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Relation between inflammatory bowel disease, depression, and inpatient outcomes in the United States

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ABSTRACT

The relationship between inflammatory bowel disease (IBD) and depression is complicated. The effect of depression on ulcerative colitis (UC) and Crohn's disease (CD) among the inpatient US population has not previously been studied. We retrospectively analyzed patients admitted with UC and CD from 2016 to 2019 using the National Inpatient Sample database. Our primary outcome was the effect of depression on hospital length of stay (LOS), costs, and mortality. Secondary outcomes included the comparison between UC and CD cases. In the UC population, 13.4% had depression, compared to 14.9% in the CD population. LOS was longer in UC and CD patients with depression ($P < 0.001$). Subgroup analysis revealed that LOS was longer in CD patients than UC patients in the depressed cohort ($P < 0.001$). Inpatient hospital costs were lower in IBD patients with depression ($P < 0.001$). Subgroup analysis revealed that hospital cost was $17,974 higher in CD patients than UC patients ($P < 0.001$). Depression did not increase mortality in the IBD population but increased LOS, with a greater impact on CD than UC. White women were found to have an increased prevalence of depression in the IBD population.

KEYWORDS Depression; inflammatory bowel disease; National Inpatient Sample; prevalence

Inflammatory bowel disease (IBD) involves various inflammatory processes in the gut, mainly classified as ulcerative colitis (UC) and Crohn's disease (CD). Patients often present with weight loss, abdominal pain, fatigue, anemia, diarrhea, or, in advanced cases, gastrointestinal bleeding.[1] In recent years, hospitalizations for UC and CD have been increasing, resulting in increased hospital charges.[2] IBD has a significant association with psychiatric conditions, including depression. Depression can lead to impaired work-life balance, medication noncompliance, and increased readmission rates, which negatively impact quality of life.[3] Studies have shown that the prevalence of mental health disorders can be as high as 50% in the IBD population, and psychological morbidity highlights the need for interventions to improve outcomes.[4,5] Patients with both psychiatric disorders and IBD have increased healthcare resource utilization, resulting in increased readmission rates, outpatient services, and emergency department visits.[6] While a causal association between depression and IBD has been described in recent literature, its effects on inpatient variables have not been studied.[7] The National Inpatient Sample (NIS) database has been utilized to investigate various inpatient variables occurring during hospitalizations for different diseases.[8] In this study, we analyzed NIS data to understand the burden of depression in the IBD population.

METHODS

We conducted a retrospective cohort study of patients hospitalized from 2016 to 2019 with a primary diagnosis of CD or UC. Patients were selected from the NIS database, the largest publicly available all-payer inpatient database in the US.[9] Detailed information on the design and sampling methods of NIS is available at https://www.hcup-us.ahrq.gov.

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The NIS has been used previously to explore health-related outcomes of patients with IBD.[10]

The *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) does not have a unified code for UC or CD. Our study included patients with a principal diagnosis specific to UC, CD, and depression. The specific codes included for both IBD and depression are listed in the Supplementary Material. In addition, only patients ≥18 years were included. We excluded patients transferred to other institutions to reduce bias regarding survival status and length of stay (LOS).

The primary outcome measure of this study was LOS, total inpatient cost, and in-hospital mortality in IBD patients with depression vs those without depression. Secondary outcomes included comparing hospital outcomes between CD and UC in the depressed cohort and the association between depression and IBD by gender. Other covariates of interest included patient age, gender, race, health insurance, hospital location, teaching status, hospital size, and patient annual income. We used the Elixhauser list of 31 comorbidities for case-mix adjustment, a well-validated algorithm for predicting in-hospital mortality caused by various conditions (categorized as 0, 1, 2, and >3 comorbidities) (Supplementary Material).

Analyses were performed using STATA version 16.0. We utilized weighted univariate linear and logistic regression models to analyze potential confounders for outcomes. Multivariate linear and logistic regression models were built based on univariate analysis to adjust for the confounding variables. Only variables associated with the outcome of interest on univariable regression analysis at $P < 0.2$ or known to be potential confounders despite P value indicating no significance were used in multivariate regression. Continuous variables were compared using the Student t test; categorical variables were compared using the chi-square test. The analysis used 0.05 as the threshold for statistical significance, and all P values were two-sided. The adjusted confounders included but were not limited to age, sex, race, location, hospital size or teaching status, types of insurance, and comorbidities listed in the Elixhauser comorbidity index score.[9] Dichotomous variables were consolidated to report adjusted odds ratios (aORs) with 95% confidence interval (CI) and P value. Continuous data were reported as adjusted standard mean differences for continuous data with P values. Standard errors were reported as ± SE in linear regression outcomes.

RESULTS

There were 130,799 discharges for UC and 141,799 discharges for CD that met the inclusion criteria from 2016 to 2019 in the NIS database. In patients with UC, 13.4% had depression. In patients with CD, 14.9% had depression. Depression was more prevalent in women with UC and CD *(Table 1)*. The mean age of patients with depression was 50.5 years for UC patients and 45.5 years for CD patients. A white racial distribution was predominant in depressed patients for both UC and CD (80% and 83%, respectively, $P < 0.001$). The distribution of the IBD population was higher in the South for both the depressed and nondepressed cohorts ($P < 0.001$). Additional demographical characteristics are presented in *Table 1*.

The mean LOS of patients with depression in the UC group was 6 days vs 5.1 days in those without depression. After adjusting for potential confounders, the difference in LOS was 0.75 ± 0.12 days ($P < 0.001$). The mean LOS of patients with depression in the CD group was 6.2 days vs 5.2 days in those without depression. After adjusting for potential confounders, the difference in LOS was 0.89 ± 0.14 days ($P < 0.001$). When comparing CD to UC in the depressed cohort, the mean LOS in the UC group was 6.1 days vs 8.2 days in the CD group. After adjusting for potential confounders, the difference in LOS in days was 2.03 ± 0.24 ($P < 0.001$) *(Table 2)*. Subgroup analysis revealed that LOS was longer in white patients with CD compared to UC *(Table 3)*. These differences were not significant for black or Asian race.

The mean inpatient cost for patients with depression in the UC group was $50,553 vs $55,431 for those without depression. Crude analysis showed that patients with depression in the UC group had an increased hospital charge of $4877 ± 1729 ($P < 0.001$). However, after adjusting for potential confounders, the difference in total charge was $-5693 ± 1871 ($P < 0.001$). The mean hospital charge for patients with depression in the CD group was $49,631 vs $55,560 for those without depression. Crude analysis showed that patients with depression in the UC group had an increased hospital charge of $5929 ± 1514 ($P < 0.001$). After adjusting for potential confounders, the difference in total charge was $-7367 ± 1589 ($P < 0.001$). When comparing CD to UC in the depressed cohort, the mean hospital charge was $63,036 in the UC group vs $77,654 in the CD group. After adjusting for potential confounders, the difference in total charge was $17,974 ± 3046 ($P < 0.001$) *(Table 3)*. Subgroup analysis revealed that the hospital costs were highest in the white race with CD compared to UC (adjusted mean difference in hospital charge, $16,674 ± 3087, $P < 0.001$) (results not shown). These differences were not significant for black or Asian race.

In patients with UC, depression did not affect mortality ($P = 0.05$). In patients with CD, a secondary diagnosis of depression was associated with lower mortality (aOR 0.31, 95% CI 0.12–0.81, $P < 0.05$). The difference in mortality between UC and CD in the depressed cohort was not significant (results not shown). UC was associated with a 13% increased risk of depression (aOR 1.13, 95% CI 1.1–1.2, $P < 0.001$). Subgroup analysis for female gender revealed a 24% increased risk of depression ($P < 0.001$) *(Table 4)*. Men had a 12% reduced association with depression in the UC group ($P < 0.001$) *(Table 4)*. CD was associated with a 4% increased risk of depression ($P < 0.03$) *(Table 4)*. Subgroup analysis for female gender revealed a 30% increased association with depression ($P < 0.001$) *(Table 4)*. Men had a 35%

Table 1. Characteristics of patients included in the study

Patient characteristics	Depression in ulcerative colitis			Depression in Crohn's disease		
	No	Yes	*P* value	No	Yes	*P* value
Patients	113,394 (86.6%)	17,405 (13.4%)	0.001	120,729 (85.1%)	21,070 (14.9%)	<0.001
Male	56,169 (50%)	6035 (35%)		61,839 (51%)	7465 (35%)	
Female	57,224 (50%)	11,370 (65%)		58,889 (49%)	13,605 (65%)	
Mean age (years)	47.7 ± 0.14	50.5 ± 0.32		44 ± 0.12	45.5 ± 0.26	
Race			<0.001			<0.001
White	76,924 (78%)	13,555 (80%)		87,529 (75%)	16,915 (83%)	
Black	13,444 (12%)	1420 (8%)		17,670 (15%)	2075 (10%)	
Hispanic	12,900 (12%)	1330 (8%)		6705 (6%)	810 (4%)	
Asian or Pacific Islander	2375 (2%)	170 (1%)		1495 (1%)	115 (1%)	
Native American	545 (<1%)	90 (1%)		370 (<1%)	65 (<1%)	
Other	3740 (3%)	420 (2%)		2945 (3%)	310 (2%)	
Elixhauser Comorbidity Index			<0.001			<0.001
0	20,905 (18%)	—		34,515 (29%)	—	
1	28,680 (25%)	1875 (11%)		34,639 (29%)	3630 (17%)	
2	25,330 (22%)	3480 (20%)		24,250 (20%)	5240 (25%)	
≥3	38,494 (34%)	12,050 (69%)		27,380 (23%)	12,210 (58%)	
Median annual income in patient's zip code			0.7			0.7
≤$24,999	27,499 (25%)	4100 (24%)		29,489 (25%)	5185 (25%)	
$25,000–$34,999	27,870 (25%)	4355 (25%)		29,774 (25%)	5800 (28%)	
$35,000–$44,999	28,589 (26%)	4465 (26%)		31,424 (26%)	5450 (26%)	
≥$45,000	27,654 (25%)	4225 (25%)		28,354 (25%)	4415 (21%)	
Insurance type			<0.001			<0.001
Medicare	29,199 (27%)	5985 (36%)		27,494 (24%)	6540 (32%)	
Medicaid	18,895 (17%)	2970 (18%)		21,069 (18%)	4790 (23%)	
Private	53,969 (50%)	7125 (42%)		61,874 (53%)	8400 (41%)	
Uninsured	6855 (6%)	715 (4%)		6070 (5%)	720 (4%)	
Hospital characteristics						
Hospital region			<0.001			<0.001
Northeast	24,225 (21%)	3750 (22%)		26,209 (22%)	4600 (22%)	
Midwest	24,235 (21%)	4235 (24%)		31,619 (26%)	6535 (31%)	
South	43,044 (38%)	6185 (36%)		44,605 (37%)	6875 (33%)	
West	21,904 (19%)	3235 (19%)		18,349 (15%)	3070 (15%)	
Hospital bed size			0.9			0.1
Small	22,079 (19%)	3385 (19%)		22,344 (18%)	3700 (18%)	
Medium	32,010 (28%)	4870 (28%)		32,049 (27%)	5435 (26%)	
Large	59,320 (52%)	9150 (53%)		66,390 (55%)	11,945 (57%)	
Hospital status			0.09			0.1
Rural	7159 (6%)	1170 (7%)		7419 (6%)	1340 (6%)	
Urban nonteaching	23,429 (21%)	3330 (19%)		20,974 (17%)	3395 (16%)	
Urban teaching	82,819 (73%)	12,905 (74%)		92,390 (76%)	16,345 (78%)	

Table 2. Multivariable logistic regression evaluating length of stay and hospital charges

Outcome	No depression	Depression	Difference	
			Crude	Adjusted
Ulcerative colitis				
Mean length of stay (days) ± SE	5.1 ± 0.03	6.03 ± 0.12	0.8 ± 0.12*	0.75 ± 0.12*
Mean total charge ($) ± SE	50,553 ± 736	55,431 ± 1741	4877 ± 1729*	5693 ± 1871*
Crohn's disease				
Mean length of stay (days) ± SE	5.2 ± 0.04	6.2 ± 0.13	0.96 ± 0.13*	0.89 ± 0.14*
Mean total charge ($) ± SE	49,631 ± 707	55,560 ± 1531	5929 ± 1514*	7367 ± 1589*

*$P < 0.001$.

Table 3. Multivariable logistic regression evaluating primary outcomes between ulcerative colitis and Crohn's disease

Outcome	Ulcerative colitis	Crohn's disease	Difference	
			Crude	Adjusted
Mean length of stay (days) ± SE	6.1 ± 0.1	8.2 ± 0.2	2.01 ± 0.22*	2.03 ± 0.24*
Mean total charge ($) ± SE	63,036 ± 1125	77,654 ± 2734	14,618 ± 2861*	17,974 ± 3046*

*$P < 0.001$.

Table 4. Multivariable logistic regression evaluating associations of depression with ulcerative colitis and Crohn's disease

Total	Adjusted odds ratio	Confidence interval	*P* value
Ulcerative colitis	1.13	1.1–1.2	<0.001
Crohn's disease	1.04	1.01–1.1	0.03
Women			
Ulcerative colitis	1.24	1.22–1.3	<0.001
Crohn's disease	1.30	1.21–1.31	<0.001
Men			
Ulcerative colitis	0.88	0.8–0.91	<0.001
Crohn's disease	0.65	0.61–0.69	<0.001

reduced association with depression in the CD group ($P < 0.001$). Comparing CD with UC, patients with CD had an increased association with depression (aOR 1.14, 95% CI 1.09–1.20, $P < 0.001$).

DISCUSSION

This study was conducted to evaluate the effect of depression on LOS among patients with IBD. Patients with depression had a significantly longer LOS in UC and CD groups compared to patients without depression ($P < 0.001$). Depression and anxiety have been associated with prolonged hospital stays, as both conditions confound the diagnosis and lead to more extensive diagnostic testing.[11] Depression can also interfere with a patient's participation in rehabilitative and other measures, resulting in prolonged stay.[12,13] In our study, CD patients had a 2-day longer inpatient stay than UC patients, which may be due to an increased number of admissions for CD and an increased number of surgeries.[14]

UC and CD were associated with an increased risk of depression in our analysis. This association was more pronounced in women. Despite recent data suggesting the involvement of the brain-gut axis as a causative factor of depression in IBD, there is still poor understanding of the underlying mechanism of depression in this population.[15] Gut microbes and their metabolic products are altered in patients with IBD. This can lead to altered levels of tryptophan, a precursor to several vital bioactive metabolites, and the neurotransmitter serotonin, resulting in depression in these patients.[16] The pro-inflammatory state in IBD patients can cause activation of various inflammation-related processes, including platelet activation factor hyperactivity, oxidative stress, and cellular damage. These mechanisms can contribute to adverse neurobiological outcomes, supporting the prevalence of depression in the IBD population.[17] Psychological diagnoses cause increased visceral hypersensitization and magnified abdominal pain severity in adult IBD populations.[18] Suppression of anti-inflammatory mechanisms can lead to more severe disease flares. This has been demonstrated in animal models, where impaired inhibition of

proinflammatory cytokines by macrophages resulted in inflammation cascades induced by depression.[19] Kappelmann et al suggested a causal relationship between cytokines and depression in patients with chronic inflammatory states.[20]

Annual IBD-related costs in the US are approximately $6.3 billion, and inpatient stays make up 40% of the cost.[21] The mean annual cost of CD was previously reported to be higher than that of UC, $8265 and $5066, respectively. Patel et al reported increased costs in IBD admissions that involved depression in the pediatric population. However, these were nonweighted samples without statistical significance.[22] Our crude analysis supports that depression increases hospital costs. However, after adjusting for in-hospital confounders, the adjusted hospital charge was lower in IBD patients with depression ($P < 0.001$). We hypothesize that potential overlapping of depressive symptoms can be interpreted as IBD patients feeling worse, resulting in admission and close monitoring. This could explain the reduced inpatient costs of patients admitted with CD or UC who had a secondary diagnosis of depression. Conversely, patients without depression would not have as many confounding symptoms, resulting in a more accurate description of symptoms.[12]

Subanalysis in the depressed cohort revealed that patients with CD had increased hospital charges of $17,974 compared to UC patients. Patients with CD had a higher medical cost, especially for the initial diagnosis, than patients with UC.[23] Previous literature in the pediatric population reported that one large factor for the higher hospital costs in CD patients compared with UC patients was pharmaceutical claims.[21] The COIN study conducted in 2014 revealed that CD is associated with three times higher healthcare costs than UC due to anti–tumor necrosis factor-α use and less so by inpatient surgeries.[24]

Evidence suggests that symptom control in the IBD population can lead to psychological improvement. Adalimumab, etanercept, infliximab, and tocilizumab have been shown to improve depressive symptoms.[20] Many patients with IBD and depression do not visit mental health professionals or psychiatrists. This negatively affects IBD patients with untreated psychiatric diagnoses, resulting in reduced compliance with IBD treatment, worsening disease outcomes.[25] Inpatient psychiatric consults can positively impact these outcomes. However, only 12% of adult patient centers are equipped to provide the necessary psychiatric resources.[26] In our analysis, the number of psychiatric consults was low; therefore, an effect on hospital outcomes could not be seen. Davis et al reported improvement in psychological outcomes including depression, anxiety, and quality of life after treatment with cognitive-behavioral therapies, mindfulness-based stress reduction, and other nonpharmacological therapies.[27] Patients with IBD are on multiple medications and may often be resistant to pharmacological therapy, furthering the need for mindfulness techniques, relaxation, and cognitive reconstruction.[28]

There are several limitations to this study. The study identified cohorts retrospectively and cannot determine causality. Additionally, the study did not have randomization and blinding, which can impact the interpretation of results. NIS does not have data for pharmacological therapies, and their impact is unknown. The data extracted were based on ICD-10 codes, and misclassification may have occurred. Some confounding factors were not coded by ICD-10 and could not be added due to data limitations by NIS. Lastly, there is the potential for missing data in the NIS.

In conclusion, the chronic inflammatory state of the gut in IBD patients can alter patients' quality of life and is associated with depression. Poor mental health in IBD patients can negatively affect overall health. IBD patients tend to have a higher prevalence of depression than the general population. Depression can increase inpatient stays in the IBD population but does not increase hospital charges or mortality. There is a stronger association of depression in women with UC and CD compared to men. CD has a stronger association with depression than UC. Identifying and treating depression in the IBD population can improve quality of life and healthcare outcomes. Depression in IBD patients is undertreated, and vigilance is needed among gastroenterologists to raise awareness about depression among patients with IBD.

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