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Retrospective Study

Major depressive disorders in patients with inflammatory bowel disease and rheumatoid arthritis

Maryam Bilal Haider, Brinda Basida, Jasleen Kaur

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Various immune-mediated inflammatory diseases consisting of inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), are found to have a substantial societal burden, increased healthcare costs, and progressive disability. Studies suggest that patients with *vs* without comorbid depression have a more significant disability, a lower likelihood of remission, and reduced adherence to therapy. Elevated interleukin (IL)-1 β , tumor necrosis factor- α , and IL-6 contribute to developing depression by the impaired physiological responses to stress, resulting in increased pain, fever, fatigue, and lack thereof of interest, and thus poor long-term outcomes. This study emphasizes the timely recognition of the prevalence of major depressive disorder (MDD) in patients with RA and IBD combined, thus preventing disability.

AIM

To identify the prevalence level and temporal trends of depression in hospitalized IBD-RA patients.

METHODS

All adult hospitalized patients from January 2000 to December 2019 in the nationwide inpatient sample (NIS) were captured. The study population included all patients with a primary or secondary IBD-RA overlap disease using corresponding international classification of diseases (ICD)-9 and ICD-10 codes. IBD includes Crohn's disease and ulcerative colitis. The study population was divided into IBD-RA without MDD (controls) and IBD-RA with MDD (cases). For group

comparison between MDD *vs* no MDD, we used Student's *t*-test for continuous variables and Rao-Scott Chi-square tests for categorical variables. For univariate analyses, we used logistic regression, and for multivariate analysis, we used a weighted multi-level mixed-effects model. We attested all hypotheses with two-tailed significance level of 0.05 ($P < 0.05$ was considered significant). The outcome is to examine the temporal trends and prevalence of depression in patients with IBD-RA by gender, race, and age.

RESULTS

A total of 133315 records were identified with IBD-RA overlap, of which 26155 patients (19.62%) had MDD. Among the IBD-RA patients, those who had MDD were younger [mean age of 56 years (SD \pm 15)] to IBD-RA without MDD patients with a $P < 0.0001$, more females (80% among cases *vs* 73% among controls) than males with a $P < 0.0001$, frequent in the white race (79% among cases *vs* 73% among controls) than black race. Over the 19 years, the number of patients with MDD in IBD-RA increased from 153 (the year 2000) to 2880 (the year 2019) in weighted NIS, representing a 1782% increase compared to the year 2000 with a $P < 0.001$. Factors associated with higher MDD included younger age, female gender, white race, alcohol, opioids, esophageal disorders, peptic ulcer disease, chronic pancreatitis, paralysis, dementia, menopausal disorders, obesity, nutritional deficiencies, diabetes mellitus with chronic complications, and osteoarthritis.

CONCLUSION

There is a rise in the prevalence of depression in younger patients with IBD-RA combined compared to their counterparts. These patients are also at higher risk for the increased cost of care and poor treatment compliance. It is crucial to educate the involved clinicians to identify the early signs and symptoms of depression in patients with IBD or RA or IBD-RA combined and treat them to have a better overall prognosis.

Key Words: Inflammatory bowel disease; Rheumatoid arthritis; Depression; Multimorbidity; Epidemiology; Demographics

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Core Tip: Our study is a nationwide inpatient sample-based study of the two decades in which we aim to analyze inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) patients' characteristics, temporal trends, sociodemographic characteristics, and predictors of major depressive disorders in the IBD-RA cohort. There is an increasing trend in the prevalence of IBD-RA, especially in younger patients. We believe this study will open the door for further research and educate the involved physicians to identify the early signs and symptoms of depression in patients with IBD or RA or IBD-RA combined and treat them or have them treated to have a better overall prognosis.

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INTRODUCTION

The coexistence between immune-mediated inflammatory diseases (IMID) with depression has long been studied[1,2]. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that primarily targets the synovial joints leading to inflammation (synovitis), joint erosion, and damage to the cartilage [3]. Inflammatory bowel disease (IBD) is broadly subdivided into ulcerative colitis and Crohn's disease. Crohn's disease is a relapsing systemic immune-mediated chronic IBD, and Ulcerative colitis is an idiopathic, chronic IBD with bloody diarrhea[4].

The global prevalence of RA is estimated at 460 *per* 100000 population, while its prevalence in the United States is 700 *per* 100000 population[5,6]. Both depression and RA contribute substantially to global disability, and the diseases often coexist. The global prevalence rate of IBD is 84.3 *per* 100000 population, while that in the United States is 464.5 *per* 100000 population[7].

Patients with RA suffer twice from depression than the general population[8], with 41%-66% reported lifetime prevalence[1,3]. The prevalence of major depressive disorders (MDDs) was 17% in patients with RA[3]. IBD patients have more than 25% lifetime diagnosis of depression[9,10].

Not many studies have identified the impact of depression in patients with both RA and IBD combined. Our study is researched using the national inpatient sampling database sought to evaluate the co-existence of depression in patients with RA and IBD. The role of the Brain-Gut axis and Brain-Joint axis in the development of depression has been illustrated before[11,12], but there is not enough literature demonstrating the combined Brain-Gut-Joint axis. Our study discusses the clinical data on this combined axis and emphasizes potentially valuable strategies for managing these patients. Our primary aim was to identify a pooled prevalence level and temporal trends of depression in hospitalized IBD-RA patients. To have a multimorbidity approach, which is more patient-focused, we aimed to investigate various comorbidities as predictors of depression.

MATERIALS AND METHODS

We analyzed the nationwide inpatient sample (NIS) database from January 2000 to December 2019. The NIS is the largest all-payer publicly available database of hospitalizations in the United States, designed to produce national and regional inpatient utilization, cost, quality, and outcomes[13]. We used the international classification of diseases (ICD)-9, diagnosis and procedures before October 1, 2015, and ICD-10 afterward[14]. In this study, we used the latest available datasets. The NIS dataset is very suitable for temporal trends, but the dataset has undergone several changes over time. We used the Healthcare Cost and Utilization Project (HCUP) recommendation to use trend weights before 2012 to make estimates comparable to the 2012 NIS design[15]. The dataset was de-identified to protect the privacy of individual patients, physicians, and hospitals. As the dataset lacks patient information, this study was exempted from Institutional Review Board-IRB approval from Wayne State University under the Health Insurance Portability and Accountability Act[16].

The study population included patients with a primary or secondary IBD-RA overlap disease using corresponding ICD-9 and ICD-10 codes. For IBD, we included Crohn's disease and ulcerative colitis patients. We used the clinical classification software refined to determine the ICD codes of depressive disorders[17,18]. The study population was divided into IBD-RA without MDD (controls) and IBD-RA with MDD (cases).

Outcomes and variables

The outcomes included temporal trends and predictors of MDDs in the IBD-RA cohort. In the first part, we performed a trend analysis of weighted prevalence, the percentage change in prevalence compared to the year 2000, mean age, gender and ethnicity, length of stay, and total hospital charges. Next, we compared baseline patient and hospital characteristics and comorbidities between cases (IBD-RA with MDD) and controls (IBD-RA without MDD). We also evaluated predictors for MDD in IBD-RA patients.

Patient demographics included gender, age, ethnicity, socioeconomic status, and primary health insurance. Socioeconomic status was defined as the median household income in the patient's zip code and was divided into quartiles by year (2019): Less than \$47999, \$48000-\$60999, \$61000-\$81999, \$82000 or more). Hospitalization care costs were adjusted using the United States Bureau of Labor and Statistics' consumer price index[19]. In addition, we used NIS characterization for hospital factors. The complete list of comorbidities is shown in [Table 1](#).

Statistical analysis

The statistical analyses are performed in SAS software (SAS Institute Inc., Cary, NC, United States). The HCUP NIS database was redesigned beginning in 2012 to improve national estimates. We deployed HCUP recommendations for trend analysis and used survey sampling and analysis procedures for weighted analysis. Continuous variables such as age, total charges, and length of stay are represented with a mean \pm SD, and categorical variables are presented with frequency and computed percentages. For group comparison between MDD *vs* no MDD, we used Student's *t*-test for continuous variables and Rao-Scott Chi-square tests for categorical variables. We used the Cochran-Armitage trend test for categorical variables and poison regression with a log link for continuous variables for temporal trends analysis. The univariate analysis is performed with logistic regression. The multivariate analysis is achieved with a weighted multi-level mixed-effects model using the Glimmix procedure with maximum likelihood estimation and Gauss-Hermite quadrature likelihood approximation. We categorized age into five sub-categories *per* HCUP standard categories (< 18, 18-44, 45-64, 65-84, and \geq 85) for group-level comparison. The missing values are categorized as either missing or unknown. All hypothesis testing is performed with two-tailed significance level of 0.05 ($P < 0.05$ was considered significant).

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the study population with and without MDD are described in [Table 2](#).

Table 1 Comorbidities comparison in inflammatory bowel disease-rheumatoid arthritis overlap patients with and without major depressive disorders, national inpatient sample year 2000 to 2019

	IBD-RA without depressive disorders, weighted, n (%)	IBD-RA with depressive disorders, weighted, n (%)	P value
Liver disease, mild	6400 (5.97)	2130 (8.14)	< 0.0001 ^a
Liver disease, moderate to severe	786 (0.73)	230 (0.88)	0.2871 ^a
Peptic ulcer disease	1709 (1.59)	632 (2.41)	< 0.0001 ^a
Esophageal disorders	30712 (28.65)	10569 (40.40)	< 0.0001 ^a
Gastritis	3781 (3.52)	1124 (4.30)	0.0095 ^a
Diabetes mellitus with chronic complications	6367 (5.94)	2005 (7.66)	< 0.0001 ^a
Diabetes mellitus without chronic complications	14014 (13.07)	3533 (13.50)	0.4244 ^a
Hypertension	40782 (38.05)	10493 (40.12)	0.0080 ^a
Heart Failure	12798 (11.94)	2908 (11.11)	0.1176 ^a
Coronary artery disease	16644 (15.53)	3549 (13.57)	0.0007 ^a
Cardiac dysrhythmias	16114 (15.04)	3299 (12.61)	< 0.0001 ^a
Myocardial infarction	1316 (1.23)	224 (0.86)	0.0237 ^a
Stroke	1530 (1.42)	230 (0.88)	0.0018 ^a
Iron Deficiency Anemia	9298 (8.68)	2296 (8.78)	0.8167 ^a
Nutritional deficiencies	4062 (3.79)	1494 (5.71)	< 0.0001 ^a
Lipid Metabolism disorders	24990 (23.32)	7036 (26.90)	< 0.0001 ^a
Thyroid disorders	18029 (16.82)	5531 (21.15)	< 0.0001 ^a
Chronic Pancreatitis	1165 (1.09)	507 (1.94)	< 0.0001 ^a
Renal failure, moderate	8563 (7.99)	2132 (8.15)	0.7113 ^a
Renal failure, severe	2965 (2.77)	767 (2.93)	0.5434 ^a
Menopausal disorders	536 (0.50)	222 (0.84)	0.0033 ^a
Osteoporosis	11752 (10.97)	3544 (13.55)	< 0.0001 ^a
Osteoarthritis	15084 (14.07)	4562 (17.44)	< 0.0001 ^a
Obesity	11706 (10.92)	4062 (15.53)	<.0001 ¹
Weight Loss	1201 (1.12)	365 (1.39)	0.1101 ^a
Protein-calorie malnutrition	8479 (7.91)	2370 (9.06)	0.0085 ^a
Leukemia	558 (0.52)	134 (0.51)	0.9401 ^a
Lymphoma	838 (0.78)	181 (0.69)	0.5132 ^a
Metastatic cancer	1381 (1.29)	329 (1.26)	0.8524 ^a
Solid tumor without metastasis, malignant	3785 (2.84)	850 (0.64)	0.8524 ^a
Paralysis	1498 (1.40)	495 (1.89)	0.0114 ^a
Dementia	2291 (2.14)	886 (3.39)	< 0.0001 ^a
AIDS	212 (0.19)	45 (0.17)	0.6818 ^a
Smoking	32336 (30.17)	9893 (37.82)	< 0.0001 ^a
Alcohol	1747 (1.63)	950 (3.63)	< 0.0001 ^a
Opioids	3180 (2.97)	1797 (6.87)	< 0.0001 ^a

^aRao-Scott Chi-Square 2-tailed Test for the association of two Categorical Variables.

IBD-RA: Inflammatory bowel disease-rheumatoid arthritis; AIDS: Acquired immunodeficiency syndrome.

From January 2000 to December 2019, we found 133315 IBD-RA overlap patients in weighted settings, of which 26155 patients (19.62%) had MDD. Among the IBD-RA patients, those who had MDD were younger [mean age of 56 years (SD \pm 15) as compared to mean age of 59 years (SD \pm 17)] in IBD-RA without MDD patients with $P < 0.0001$, more females (80% among cases *vs* 73% among controls) than males (20% for cases *vs* 17% for controls) with $P < 0.0001$, frequent in the white race (79% among cases *vs* 73% among controls) than black race (7% for cases *vs* 10% for controls) and Hispanic (4.00% among cases *vs* 4.63% among controls) with $P < 0.0001$, and more frequent in patients with Medicaid (12% among cases *vs* 9% among controls) than patients with private insurance (28% among cases *vs* 31% among controls) $P < 0.0001$. A comparison of comorbidities of the study population with and without MDD is described in [Table 1](#).

Temporal trends

Over the 19 years, the number of patients with MDD in IBD-RA increased from 153 (the year 2000) to 2880 (the year 2019) in weighted NIS ([Figure 1](#)), representing a 1782% increase ([Figure 2](#)) compared to the year 2000 with $P < 0.001$. The mean age of IBD-RA in MDD patients was 56.36 years in 2000 compared with 59.8 years in 2019, with a $P < 0.001$ ([Figure 3A](#)). There was no significant change in the male *vs* female trend of MDD in the IBD-RA cohort ([Figure 3B](#)). Overall, the white race among IBD-RA with MDD is 78.80%. We observed a decreasing trend in the white race with $P = 0.03$. The black race is 7.07%, and no change is followed over time. The Hispanic ethnicity is 3.99%, and we noted an increasing trend with $P = 0.02$ ([Figure 3C](#)). In terms of hospital burden, the mean length of stay of IBD-RA with MDD patients decreased from 5.69 d in 2000 to 5.35 d in 2019 with a $P < 0.001$ ([Figure 3D](#)), and the mean total cost of care (inflation-adjusted) increased from \$20564 in 2000 to \$60428 in 2019 with $P < 0.001$ ([Figure 3E](#)).

Predictors for MDDs

The univariate and multivariate analyses for IBD-RA patients with MDD are shown in [Table 3](#). The multivariate analyses showed that demographic factors associated with higher MDD included female gender [adjusted odds ratios (aOR): 1.52; 95%CI: 1.46-1.58; $P < 0.0001$], patients aged 18-44 (aOR: 1.89; 95%CI: 1.79-1.99; $P < 0.0001$) and patients aged 45-64 (aOR: 1.69; 95%CI: 1.63-1.76; $P < 0.0001$) as compared to the reference group (patients aged 65-84), white (aOR: 1.83; 95%CI: 1.73-1.94; $P < 0.0001$) and Hispanic race (aOR: 1.39; 95%CI: 1.27-1.52; $P < 0.0001$) as compared to the black race, and median socioeconomic status in the second quartile (aOR: 1.07; 95%CI: 1.03-1.12; $P = 0.002$) as compared to quartile 1.

Comorbidities associated with higher MDD in IBD-RA patients included alcohol (aOR: 2.11; 95%CI: 1.93-2.31; $P < 0.0001$), opioids (aOR: 2.00; 95%CI: 1.83-2.15; $P < 0.0001$), smoking (aOR: 1.23; 95%CI: 1.19-1.27; $P < 0.0001$), esophageal disorders (aOR: 1.53; 95%CI: 1.48-1.58; $P < 0.0001$), peptic ulcer disease (PUD) (aOR: 1.26; 95%CI: 1.13-1.39; $P < 0.0001$), chronic pancreatitis (aOR: 1.36; 95%CI: 1.21-1.53; $P < 0.0001$), mild liver disease (aOR: 1.16; 95%CI: 1.09-1.23; $P < 0.0001$), gastritis (aOR: 1.10; 95%CI: 1.09-1.18; $P = 0.02$), paralysis (aOR: 1.48; 95%CI: 1.32-1.66; $P < 0.0001$), dementia (aOR: 2.08; 95%CI: 1.91-2.27; $P < 0.0001$), menopausal disorders (aOR: 1.43; 95%CI: 1.21-1.70; $P < 0.0001$), obesity (aOR: 1.29; 95%CI: 1.18-1.28; $P < 0.0001$), nutritional deficiencies (aOR: 1.28; 95%CI: 1.20-1.37; $P < 0.0001$), weight loss (aOR: 1.21; 95%CI: 1.07-1.38; $P < 0.0001$), protein-calorie malnutrition (aOR: 1.10; 95%CI: 1.05-1.16; $P = 0.0002$), thyroid disorders (aOR: 1.25; 95%CI: 1.20-1.30; $P < 0.0001$), osteoarthritis (aOR: 1.22; 95%CI: 1.17-1.27; $P < 0.0001$), osteoporosis (aOR: 1.21; 95%CI: 1.16-1.27; $P < 0.0001$), diabetes mellitus with chronic complications (aOR: 1.20; 95%CI: 1.13-1.28; $P < 0.0001$), lipid metabolism disorders (aOR: 1.19; 95%CI: 1.15-1.24; $P < 0.0001$), and severe renal failure (aOR: 1.12; 95%CI: 1.02-1.23; $P < 0.0001$).

DISCUSSION

Various studies have been done in the past, which show a higher rate of depression in patients with IMIDs like RA and IBD than in the general population[20,21]. Patients with coexisting IMID and depression tend to have higher disease activity[1], more fatigue[22], distressing symptoms of pain[23], lower health-related quality of life, and increasing health care costs[24] than patients without depression [1]. Depression as a comorbidity negatively impacts IMID patients' physical function, mental health, symptom severity, overall morbidity, and mortality[24].

RA is an autoimmune-mediated disease leading to joint destruction, directed mainly by the action of T cells and inflammatory cytokines[3,22]. There is a lack of complete understanding of the biological mechanism responsible for this association of depression with these autoimmune inflammatory disorders. It is mainly attributed to chronic inflammation caused by elevated cytokines like interleukin (IL)-1 β , tumor necrosis factor- α , and IL-6. These cytokines decrease neurogenesis and influence the

Table 2 Comparison of Patients' demographics and hospital Characteristics of inflammatory bowel disease-rheumatoid arthritis overlap patients with and without depressive disorders, national inpatient sample year 2000 to 2019

	IBD-RA without MDD, weighted, <i>n</i> (%)	IBD-RA with MDD, weighted, <i>n</i> (%)	<i>P</i> value
Weighted total, <i>n</i> (%)	107160 (80.38)	26155 (19.62)	
Sex			< 0.0001 ^a
Female	78088 (72.87)	21052 (80.49)	
Male	29073 (27.13)	5103 (19.51)	
Age (yr), mean ± SD	58.70 ± 16.89	56.36 ± 15.47	< 0.0001 ^b
Age groups (yr)			< 0.0001 ^c
< 18	319 (0.29)	25 (0.10)	
18-44	22215 (20.73)	5887 (22.50)	
45-64	40363 (37.67)	11544 (44.14)	
65-84	39111 (36.50)	7902 (30.21)	
≥ 85	5152 (4.81)	798 (3.05)	
Ethnicity			< 0.0001 ^c
White	77818 (72.62)	20612 (78.80)	
Black	10543 (9.83)	1850 (7.07)	
Hispanic	4963 (4.63)	1045 (3.99)	
Asian or Pacific Islander	741 (0.69)	94 (0.36)	
Native American	500 (0.47)	91 (0.35)	
Other	12596 (11.75)	2464 (9.42)	
Primary payer status			< 0.0001 ^c
Medicare	59738 (55.75)	14522 (55.52)	
Medicaid	10128 (9.45)	3257 (12.45)	
Private	32808 (30.62)	7239 (27.68)	
Self-Pay	2034 (1.89)	505 (1.93)	
No charge	186 (0.17)	40 (0.15)	
Other	2266 (2.11)	592 (2.26)	
Median socioeconomic status by national quartiles			0.0008 ^c
0-25	24484 (22.85)	6111 (23.37)	
25-50	26531 (24.75)	6690 (25.58)	
50-75	27857 (26.00)	7171 (27.42)	
75-100	26431 (24.66)	5876 (22.46)	
Other	1857 (1.73)	307 (1.17)	
Hospital bed size			0.0147 ^c
Small	16789 (15.67)	4496 (17.19)	
Medium	28359 (26.46)	7067 (27.02)	
Large	62012 (57.87)	14592 (55.79)	
Location/teaching status of the hospital			< 0.0001 ^c
Rural	10398 (9.70)	2299 (8.79)	
Urban nonteaching	36576 (34.13)	7801 (29.83)	
Urban teaching	60186 (56.17)	16055 (61.38)	

Hospital region			< 0.0001 ^c
Northeast	21819 (20.36)	4601 (17.59)	
Midwest or North Central	27596 (25.75)	7636 (29.19)	
South	40204 (37.52)	9583 (36.64)	
West	17541 (16.36)	4335 (16.57)	
Discharge outcomes			
Routine Discharge	69143 (64.52)	16289 (62.28)	< 0.0031 ^a
Transfer to Short-term Hospital	2240 (2.09)	475 (1.82)	0.2013 ^a
Transfer to other facilities	16349 (15.26)	4612 (17.63)	< 0.0001 ^a
HHC	17635 (16.45)	4536 (17.34)	0.1373 ^a
In-hospital mortality	1792 (1.67%)	243 (0.93%)	< 0.0001 ^a
Length of stay (days), mean \pm SD	5.49 \pm 5.75	5.65 \pm 5.79	0.0738 ^a
Total charges (USD), mean \pm SD	43881 \pm 61300	45157 \pm 60859	0.1762 ^a

^aTwo-sample Student *t*-test, 2-tailed for comparing means of two Continuous Variables.

^bRao-Scott Chi-Square 2-tailed Test for the association of two Categorical Variables.

^cRao-Scott Chi-square, 2-tailed Test for two by *n* table. Statistical significance illustrates that the two groups differ.

IBD-RA: Inflammatory bowel disease-rheumatoid arthritis; HHC: Home health care.

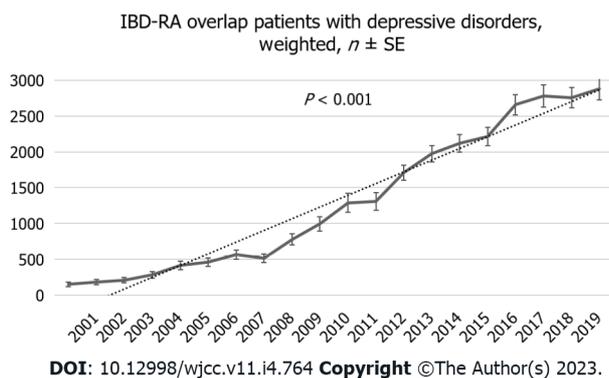


Figure 1 Weighted trend of inflammatory bowel disease-rheumatoid arthritis overlap patients with major depressive disorders, national inpatient sample year 2000 to 2019. IBD-RA: Inflammatory bowel disease-rheumatoid arthritis.

homeostasis of the neurotransmission axis, like glutamate-dependent pathways, monoaminergic pathways, and the hypothalamic-pituitary-adrenal (HPA) axis[8]. Hence, these factors contribute to the development of depression by the impaired physiological responses to stress, resulting in increased pain, fever, fatigue, lack of interest, and thus poor long-term outcomes[3].

Due to the bidirectional communication *via* the gut-brain axis, reduced social functioning, and impaired quality of life, patients with IBD have increased rates of psychiatric disorders as compared to the general population. Walker *et al*[10] demonstrated that individuals with IBD have more than double the lifetime prevalence of MDD compared to the general population[10]. Marrie *et al*[25] showed that the incidence and prevalence of depression, anxiety, and bipolar disorders are elevated in RA patients compared to a matched population[25]. The prevalence of depression in patients with RA is approximately 19%, with conservative estimates, most common in females and younger age groups[5]. In our study, the prevalence of depression in the IBD-RA cohort is approximately 20%, females have 50% more odds of depression than males, and younger patients have higher odds of depression (patients aged 18-44 have 88% higher odds of depression than patients aged 65-84 years). We noted an increasing trend of MDD in the IBD-RA cohort (Figure 1) and an increasing trend in the mean age (Figure 3A). We also exhibited a growing trend in hospital charges (Figure 3E) with a decreasing trend in the length of stay (Figure 3D).

Pezzato *et al*[26] assessed 490 Italian patients with RA and found that depression was more frequent in females and unemployed patients[26]. In our study, patients with private insurance have lower odds of depression than patients with Medicare. Physicians should be aware that women and those of lower socioeconomic status are at increased risk of these disorders.

Table 3 Univariate and multivariate analyses of demographics and comorbidities associated with major depressive disorders in the inflammatory bowel disease-rheumatoid arthritis cohort, national inpatient sample year 2000 to 2019

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted odds ratio ¹ (95%CI)	P value	Adjusted odds ratio ² (95%CI)	P value
Gender, Female vs Male	1.533 (1.424–1.651)	< 0.0001	1.518 (1.463–1.575)	< 0.0001
Age groups (yr)				
< 18	0.380 (0.153–0.944)	0.0371	0.793 (0.523–1.203)	0.2842
18–44	1.320 (1.214–1.434)	< 0.0001	1.888 (1.790–1.991)	< 0.0001
45–64	1.418 (1.321–1.521)	< 0.0001	1.693 (1.625–1.764)	< 0.0001
65–84	Reference	NA	Reference	NA
≥ 85	0.773 (0.649–0.920)	0.0037	0.749 (0.688–0.814)	< 0.0001
Race				
White	1.500 (1.338–1.682)	< 0.0001	1.830 (1.728–1.939)	< 0.0001
Black	Reference	NA	Reference	NA
Hispanic	1.193 (0.993–1.434)	0.0598	1.391 (1.272–1.521)	< 0.0001
Asian or Pacific Islander	0.720 (0.441–1.174)	0.1876	0.856 (0.679–1.078)	0.1876
Native American	1.029 (0.616–1.720)	0.9120	0.937 (0.733–1.198)	0.6120
Other	1.109 (0.959–1.282)	0.1627	1.456 (1.351–1.568)	< 0.0001
Primary payer status				
Medicare	Reference	NA	Reference	NA
Medicaid	1.327 (1.205–1.462)	< 0.0001	1.043 (0.99–1.10)	0.1148
Private	0.911 (0.850–0.977)	0.0085	0.774 (0.744–0.805)	< 0.0001
Self-Pay	1.035 (0.831–1.289)	0.7616	0.892 (0.800–0.994)	0.0382
No charge	0.853 (0.398–1.827)	0.6825	0.698 (0.485–1.005)	0.0555
Other	1.069 (0.871–1.311)	0.5255	0.974 (0.88–1.077)	0.5930
Median socioeconomic status by national quartiles				
0–25	Reference	NA	Reference	NA
25–50	1.006 (0.923–1.097)	0.8836	1.031 (0.988–1.075)	0.1595
50–75	1.026 (0.943–1.117)	0.5455	1.071 (1.025–1.118)	0.0019
75–100	0.890 (0.814–0.972)	0.0095	0.998 (0.952–1.045)	0.9323
Other	0.664 (0.505–0.873)	0.0034	0.697 (0.61–0.795)	< 0.0001
Hospital bed size				
Small	Reference	NA	Reference	NA
Medium	1.061 (0.967–1.164)	0.2109	0.956 (0.913–1.002)	0.0585
Large	0.936 (0.873–1.005)	0.0669	0.926 (0.888–0.966)	0.0004
Location/teaching status of the hospital				
Rural	Reference	NA	Reference	NA
Urban nonteaching	1.028 (0.917–1.152)	0.6376	0.994 (0.938–1.054)	0.8450
Urban teaching	1.253 (1.172–1.339)	< 0.0001	1.235 (1.168–1.306)	< 0.0001
Hospital region				
Northeast	Reference	NA	Reference	NA
Midwest or North Central	1.312 (1.199–1.437)	< 0.0001	1.223 (1.162–1.286)	< 0.0001

South	1.124 (1.031-1.225)	0.0078	1.083 (1.032-1.137)	0.0015
West	1.179 (1.065-1.306)	0.0015	1.148 (1.085-1.213)	< 0.0001
Comorbidities				
Liver disease, mild	1.401 (1.251-1.569)	< 0.0001	1.156 (1.091-1.224)	< 0.0001
Liver disease, moderate to severe	1.206 (0.867-1.677)	0.2655	0.976 (0.827-1.152)	0.7708
Peptic ulcer disease	1.532 (1.247-1.881)	< 0.0001	1.254 (1.133-1.387)	< 0.0001
Esophageal disorders	1.684 (1.582-1.792)	< 0.0001	1.528 (1.481-1.576)	< 0.0001
Gastritis	1.236 (1.063-1.436)	0.0059	1.096 (1.018-1.18)	0.0145
Diabetes mellitus with chronic complications	1.326 (1.181-1.489)	< 0.0001	1.201 (1.131-1.274)	< 0.0001
Diabetes mellitus without chronic complications	1.033 (0.946-1.128)	0.4688	1.064 (1.018-1.113)	0.0059
Hypertension	1.082 (1.018-1.151)	0.0115	1.091 (1.055-1.128)	< 0.0001
Heart Failure	0.922 (0.839-1.014)	0.0943	1.005 (0.955-1.058)	0.8505
Coronary artery disease	0.858 (0.787-0.936)	0.0005	0.901 (0.861-0.944)	< 0.0001
Cardiac dysrhythmias	0.811 (0.742-0.887)	< 0.0001	0.884 (0.844-0.925)	< 0.0001
Myocardial infarction	0.703 (0.512-0.965)	0.0295	0.684 (0.587-0.797)	< 0.0001
Stroke	0.604 (0.443-0.825)	0.0015	0.564 (0.484-0.656)	< 0.0001
Iron Deficiency Anemia	1.009 (0.908-1.122)	0.8635	1.017 (0.966-1.071)	0.5143
Nutritional deficiencies	1.539 (1.344-1.762)	< 0.0001	1.282 (1.199-1.37)	< 0.0001
Lipid Metabolism disorders	1.210 (1.130-1.296)	< 0.0001	1.192 (1.15-1.237)	< 0.0001
Thyroid disorders	1.327 (1.231-1.430)	< 0.0001	1.247 (1.201-1.295)	< 0.0001
Chronic Pancreatitis	1.788 (1.415-2.259)	< 0.0001	1.356 (1.207-1.524)	< 0.0001
Renal failure, moderate	1.026 (0.919-1.145)	0.6530	1.04 (0.981-1.102)	0.1839
Renal failure, severe	1.072 (0.897-1.282)	0.4445	1.117 (1.02-1.223)	0.0172
Menopausal disorders	1.716 (1.211-2.432)	0.0024	1.433 (1.206-1.702)	< 0.0001
Osteoporosis	1.280 (1.171-1.399)	< 0.0001	1.21 (1.157-1.265)	< 0.0001
Osteoarthritis	1.287 (1.187-1.395)	< 0.0001	1.215 (1.167-1.264)	< 0.0001
Obesity	1.500 (1.377-1.635)	< 0.0001	1.228 (1.176-1.283)	< 0.0001
Weight Loss	1.253 (0.964-1.628)	0.0913	1.212 (1.067-1.378)	0.0032
Protein-calorie malnutrition	1.162 (1.045-1.291)	0.0054	1.103 (1.047-1.162)	0.0002
Leukemia	0.980 (0.643-1.492)	0.9237	1.05 (0.856-1.288)	0.6351
Lymphoma	0.875 (0.610-1.255)	0.4685	1.014 (0.852-1.207)	0.8744
Metastatic cancer	0.975 (0.744-1.277)	0.8532	1.095 (0.948-1.265)	0.2168
Solid tumor without metastasis, malignant	0.917 (0.775-1.085)	0.3140	0.944 (0.863-1.034)	0.2131
Paralysis	1.391 (1.110-1.744)	0.0042	1.48 (1.32-1.659)	< 0.0001
Dementia	1.601 (1.344-1.908)	< 0.0001	2.082 (1.906-2.274)	< 0.0001
AIDS	0.866 (0.422-1.776)	0.6938	0.826 (0.58-1.178)	0.2847
Smoking	1.410 (1.325-1.502)	< 0.0001	1.231 (1.193-1.271)	< 0.0001
Alcohol	2.296 (1.922-2.743)	< 0.0001	2.109 (1.927-2.308)	< 0.0001
Opioids	2.430 (2.128-2.774)	< 0.0001	2.009 (1.882-2.145)	< 0.0001

¹Univariate analysis is performed with logistic regression.²Multivariate analysis is performed with weighted multi-level mixed effect models.

NA: No application; AIDS: Acquired immunodeficiency syndrome.

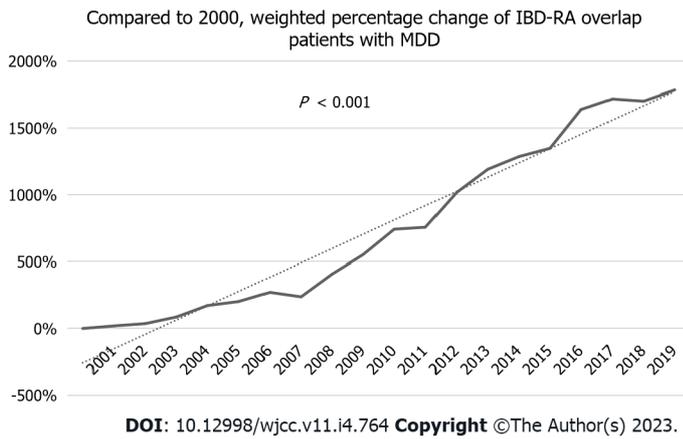


Figure 2 Percentage change of inflammatory bowel disease-rheumatoid arthritis overlap patients with major depressive disorder, compared to baseline 2000, national inpatient sample year 2000 to 2019. MDD: Major depressive disorder; IBD-RA: Inflammatory bowel disease-rheumatoid arthritis.

Multimorbidity, defined as the coexistence of multiple health conditions, is a growing public health challenge[27]. EULAR considers comorbidities like cardiovascular diseases, malignancy, osteoporosis, infection, and depression in rheumatic diseases[28]. Depression screening may be a valuable tool for interventions to improve health-related quality of life in individuals with IMIDs. In our study, various comorbidities are independently linked with depression.

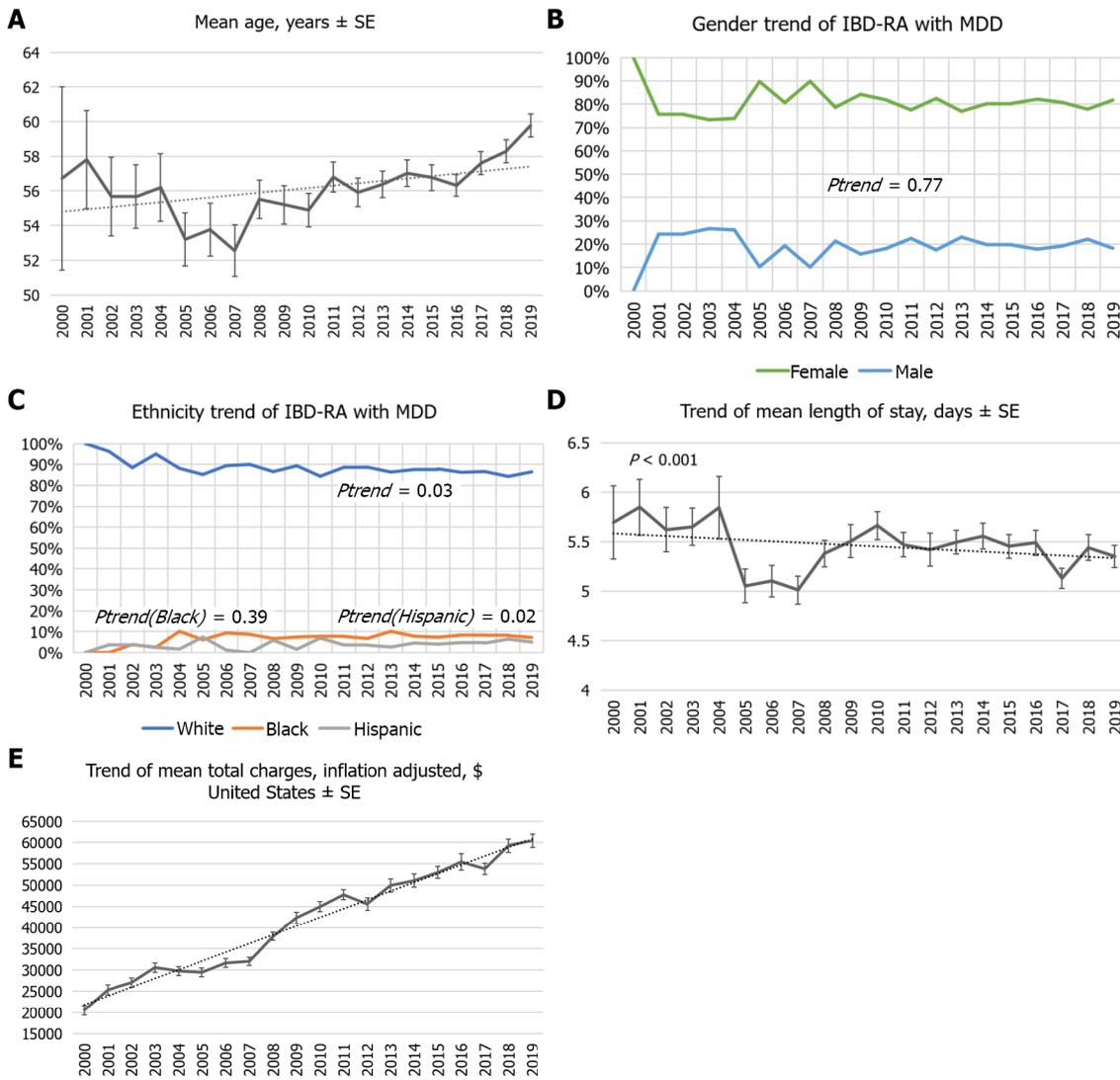
GI diseases are closely linked with depression, possibly due to the gut-brain axis. A literature review showed a positive correlation between the severity of reflux esophagitis with depression[29]. In our study, patients with esophageal disorders are at 1.5 times increased risk of MDDs. Kim *et al*[30] demonstrated that patients with PUD have 1.47 times higher odds of depression. Alkhayyat *et al*[31] showed that chronic pancreatitis patients are at an increased risk of depression than those without it. Our study showed a 1.3 times increase in risk with chronic pancreatitis and 1.2 times with PUD. Kim *et al*[30] mentioned the bidirectional relationship between PUD and depression, as depression causes consistent activation of the HPA axis, leading to immune dysfunction and elevating the risk of PUD. Conversely, PUD increases the risk of depression by increasing neuropeptide expression of substance P and its receptors.

Among the elderly, malnourished subjects were 31% more likely to have symptoms of depression than those with normal nutritional status[32,33]. Our results showed that nutritional deficiencies are 1.3 times higher in the depression cohort. There is growing evidence of the crucial necessity of neuron membrane cholesterol in the organization and function of the 5-HT_{1A} serotonin receptor. Hence, low cholesterol level is associated with depression and suicidality[34]. Our study also found lipid metabolism disorders as an independent predictor of depression.

In our study, severe renal failure is an independent predictor of depression in IBD-RA subjects. The literature review showed that about one-quarter of dialysis patients suffer from a MDD. Medications reduced physical function, and dietary restrictions are the main contributing factors[35]. The prevalence of depression in chronic kidney disease (CKD) stage 5 was 39 times higher than in CKD stages 1-5[36].

Depression has also been associated with elevated pain and enhanced functional disability in patients with osteoarthritis. Depression affects the HPA axis by altering the release of hypothalamic corticotropin-releasing hormone, increasing its levels in the cerebrospinal fluid and changing the set point threshold for negative feedback, which results in hypercortisolism and thus increased bone loss[37]. Stubbs *et al*[38] meta-analysis showed that patients with depression had lower bone mass than controls [38]. Our study showed 1.2 times higher odds of having depression with both osteoporosis and osteoarthritis. Our study results agree with Stubbs *et al*[38] findings that showed a 1.17% relative risk of depression in osteoarthritis patients compared with the non-osteoarthritis group[38].

Obesity at baseline increased the risk of the onset of depression at follow-up. However, depression increased the odds of developing obesity (OR: 1.58; 95%CI: 1.33-1.87; $P < 0.001$)[39]. Our study also exhibited increased odds of depression with obesity (aOR: 1.29; 95%CI: 1.18-1.28; $P < 0.0001$). Interestingly, our study also increased the odds of depression with weight loss (aOR: 1.21; 95%CI: 1.07-1.38; $P < 0.0001$). Dietary effects on mental health can be explained by the anti-inflammatory effect (*i.e.*, omega-3 polyunsaturated fatty acids), antioxidant effect (anthocyanins, *etc.*), or functional modulation (group B vitamins, L-ornithine, tryptophan amino acids, glycine, *etc.*)[40,41]. A National Health and Nutrition Examination Survey study reported that using even a single unhealthy weight-loss strategy was significantly linked with depression[42]. In our study, the odds of depression are 28% higher in patients with nutritional deficiencies.



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Figure 3 Inflammatory bowel disease-rheumatoid arthritis overlap patients identified with depressive disorders, national inpatient sample year 2000 to 2019. A: Trend of mean age (years) inflammatory bowel disease-rheumatoid arthritis (IBD-RA) overlap patients identified with depressive disorders; B: Trend of male and female (percentages) of IBD-RA overlap patients identified with depressive disorders; C: Trend of ethnicity (percentages) of IBD-RA overlap patients identified with depressive disorders; D: Mean hospital stay (days) of IBD-RA overlap patients with depressive disorders; E: Mean total cost of care (the United States\$) of IBD-RA overlap patients with depressive disorders. IBD-RA: Inflammatory bowel disease-rheumatoid arthritis.

Depression can be both a risk factor and a prodrome for dementia. Amongst all the proposed mechanisms, trophic, inflammatory, and cerebrovascular factors may contribute, along-with monoamine deficiency and severity of plaques and tangle pathology[43]. In a meta-analysis that included 5897 subjects with dementia from 20 studies, the prevalence rates of depression in mild, moderate, and severe dementia were 38%, 41%, and 37%, respectively[44]. In our study, patients with dementia have two times increased likelihood of depression.

Nearly one-third of patients with MDD also have substance use disorders. It yields a higher risk of suicide and greater social and personal impairment[45]. Alcohol use disorder is notable in our society (lifetime prevalence of 29.1%) and is associated with MDD[46]. We also found alcohol an independent predictor of depression in patients with RA-IBD. Other Substance abuses include nicotine; its withdrawal is known to cause a marked increase in negative affect among smokers in the general population[47]. A group of cross-sectional studies showed that current smokers were more depressed than never-smokers and former smokers[48]. In our study, smoking is independently associated with 1.2 times higher odds of depression. Similarly, the literature review showed that opioids were associated with higher odds of new-onset major depressive symptoms without baseline symptoms of MDD[49]. These findings correspond with our results that showed opioid use doubled the risk of depression in the IBD-RA group.

Another vital study finding includes thyroid disorders as an independent predictor of depression. A literature search showed depression is associated with a functional interruption of the hypothalamus,

causing dysregulation of the hippocampal inhibitory glucocorticoid feedback pathway to the hypothalamus. This results in increased cortisol levels and impaired dexamethasone suppression. A similar situation exists with the thyroid axis. An increased T4 and blunted thyrotropin response to exogenous thyrotropin-releasing hormone (TRH) in depression. This is due to the glucocorticoid activation of the TRH neuron that increases TRH secretion and down-regulates the TRH receptor on the thyrotrope [50,51]. In our study, patients with lipid disorders have an increased likelihood of depression. It correlates with a meta-analysis Wei *et al* [52] that showed that hyperlipidemia patients have 1.7 times more odds of MDD than the general population [52].

Strengths and limitations

To our best knowledge, this is the first large study performed in the United States, analyzing twenty years of inpatient sample data ($n = 26155$) of patients with depression affected by RA and IBD. This study's biggest strength is identifying the prevalence of depression among patients with dual autoimmune diseases and a motivation to incorporate such values of depression screening in outpatient clinics. Our analysis also recommends the possibility of a Rheumatology-Gastroenterology Comorbidity clinic initiative, which could identify various comorbidities like depression and substance use disorder among IMID patients. This is an area that requires more attention. Most rheumatologists and gastroenterologists do not routinely screen their RA patients for depression which was evident during the verbal surveys taken at the various conferences. It could be related to time limitations, inadequate psychiatry referral services, lack of training, or even lack of confidence in managing mental health problems. A simple Patient Health Questionnaire (PHQ-2) or PHQ-9 questionnaire can be incorporated into the clinic outflow, especially at the onset of the diagnosis. Such efforts are pivotal in identifying depression in our patients, ensuring patient-mental health support system interrelation, and hence normalizing the discussion around their mental health. This study's biggest strength is identifying the prevalence of depression among patients with dual autoimmune diseases and a motivation to incorporate such values in our outpatient clinics. This is pivotal for healthcare delivery systems and economies in the global context of treating chronic diseases like RA and IBD, especially in the era of the coronavirus disease 2019 pandemic as we understand that the standard care for these conditions, particularly immunomodulators, is extremely costly.

This study has several limitations using the NIS dataset, including the inability to access laboratory values, treatment options, and testing conditions, including colonoscopy findings and severity of IBD based on histology. We intended to investigate the prevalence of IMIDs and depression; it's challenging to know the clinical correlates of depression regarding RA/IBD disease activity and disability. This study is performed on the inpatient population. However, IBD/RA and MDD are outpatient diagnoses except for IBD flare-ups. Individuals with fibromyalgia, connective tissue diseases (Sjogren, scleroderma, dermatomyositis, polymyositis), vasculitis, gout, infective arthritis, polymyalgia rheumatica, or other IBDs were excluded or not chosen as comorbidity which could also be a reason for depressive symptoms. However, these ailments were not selected as they have been known from previous studies, and other co-morbidities mentioned in our research could be highlighted. NIS entry is equivalent to one hospitalization. If a patient is admitted more than once, one patient may contribute multiple entries. Finally, inherent database limitations include a lack of disease process-specific variables and coding errors without formal validation.

CONCLUSION

This study offers the opportunity to increase our knowledge of the various comorbidities by investigating depression and its clinical correlates as part of the routine clinical monitoring in the outpatient clinic setting and, hence, a multimorbidity approach that is more patient-focused. There is an inevitable rise in the prevalence of depression in younger patients with IBD-RA combined autoimmune disease compared to their counterparts. These patients are also at higher risk of the increased cost of care, disability, and poor treatment adherence. It is crucial to educate the involved physicians to identify the early signs and symptoms of depression in patients with IBD or RA or IBD-RA combined and treat them or have them treated to have a better overall prognosis. As physicians, we can play an important role as part of social determinants of health by giving good quality of care. Timely recognition of depression in these patients is critical to preventing disability.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), are found to have a substantial societal burden, increased healthcare costs, and progressive disability. Studies suggest that patients with *vs* without depression have a more significant disability, a lower likelihood of remission, and reduced

adherence to therapy.

Research motivation

The role of the Brain-Gut axis and Brain-Joint axis in the development of depression has been discussed, but there is not enough literature demonstrating the combined Brain-Gut-Joint axis.

Research objectives

Our primary aim is to identify a pooled prevalence level and temporal trends of depression in hospitalized IBD-RA patients. We aimed to investigate clinical factors associated with depression in these patients.

Research methods

All adult hospitalized patients from January 2000 to December 2019 in the nationwide inpatient sample were captured. The study population included all patients with a primary or secondary IBD-RA overlap disease using corresponding international classification of diseases (ICD)-9 and ICD-10 codes.

Research results

Other factors associated with higher major depressive disorder included younger age, female gender, white race, alcohol, opioids, esophageal disorders, peptic ulcer disease, chronic pancreatitis, paralysis, dementia, menopausal disorders, obesity, nutritional deficiencies, diabetes mellitus with chronic complications, and osteoarthritis.

Research conclusions

There is an inevitable rise in the prevalence of depression in younger patients with IBD-RA combined autoimmune diseases. As physicians, we can play an important role in social determinants of health by giving good quality care. Timely recognition of depression in these patients is critical to preventing disability.

Research perspectives

Our study discusses the clinical data on this combined axis and emphasizes potentially valuable strategies for managing these patients. This study will open the door for further research and educate the involved physicians to identify the early signs and symptoms of depression in patients with IBD or RA or IBD-RA combined and treat them or have them treated to have a better overall prognosis.

FOOTNOTES

Author contributions: Haider MB, Basida B and Kaur J contributed equally to this work; Haider MB and Kaur J designed the research study; Kaur J and Basida B performed the research; Haider MB analyzed the data; Haider MB, Basida B and Kaur J wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: Data from this study used de-identified data from the National Inpatient Sample Database (NIS) 2000-2019. A publicly available all-payer inpatient care database in the United States. Institutional Review Board Approval Form or Document is not required.

Informed consent statement: Data from this study used de-identified data from the National Inpatient Sample Database. A publicly available all-payer inpatient care database in the United States. Informed patient consent is not required.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Data that support the findings of this study are publicly available at <https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp>.

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