression might be associated with increased disease activity in patients with UC, the causal relationship is still unclear. Further prospective studies are warranted.

Introduction

Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disease that is characterized by repeated cycles of exacerbation and remission. IBD comprises Crohn's disease (CD) and ulcerative colitis (UC). Although the etiology of IBD is still unknown, there are several factors that correlate with its development[1–3] and recurrence.[4,5]

Regarding psychological factors, several studies reported that psychiatric disorders, including depression and anxiety, could negatively impact the clinical course of IBD,[6–9] especially UC.[10] One study reported that antidepressant therapy could protect against IBD.[11] In contrast, several studies have shown no association between psychiatric disorders and IBD activity.[12–15] Whether psychiatric disorders could affect the clinical course of IBD is uncertain and controversial. However, a retrospective database study demonstrated that the incidence and prevalence of psychiatric disorders were elevated in the IBD population.[16] Another study also reported that the prevalence of depression in patients with IBD was 25.8%.[17] Therefore, it is essential to evaluate the effect of psychiatric disorders on IBD activity in clinical practice.

We have previously conducted clinical studies on IBD and other lower intestinal tract diseases using the Diagnostic Procedure Combination (DPC) nationwide database.[18–21] The DPC database contains a large number of admissions and enables analysis of IBD comorbidities, which makes it difficult to collect enough samples for a single-center study.

In this study, we aimed to evaluate the impact of psychiatric disorders, particularly depression, on the clinical course of IBD using the DPC database.

Methods

DPC system. The DPC database, introduced in 2003, is a medical claims database of admissions to acute-care hospitals in Japan. The DPC system was adopted at 1730 hospitals in 2018 and covers approximately 83% of the acute-care beds in Japan.[22] The DPC database contains patients' demographics, diagnosis, main disease triggering admission, comorbidities at admission, complications after admission, medications, and procedures (including surgeries and inpatient psychotherapy). Inpatient psychotherapy is a medical intervention performed by psychiatrists for inpatients with depressive symptoms. Physicians input patients' diagnoses into the DPC database according to the International Classification of Diseases, Tenth Revision (ICD-10) codes. The diagnostic validity of the DPC database has been recognized.[23]

Patients. We collected administrative claims dates of inpatients discharged from more than 1100 participating hospitals. This study included patients with UC or CD who were over 20 years of age and admitted to a DPC-participating hospital from April 2012 to March 2020. Eligible patients were identified using a DPC diagnosis containing the phrase "ulcerative colitis" or "Crohn's disease" in their main diagnosis, main disease triggering admission, or most resource-consuming diagnosis. ICD-10 codes for ulcerative colitis and Crohn's disease are "K51" and "K50," respectively.

Data collection. We collected the following data on patients and their clinical characteristics and procedures from the DPC database: age, sex, body mass index (BMI), smoking history (Yes: current or ex-smokers *vs* No: non-smokers, classified based on Brinkman index), Charlson comorbidity index (CCI),[24] hospital type (academic hospital or not), duration of admission, medication for IBD (systemic steroid administrations and molecular targeted drugs), surgeries for IBD, prescription of antidepressants, and inpatient psychotherapy conducted by a psychiatrist. Molecular targeted drugs are defined as follows: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tacrolimus, and tofacitinib. The antidepressants selected were tricyclic antidepressants, tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, vortioxetine, and trazodone. Surgeries, including colectomy, small bowel resection, anal fistula radical surgery, stenosis dilation, and stoma creation (colostomy and ileostomy), were also detected using ICD-10 codes.

Data analysis. We classified eligible patients into two groups according to their age (elderly group: age ≥65 years, non-elderly group: age ≤64 years) based on the World Health Organization classification.[25] We also classified them into three categories according to their BMI (underweight: <18.5 kg/m^2, normal range: 18.5–24.9 kg/m^2, overweight: ≥25.0 kg/m^2), based on the World Health Organization classification.[26] We further classified eligible patients into groups depending on the presence or absence of depression (depression and non-depression groups). The presence of depression was defined as an inpatient using both antidepressants and inpatient psychotherapy. Inpatient psychotherapy is calculated when a psychiatrist examines the patient and diagnoses any psychiatric disorders, and antidepressants are ordinarily prescribed for depression. Therefore, patients meeting these two conditions were considered as having depression in this study.

We conducted a propensity score matching analysis to eliminate bias as much as possible and to investigate the impact of depression on the clinical course of IBD. We used the following variables for propensity score matching: sex, age, BMI categories, smoking status, academic hospital admission, and CCI. We compared the patients' background and medical therapies, including systemic steroid administrations, use of two or more molecular targeted drugs in admissions due to UC (one or more molecular targeted drugs in admissions due to CD), and surgery, between the two groups using the chi-square test and Wilcoxon's signed-rank test. However, golimumab, tacrolimus, and tofacitinib are not approved for Crohn's disease in Japan; therefore, we compared the use of one or more of infliximab, adalimumab, vedolizumab, and ustekinumab as biological therapies. The difference of the criteria between UC and CD also based on the number of use of molecular targeted drugs (Table S1, Supporting information). Admissions due to UC were prescribed more molecular targeted drugs compared to CD. Therefore, we selected different criteria in each disease.

We also performed a multivariate logistic regression analysis to identify clinical factors that could have affected the use of systemic steroid administrations, molecularly targeted drugs, and surgery, using data before propensity score matching. The threshold for statistical significance was set at a P-value of <0.05. All statistical analyses were performed using JMP Pro16 (SAS Institute, Tokyo, Japan).

Ethics. The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2019-1-415) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived because of the anonymity of data.

Results

Patient characteristics. We included 81 251 eligible cases with UC, of whom 611 were assigned to the UC depression group and the remaining 80 640 to the UC non-depression group. We also included 78 230 eligible cases with CD, of whom 524 were assigned to the CD depression group and the remaining 77 706 to the CD non-depression group (Fig. 1). The characteristics of the study population are summarized in Tables 1 and 2.

The proportion of women in the UC depression group was significantly higher than that in the UC non-depression group (50.4% *vs* 43.3%, $P = 0.0005$). The average age of the UC depression group was higher than that of the UC non-depression group (51.7 *vs* 49.0 years, $P = 0.0003$). The rate of admission to academic hospitals in the UC depression group was higher than that in the UC non-depression group (39.6% *vs* 25.3%,

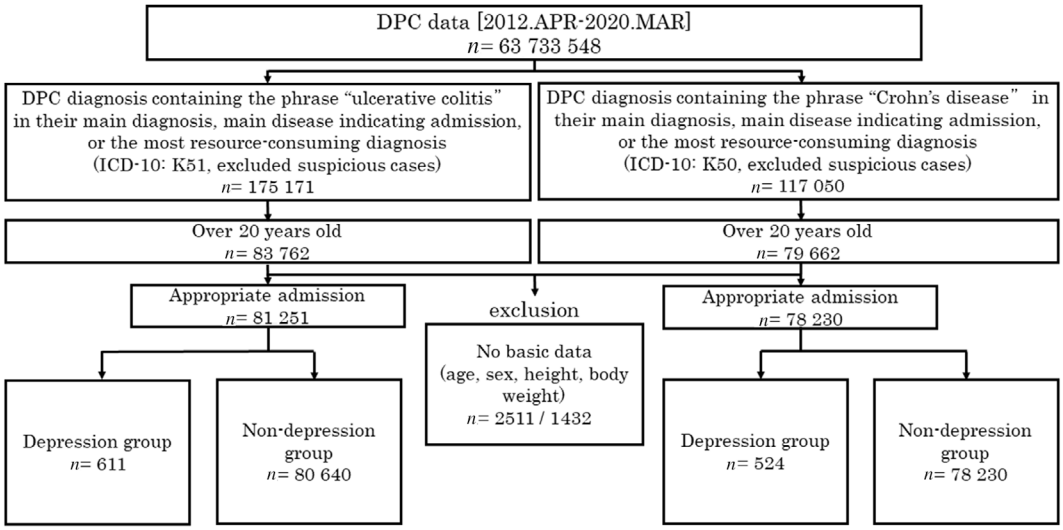

Figure 1 The flowchart of patient extraction. The eligible admissions were extracted as per this flow.

$P < 0.0001$). There was no difference in smoking history between the UC depression and non-depression groups.

The number of academic hospitals in the CD depression group was significantly higher than that in the CD non-depression group, while there were no differences in sex, age, and smoking history.

The results of the propensity score matching analysis are shown in Table 1. The standardized difference in each covariable was less than 0.1 in both UC and CD. The *C*-statistics were 0.63 and 0.60 for UC and CD, respectively.

Comparison of medical treatments, complications, and clinical events after propensity score matching. The comparison of medical treatments, complications, and clinical events between the two groups of patients with UC and CD is summarized in Tables 3 and 4.

The rates of use of two or more molecular targeted therapies and systemic steroid administrations in the UC depression group were higher than in the UC non-depression group (4.1% *vs* 2.0%, $P = 0.044$; 60.1% *vs* 48.8%, $P < 0.0001$). The rates of surgery and in-hospital death were also significantly higher in the UC depression group (23.1% *vs* 12.6%, $P < 0.0001$; 3.6% *vs* 1.3%, $P < 0.0001$). The results were similar in the analysis before propensity score matching (Table 2).

The rates of systemic steroid administration in the CD depression group were higher than that in the CD non-depression group (29.4% *vs* 19.5%, $P = 0.0002$), whereas there were no differences in the rates of others.

Multivariate analysis for systemic steroid administrations, molecular targeted therapy, and surgery using data before propensity score matching. The results of the multivariate analysis for systemic steroid administrations, use of two or more molecular targeted drugs, and surgery in the UC groups are summarized in Table 5. After multivariate analysis, depression was identified as a clinical factor that affected systemic steroid administrations (odds ratio [OR] = 1.80, 95% confidence interval [CI]: 1.53–2.12, $P < 0.0001$), use of two or more molecular targeted drugs (OR = 1.73, 95% CI: 1.15–2.60, $P = 0.0084$), and surgery (OR = 2.64, 95% CI: 2.16–3.22, $P < 0.0001$).

The results of the multivariate analysis for systemic steroid administrations, use of one or more biological drugs, and surgery in the CD groups are summarized in Table 6. Although depression was associated with the risk of systemic steroid administrations (OR = 2.02, 95% CI: 1.67–2.45, $P < 0.0001$), no associations were observed between biological drugs and surgery rates.

Discussion

Herein, we compared the disease activity of IBD patients with and without concomitant depression using a nationwide database in Japan. Our research showed that after propensity score matching analysis of patients with UC, the rates of surgery, use of two or more molecular targeted drugs, systemic steroid administrations, and in-hospital deaths in the UC depression group were higher than those in the UC non-depression group. However, after the analysis of patients with CD, only the rates of systemic steroid administrations in the CD depression group were higher than those in the CD non-depression group. After multivariate analysis of patients with UC, depression was found to increase the odds of systemic steroid administrations, use of two or more molecular targeted drugs, and surgery; after analysis of patients with CD, depression was found to increase the odds of only systemic steroid administrations.

The rates of surgery and use of molecularly targeted drugs are thought to indirectly reflect IBD activity. Our results demonstrated an association between concomitant depression and a worse clinical course of UC. Several studies have also reported an association between psychological stress and a negative clinical course of UC.[7,10] To the best of our knowledge, only one study has clarified the association between clinical recurrence of

Table 1 Comparison of clinical characteristics of the patients with UC before and after propensity score matching

	UC						
	Before propensity score matching Total $n = 81\,251$			After propensity score matching Total $n = 1222$			
	UC non-depression group $n = 80\,640$	UC depression group $n = 611$	*P*-value	UC non-depression group $n = 611$	UC depression group $n = 611$	*P*-value	Standardized difference
Sex (male/female)	45 713/34 927	303/308	0.0005	303/308	303/308	1	0
Age (mean ± SD), years	49.0 ± 18.3	51.7 ± 18.0	0.0003	51.7 ± 18.0	51.7 ± 18.0	0.94	0
Age categories							
≥65 years	19 298 (23.9)	186 (30.4)		175 (28.6)	186 (30.4)		0.039
20–64 years	61 342 (76.1)	425 (69.6)		436 (71.4)	425 (69.6)		0.039
Body mass index (mean ± SD), kg/m^2	21.4 ± 5.5	21.1 ± 4.5	0.0005	21.3 ± 4.1	21.1 ± 4.5	0.2	0.046
BMI categories							
Overweight (>25.0 kg/m^2)	12 321 (15.3)	109 (17.8)		109 (17.8)	109 (17.8)		0
Normal range (18.5–24.9 kg/m^2)	50 351 (62.4)	315 (51.6)		315 (51.6)	315 (51.6)		0
Underweight (<18.5 kg/m^2)	17 968 (22.3)	187 (30.6)		187 (30.6)	187 (30.6)		0
Smoking history, *n* (%)	18 185 (22.6)	135 (22.1)	0.8459	134 (21.9)	135 (22.1)	1	0.004
Academic hospital, *n* (%)	20 408 (25.3)	242 (39.6)	<0.0001	242 (39.6)	242 (39.6)	1	0
Charlson comorbidity index score			<0.0001			1	
0	59 451 (73.7)	410 (67.1)		410 (67.1)	410 (67.1)		0
1	14 658 (18.2)	125 (20.5)		125 (20.5)	125 (20.5)		0
2	4652 (5.8)	52 (8.5)		53 (8.7)	52 (8.5)		0.0058
>3	1879 (2.3)	24 (3.9)		23 (3.8)	24 (3.9)		0.0085
Acute myocardial infarction, *n* (%)	471 (0.58)	3 (0.49)	1				
Heart failure, *n* (%)	811 (1.0)	16 (2.6)	0.0006				
Peripheral vascular disease, *n* (%)	355 (0.44)	5 (0.82)	0.20				
Cerebral vascular disease, *n* (%)	1269 (1.6)	15 (2.5)	0.10				
Dementia, *n* (%)	435 (0.54)	19 (3.1)	<0.0001				
Pulmonary disease, *n* (%)	1965 (2.4)	19 (3.1)	0.29				
Connective tissue disorder, *n* (%)	879 (1.1)	7 (1.2)	0.84				
Peptic ulcer, *n* (%)	7755 (9.6)	51 (8.4)	0.33				
Liver disease, *n* (%)	2168 (2.7)	14 (2.3)	0.71				
Diabetes without complication, *n* (%)	5379 (6.7)	55 (9.0)	0.03				
Diabetes with complication, *n* (%)	535 (0.66)	9 (1.5)	0.02				
Paraplegia, *n* (%)	53 (0.07)	0 (0)	1				
Renal disease, (%)	584 (0.72)	6 (0.98)	0.46				
Cancer, *n* (%)	2834 (3.5)	31 (5.1)	0.05				
Metastatic cancer, *n* (%)	218 (0.27)	5 (0.82)	0.03				
Severe liver disease, *n* (%)	48 (0.06)	0 (0)	1				
HIV, *n* (%)	37 (0.05)	1 (0.16)	0.25				

BMI, body mass index; CD, Crohn's disease; HIV, human immunodeficiency virus; SD, standard deviation; UC, ulcerative colitis.

Table 2 Comparison of clinical characteristics of the patients with CD before and after propensity score matching

	CD						
	Before propensity score matching Total $n = 78\,230$			After propensity score matching Total $n = 1048$			
	CD non-depression group $n = 77\,706$	CD depression group $n = 524$	*P*-value	CD non-depression group $n = 524$	CD depression group $n = 524$	*P*-value	Standardized difference
Sex (male/female)	53 350/24 356	350/174	0.37	351/173	350/174	1	0.0041
Age (mean ± SD), years	41.2 ± 13.7	42.0 ± 14.3	0.22	42.2 ± 14.3	42.0 ± 14.3	0.85	0.014
Age categories							
≥65 years	5340 (6.9)	32 (6.1)		38 (7.3)	32 (6.1)		0.046
20–64 years	72 366 (93.1)	492 (93.9)		486 (92.8)	492 (93.9)		0.046
Body mass index (mean ± SD), kg/m^2	20.6 ± 4.4	20.5 ± 3.5	0.69	20.7 ± 3.6	20.5 ± 3.5	0.58	0.056
BMI categories							
Overweight (>25.0 kg/m^2)	8368 (10.8)	52 (9.9)		52 (9.9)	52 (9.9)		0
Normal range (18.5–24.9 kg/m^2)	45 902 (59.1)	328 (62.6)		328 (62.6)	328 (62.6)		0
Underweight (<18.5 kg/m^2)	23 436 (30.2)	144 (27.5)		144 (27.5)	144 (27.5)		0
Smoking history, *n* (%)	20 720 (26.7)	128 (24.4)	0.25	127	128 (24.4)	1	0.0045
Academic hospital, *n* (%)	27 064 (34.8)	237 (45.2)	<0.0001	237 (45.2)	237 (45.2)	1	0
Charlson comorbidity index score			<0.0001			1	
0	62 357 (80.3)	365 (70.0)		366 (69.9)	365 (69.7)		0.0042
1	10 518 (13.5)	100 (19.1)		99 (18.9)	100 (19.1)		0.0049
2	3290 (4.2)	33 (6.3)		33 (6.3)	33 (6.3)		0
>3	1541 (2.0)	26 (5.0)		26 (5.0)	26 (5.0)		0
Acute myocardial infarction, *n* (%)	174 (0.22)	0 (0)	0.64				
Heart failure, *n* (%)	589 (0.76)	10 (1.9)	0.0078				
Peripheral vascular disease, *n* (%)	204 (0.26)	3 (0.57)	0.16				
Cerebral vascular disease, *n* (%)	573 (0.74)	6 (1.2)	0.29				
Dementia, *n* (%)	130 (0.17)	2 (0.38)	0.22				
Pulmonary disease, *n* (%)	1424 (1.8)	14 (2.7)	0.14				
Connective tissue disorder, *n* (%)	792 (1.0)	5 (0.95)	1				
Peptic ulcer, *n* (%)	6231 (8.0)	49 (9.4)	0.26				
Liver disease, *n* (%)	2052 (2.6)	21 (4.0)	0.06				
Diabetes without complication, *n* (%)	2178 (2.8)	27 (5.2)	0.0031				
Diabetes with complication, *n* (%)	346 (0.45)	5 (9.5)	0.09				
Paraplegia, *n* (%)	42 (0.05)	0 (0)	1				
Renal disease, *n* (%)	1147 (1.5)	20 (3.8)	0.0002				
Cancer, *n* (%)	1603 (2.1)	18 (3.4)	0.043				
Metastatic cancer, *n* (%)	483 (0.6)	9 (1.7)	0.0065				
Severe liver disease, *n* (%)	109 (0.14)	3 (0.57)	0.04				
HIV, *n* (%)	12 (0.02)	0 (0)	1				

BMI, body mass index; CD, Crohn's disease; HIV, human immunodeficiency virus; SD, standard deviation; UC, ulcerative colitis.

UC and psychological disorders, including depression.[27] However, although the association between depression and poor clinical course of UC has been clarified, the causal relationship between these two entities remains unclear. In other words, whether depression is a cause of worsening UC or whether depression is only a result of the poor clinical course of UC is

Table 3 Comparison of medical treatments, complications, and clinical events of patients with ulcerative colitis (UC)

	UC					
	Before propensity score matching Total $n = 81\,251$			After propensity score matching Total $n = 1222$		
	UC non-depression group $n = 80\,640$	UC depression group $n = 611$	*P*-value	UC non-depression group $n = 611$	UC depression group $n = 611$	*P*-value
Surgery, *n* (%)	7906 (9.8)	141 (23.1)	<0.0001	77 (12.6)	141 (23.1)	<0.0001
Two or more molecular targeted drugs, *n* (%)	1620 (2.0)	25 (4.1)	0.0012	12 (2.0)	25 (4.1)	0.044
Systemic steroid administrations, *n* (%)	38 732 (48.0)	367 (60.1)	<0.0001	298 (48.8)	367 (60.1)	<0.0001
In-hospital death, *n* (%)	591 (0.73)	22 (3.6)	<0.0001	8 (1.3)	22 (3.6)	0.015

Table 4 Comparison of medical treatments, complications, and clinical events of patients with Crohn's disease (CD)

	CD					
	Before propensity score matching Total $n = 78\,230$			After propensity score matching Total $n = 1048$		
	CD non-depression group $n = 77\,706$	CD depression group $n = 524$	*P*-value	CD non-depression group $n = 524$	CD depression group $n = 524$	*P*-value
Surgery, *n* (%)	14 144 (18.2)	92 (17.6)	0.73	113 (21.6)	92 (17.6)	0.12
One or more biological therapy, *n* (%)	29 183 (37.5)	192 (36.6)	0.79	189 (36.1)	192 (36.6)	0.9
Systemic steroid administrations, *n* (%)	13 267 (17.1)	154 (29.4)	<0.0001	102 (19.5)	154 (29.4)	0.0002
In-hospital death, *n* (%)	224 (0.29)	0 (0)	0.41	4 (0.76)	0 (0)	0.12

unclear. Further prospective investigations are required to clarify this issue. We have been conducting a prospective questionnaire survey to investigate the causal relationship. One observational study after a devastating earthquake reported that patients with IBD who had experienced the death of family members or friends were likely to need additional treatments.[28] This study indicated that depression could be a cause of worsening disease activity rather than depression being a result of a poor clinical course. Furthermore, this result indicates that the disease activity of patients with UC who have depressive symptoms could be improved by prompt intervention performed by a psychiatrist, which might ultimately contribute to an improved prognosis. Further investigation is warranted to clarify this issue.

In contrast to UC, depression was not associated with the rates of surgery or the use of molecularly targeted drugs in patients with CD. This result indicates that the impact of depression on the clinical course of IBD might differ between patients with UC and CD. Several previous studies did not separate IBD into CD and UC when evaluating the impact of concomitant psychologic disorders.[7–9,15] One observational prospective study reported that CD patients with psychological stress are at a lower risk than patients with UC.[13] However, a prospective cohort study reported an association between depression symptoms and relapse of CD.[27] These inconsistencies might be due to differences in study design and the number of participants in each study.

Data after propensity score matching showed a significant difference in the rate of systemic steroid administrations between the UC non-depression and depression groups. Depression was also identified as a clinical factor affecting systemic steroid administrations in the multivariate analysis. These results might reflect steroid-induced depression. The same tendency was observed in the analysis of patients with CD, despite there being no difference in other clinical outcomes between the CD depression and non-depression groups. Furthermore, inpatients in Japan are expected to have a certain disease activity. Thus, physicians might have already prescribed steroids to these patients before admission. Further investigation is required to clarify this point.

Our analysis also showed a higher in-hospital death rate in the UC depression group than in the non-depression group. However, the reason for this result remains unclear. Several studies have reported shorter life expectancy or higher mortality rates in patients with depression than in the general population.[29–32] Furthermore, the causes of death in these patients are not only suicide but also various physical disorders.[29,32,33] Although the details of the cause of death in this study population are unclear, our results are compatible with previous reports and indicate that it might be better to treat such psychological problems as quickly as possible.

This study has several limitations. First, the DPC database does not contain details of the patients' conditions, such as the period when IBD disease activity worsened, endoscopic and pathological findings, laboratory data, computed tomography findings, and information on intestinal and extraintestinal manifestations. Therefore, we indirectly evaluated disease severity by investigating the therapeutic agents used and the surgery rate.

Table 5 Multivariate analysis[†] of the association among clinical factors and medical treatments in ulcerative colitis (UC)

Clinical factors	Number of patients $n = 81\,251$	Systemic steroid administrations			Two or more molecular targeted drug			Surgery		
		Odds ratio	95% confidence interval (CI)	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Sex	Male: 46 016	Reference		<0.0001	Reference		0.0004	Reference		<0.0001
	Female: 35 235	0.85	0.83–0.88		0.83	0.75–0.92		0.66	0.62–0.69	
Age categories	≥65 years: 19 484	Reference		<0.0001	Reference		<0.0001	Reference		<0.0001
	20–64 years: 61 767	1.31	1.27–1.36		1.60	1.40–1.83		1.22	1.15–1.29	
BMI categories	Overweight: 12 430	0.85	0.81–0.88	<0.0001	0.84	0.72–0.98	0.025	0.77	0.72–0.83	<0.0001
	Normal range: 50 666	Reference			Reference			Reference		
	Underweight: 18 155	1.21	1.16–1.25	<0.0001	1.36	1.22–1.52	<0.0001	1.45	1.38–1.54	<0.0001
Smoking history	Yes: 18 320	1.07	1.03–1.10	0.0002	0.99	0.87–1.12	0.86	1.03	0.97–1.09	0.40
	No: 62931	Reference			Reference			Reference		
Academic hospital	Yes: 20 650	0.99	0.95–1.02	0.37	2.09	1.88–2.31	<0.0001	3.58	3.41–3.75	<0.0001
	No: 60 601	Reference			Reference			Reference		
Surgery	Yes: 8047	0.54	0.51–0.56	0.10	1.17	1.00–1.35	0.0441			
	No: 73 204	Reference			Reference					
Use of two or more molecular-targeted drugs	Yes: 1645	1.89	1.71–2.10	<0.0001				1.13	0.98–1.32	0.10
	No: 79 606	Reference						Reference		
Systemic steroid administrations	Yes: 39 099				1.90	1.72–2.11	<0.0001	0.54	0.51–0.57	<0.0001
	No: 42 152				Reference			Reference		
Depression (antidepressant and inpatient psychotherapy)	Yes: 611	1.80	1.53–2.12	<0.0001	1.73	1.15–2.60	0.0084	2.64	2.16–3.22	<0.0001
	No: 80 640	Reference			Reference			Reference		

[†]Logistic regression analysis.

Table 6 Multivariate analysis[†] of the association among clinical factors and medical treatments in Crohn's disease (CD)

		Systemic steroid administrations			One or more biological therapy			Surgery		
Clinical factors	Number of patients $n = 78\ 230$	Odds ratio	95% confidence interval (CI)	*P*-value	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Sex	Male: 53 700	Reference		0.84	Reference		0.62	Reference		0.71
	Female: 24 530	1.00	0.95–1.04		1.01	0.98–1.04		1.01	0.97–1.05	
Age categories	≥65 years: 5372	Reference		1.00	Reference		0.0017	Reference		0.095
	20–64 years: 72 858	1.00	0.93–1.08		0.91	0.86–0.97		1.07	0.99–1.15	
BMI categories	Overweight: 6714	0.98	0.92–1.04	0.53	0.99	0.94–1.04	0.57	0.95	0.89–1.01	0.10
	Normal range: 46 230	Reference			Reference			Reference		
	Underweight: 23 580	0.97	0.93–1.02	0.21	1.01	0.97–1.04	0.72	1.01	0.97–1.05	0.67
Smoking history	Yes: 20 848	1.00	0.96–1.05	0.93	1.02	0.98–1.05	0.37	0.98	0.94–1.03	0.46
	No: 57 382	Reference			Reference			Reference		
Academic hospital	Yes: 27 301	1.11	1.07–1.15	<0.0001	1.17	1.13–1.20	<0.0001	1.62	1.56–1.69	<0.0001
	No: 50 929	Reference			Reference			Reference		
Surgery	Yes: 14 236	0.79	0.74–0.83	<0.0001	0.46	0.44–0.48	<0.0001			
	No: 63 994	Reference			Reference					
Use of one or more biological therapy	Yes: 29 183	1.64	1.58–1.70	<0.0001				0.46	0.44–0.48	<0.0001
	No: 49 047	Reference						Reference		
Systemic steroid administrations	Yes: 13 421				1.64	1.58–1.70	<0.0001	0.78	0.75–0.83	<0.0001
	No: 64 809				Reference			Reference		
Depression (antidepressant and inpatient psychotherapy)	Yes: 524	2.02	1.67–2.45	<0.0001	0.90	0.75–1.07	0.23	0.93	0.74–1.17	0.53
	No: 77 706	Reference			Reference			Reference		

[†]Logistic regression analysis.

Second, the DPC database targets only admissions and not out-of-hospital patients. DPC-participating hospitals were typically acute-care and relatively large-volume hospitals. Therefore, these data do not necessarily reflect all patients with IBD. Furthermore, if the patients were transferred to another hospital, they could not be followed up. Third, the DPC database is suitable for cross-sectional analysis rather than longitudinal analysis because of the nature of the DPC system. As described above, our results showed an association between a worse clinical course of UC and depression, not a causal relationship between these two entities. Further prospective studies are warranted to clarify the causal relationship. Fourth, although the incidence of depression is known to be 6–7% in Japan,[34,35] our results contain a much smaller number of cases with depression. This might be because concomitant depression was not defined only by the disease name or prescription of antidepressants. Antidepressants can be prescribed for other diseases in clinical practice in Japan. We defined the presence of depression as an inpatient who used both antidepressants and inpatient psychotherapy, which is a medical practice that can only be performed by psychiatrists in Japan. Although it is important to distinguish between depression and delirium in patients who are prescribed antidepressants, inpatient psychotherapy is a medical practice that is not performed for delirium in Japan. Therefore, it is possible to exclude steroid-induced delirium simultaneously. We believe that our definition is effective in precisely selecting patients with depression. Therefore, our results may contain a small number of cases with depression.

In conclusion, our study demonstrated an association between concomitant depression and a worse clinical course of UC. Although this result indicates that depression might be associated with increased disease activity in patients with UC, the causal relationship is still unclear. We should conduct further prospective studies to clarify the causal relationship.

Acknowledgments

I would like to thank the co-authors for their advice.

References

1 Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: East meets west. *J. Gastroenterol. Hepatol.* 2020; **35**: 380–9.
2 Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World J. Gastroenterol.* 2014; **20**: 91–9.
3 Guan Q. A comprehensive review and update on the pathogenesis of inflammatory bowel disease. *J. Immunol. Res.* 2019; **2019**: 7247238.
4 Doherty G, Katsanos KH, Burisch J *et al*. European Crohn's and Colitis organisation topical review on treatment withdrawal ['exit strategies'] in inflammatory bowel disease. *J. Crohns Colitis*. 2018; **12**: 17–31.
5 Petagna L, Antonelli A, Ganini C *et al*. Pathophysiology of Crohn's disease inflammation and recurrence. *Biol. Direct*. 2020; **15**: 23.
6 Addolorato G, Capristo E, Stefanini GF, Gasbarrini G. Inflammatory bowel disease: A study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scand. J. Gastroenterol.* 1997; **32**: 1013–21.
7 Araki M, Shinzaki S, Yamada T *et al*. Psychologic stress and disease activity in patients with inflammatory bowel disease: A multicenter cross-sectional study. *PLoS One.* 2020; **15**: e0233365.
8 Narula N, Pinto-Sanchez MI, Calo NC *et al*. Anxiety but not depression predicts poor outcomes in inflammatory bowel disease. *Inflamm. Bowel Dis.* 2019; **25**: 1255–61.
9 Mittermaier C, Dejaco C, Waldhoer T *et al*. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom. Med.* 2004; **66**: 79–84.
10 Bitton A, Sewitch MJ, Peppercorn MA *et al*. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am. J. Gastroenterol.* 2003; **98**: 2203–8.
11 Frolkis AD, Vallerand IA, Shaheen AA *et al*. Depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. *Gut*. 2019; **68**: 1606–12.
12 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.
13 Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Holtmann GJ, Andrews JM. Does psychological status influence clinical outcomes in patients with inflammatory bowel disease (IBD) and other chronic gastroenterological diseases: an observational cohort prospective study. *Biopsychosoc. Med.* 2008; **2**: 11.
14 Riley SA, Mani V, Goodman MJ, Lucas S. Why do patients with ulcerative colitis relapse? *Gut*. 1990; **31**: 179–83.
15 Vidal A, Gómez-Gil E, Sans M *et al*. Life events and inflammatory bowel disease relapse: a prospective study of patients enrolled in remission. *Am. J. Gastroenterol.* 2006; **101**: 775–81.
16 Bernstein CN, Hitchon CA, Walld R *et al*. Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflamm. Bowel Dis.* 2019; **25**: 360–8.
17 Byrne G, Rosenfeld G, Leung Y *et al*. Prevalence of anxiety and depression in patients with inflammatory bowel disease. *Can. J. Gastroenterol. Hepatol.* 2017; **2017**: 6496727.
18 Moroi R, Shiga H, Tarasawa K *et al*. The clinical practice of ulcerative colitis in elderly patients: an investigation using a nationwide database in Japan. *JGH Open.* 2021; **5**: 842–8.
19 Moroi R, Tarasawa K, Shiga H *et al*. Efficacy of urgent colonoscopy for colonic diverticular bleeding: a propensity score-matched analysis using a nationwide database in Japan. *J. Gastroenterol. Hepatol.* 2021; **36**: 1598–604.
20 Yano K, Moroi R, Shiga H *et al*. Analysis of the disease activity of ulcerative colitis with and without concomitant primary sclerosing cholangitis: an investigation using a nationwide database in Japan. *JGH Open.* 2022; **6**: 50–6.
21 Moroi R, Tarasawa K, Shimoyama Y *et al*. Effectiveness of colonic stent placement for obstructive colorectal cancers: an analysis of short-term results using a nationwide database in Japan. *J. Gastroenterol. Hepatol.* 2022; **37**: 1316–25.
22 Medical Division IB, Ministry of Health, Labor, Welfare. *Outline of medical fee revision in 2018*. Available from URL: https://www.mhlwgojp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000197983pdf (In Japanese).
23 Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. *J. Epidemiol.* 2017; **27**: 476–82.
24 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 1987; **40**: 373–83.
25 Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. *Gastrointest. Endosc.* 2010; **71**: 560–72.
26 WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ. Tech. Rep. Ser.* 2000; **894**: i–xii 1–253.

27 Mikocka-Walus A, Pittet V, Rossel JB, von Känel R. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin. Gastroenterol. Hepatol.* 2016; **14**: 829–35.e1.
28 Miyazawa T, Shiga H, Kinouchi Y *et al*. Long-term course of inflammatory bowel disease after the Great East Japan Earthquake. *J. Gastroenterol. Hepatol.* 2018; **33**: 1956–60.
29 Korhonen K, Moustgaard H, Tarkiainen L *et al*. Contributions of specific causes of death by age to the shorter life expectancy in depression: a register-based observational study from Denmark, Finland, Sweden and Italy. *J. Affect. Disord.* 2021; **295**: 831–8.
30 Laursen TM, Musliner KL, Benros ME, Vestergaard M, Munk-Olsen T. Mortality and life expectancy in persons with severe unipolar depression. *J. Affect. Disord.* 2016; **193**: 203–7.
31 Pan YJ, Yeh LL, Chan HY, Chang CK. Excess mortality and shortened life expectancy in people with major mental illnesses in Taiwan. *Epidemiol. Psychiatr. Sci.* 2020; **29**: e156.
32 Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med.* 2013; **11**: 129.
33 Zivin K, Yosef M, Miller EM *et al*. Associations between depression and all-cause and cause-specific risk of death: a retrospective cohort study in the Veterans Health Administration. *J. Psychosom. Res.* 2015; **78**: 324–31.
34 Kawakami N. Epidemiology of depressive disorders in Japan and the world. *Nihon Rinsho Jpn. J. Clin. Med.* 2007; **65**: 1578–84.
35 Inagaki M, Ohtsuki T, Yonemoto N *et al*. Prevalence of depression among outpatients visiting a general internal medicine polyclinic in rural Japan. *Gen. Hosp. Psychiatry*. 2013; **35**: 286–90.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Comparison of the number of users of molecular targeting drugs between UC and CD.