

# Epidemiology of irritable bowel syndrome in hospitalized patients with inflammatory bowel disease: Nationwide Inpatient Sample analysis from 2007-2016

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## Abstract

**Background** Despite effective treatments for inflammatory bowel disease (IBD), patients in remission may still suffer from gastrointestinal symptoms attributable to overlying irritable bowel syndrome (IBS). In this population-based cohort study, we investigated the epidemiology of IBS in hospitalized IBD patients and explored the differences between hospitalized IBD-IBS vs. IBD patients to distinguish this patient population.

**Methods** Using the Nationwide Inpatient Sample database from 2007-2016, we identified patients with a primary or secondary discharge diagnosis of IBD, with or without IBS, using ICD-9 and ICD-10 codes. We extracted information on demographics, psychological comorbidities, IBD complications, cost and duration of stay of each group, from either discharge records or diagnosis codes. These were analyzed using SAS version 4.0.

**Results** There was a rise in the prevalence of IBS among inpatients with ulcerative colitis ( $P=0.025$ ) and Crohn's disease ( $P=0.0014$ ) over the study period. This study revealed that IBD patients with IBS tend to be female, younger, are less likely to be morbidly obese and have higher rates of psychological disorders ( $P<0.001$ ) compared to IBD patients with no IBS co-diagnosis. They also have fewer IBD-specific complications, such as strictures, obstruction, fistula and abdominal abscess ( $P<0.001$ ). Shorter hospital stays ( $P<0.001$ ) and lower hospital charges ( $P<0.001$ ) were also noted in these patients.

**Conclusions** IBD patients with IBS are significantly different from other IBD patients, and are associated with less severe disease, a shorter hospital stay and lower hospital expenses. Early and accurate classification of this patient population may prevent unnecessary treatment and hospitalization in the future.

**Keywords** Irritable bowel disease, inflammatory bowel disease, epidemiology

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## Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is characterized by inflammation or ulceration in the intestinal tract from the activation of the mucosal immune system [1,2]. Irritable bowel syndrome (IBS), on the other hand, is a functional gut disorder with an altered gut-brain axis causing recurrent abdominal pain and changing bowel habits [3]. Despite the fact that they are separate disease entities, there is evidence that these 2 conditions frequently overlap. From 25-46% of IBD patients in remission suffer from IBS-like symptoms, a higher prevalence compared to the general population without IBD [4,5].

The association between IBS and IBD has been extensively investigated for decades, but the etiology of IBS-type symptoms in patients with IBD is a source of ongoing research [6]. Some have suggested that IBS and IBD represent a spectrum of disease,

and that IBS could represent subclinical inflammation and a prodrome of IBD; evidence to support this includes inflammation with elevated colonic mucosal inflammatory cell infiltrate, and mucosal tumor necrosis factor- $\alpha$  mRNA protein expression in patients with IBS symptoms [7,8]. Others have argued that chronic inflammation from IBD may progress to IBS-like symptoms by changing the enteric nervous system and intestinal wall, which consequently leads to alteration of motility and visceral hypersensitivity [9,10]. Yet another argument considers IBS and IBD to be unrelated entities, given the poor correlation between IBD disease activity and IBS-like symptoms [11].

Because of the overlap of symptoms in IBD and IBS, the diagnosis of IBS is only made when patients have persistent gastrointestinal (GI) symptoms in the setting of clinical and endoscopic remission of IBD. The current American Gastroenterological Association guideline recommends using fecal calprotectin, endoscopy with biopsy, and cross-sectional imaging to rule out active inflammatory activity and determine remission in IBD patients. The standard of care of IBS in IBD patients does not differ from the current treatments for IBS, consisting of a combination of dietary changes, psychological therapy, antispasmodic, laxative or hypomotility agents, and probiotics [12].

The economic impact of IBD patients is large. A study by Xu *et al* revealed that the annual estimated costs of IBD hospitalization are \$11,345 for CD and \$13,412 for UC, and the total costs has been annually increasing by 3-4% for both CD and UC, of which a certain percentage may be due to IBS overlap and potentially avoidable [13]. As of yet, there has not been a large inpatient epidemiology study that closely looks at IBD patients with an additional IBS diagnosis. The aim of our study was to assess the prevalence and describe the demographic, complications, comorbidities, and hospital utilization of the IBD inpatient population with a co-diagnosis of IBS, in order to better understand this subgroup.

## Materials and methods

### Study data and design

This study cohort was obtained from the Nationwide Inpatient Sample database from 2007-2016 [14]. That database contains discharge records from over 7 million hospital visits representative of discharges from a random 20% stratified sample of United States (US) hospitals per year. It provides a useful representation of national US statistics and includes patient demographics, admission status, up to 30 primary and secondary discharge diagnoses, and 15 procedures coded using ICD-9 and ICD-10. Because of the de-identified nature of this publicly available data, our study did not require Institutional Review Board approval.

### Study population

All subjects aged 18 years or older with a primary or secondary discharge diagnosis of IBD (including UC and

CD), according to ICD-9 and ICD-10 codes, were identified. The diagnosis codes used for UC were 5560 to 5569, K5180, K5120, K5130, K5140, K5150, K5100, K5180 and K5190, while the diagnosis codes used for CD were 5550, 5551, 5552, 5559, K5000, K5010, K5080 and K5090. They were divided into 2 groups based on the presence or absence of IBS codes, including 5641, K58, K580, K581, K582, K588, K589. The sex, age, body mass index (BMI), race, insurance, hospital location, psychological comorbidities and IBD complications were directly collected through either discharge records or diagnosis codes.

### Statistical analysis

Descriptive statistics, such as total numbers, means, frequencies and percentages, were calculated using appropriate procedures. Categorical and continuous variables were compared using the chi-square test or a 2-group *t*-test, respectively. A 2-tailed P-value of 0.05 was considered as statistical significance. Standardized residuals were calculated for chi-square values. The yearly prevalence was analyzed using Pearson's correlation coefficient. All analyses were performed using the SAS software (version 4.0, Cary, North Carolina).

## Results

A total of 577,576 discharges of patients with a diagnosis of UC or CD hospitalized across the US based on the Nationwide Inpatient Sample database from 2007-2016 were included in the study. There were 212,318 discharges of UC patients, of which 6412 (3.0%) also had a co-diagnosis of IBS. Similarly, of 365,258 discharges of CD patients, 10,717 (2.9%) had IBS as a co-diagnosis. Overall, there was an annual rise in the prevalence of IBS in inpatient IBD patients over the study period ( $P=0.025$  for UC and  $P=0.0014$  for CD), as shown in Fig. 1. The demographic characteristics, length of stay and hospital charges per admission are summarized in Table 1. Complications and comorbidities of IBD-IBS vs. IBD groups are summarized in Tables 2 and 3, respectively. Types of admission, primary payer, and hospital location are summarized in Supplementary Table 1.

As shown in Table 1, most patients with IBS in the UC and CD cohorts were young, female, Caucasian and obese. When the IBD-IBS group and IBD group were compared side by side, the IBD-IBS patient was more likely to be female ( $P<0.001$ ) and younger ( $P<0.001$ ) than the IBD patient. The IBD-IBS group was more likely to be of Caucasian race, while less likely to be Black or Other, compared to the IBD group ( $P<0.001$ ). Most patients in the study were morbidly obese, with a BMI of 40 kg/m<sup>2</sup> or greater (60.0-71.5%); however, when the 2 groups were compared the IBD-IBS group had overall lower BMI ( $P<0.001$ ) compared to the IBD group. IBD patients who had IBS had lower hospital expenses (\$40418 vs. \$48414 for UC and \$33713 vs. \$39018 for CD,  $P<0.001$ ) and shorter hospital

**Table 1** Patient demographics, cost and length of each hospital stay

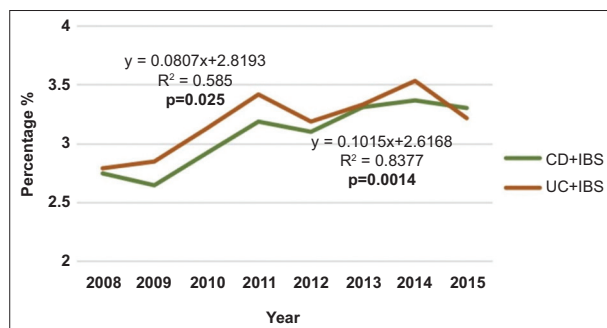
Variable, n (%)	UC+IBS	UC	P-value	CD+IBS	CD	P-value
Sex			<0.001			<0.001
Male	2056 (32.0%)	95484 (46.4%)		2994 (27.9%)	145892 (41.2%)	
Female	4356 (67.9%)	110283 (53.6%)		7721 (72.1%)	208510 (58.8%)	
Race			<0.001			<0.001
White	4759 (81.3%)	145138 (78.8%)		7933 (82.3%)	254297 (81.1%)	
Black	504 (8.6%)	16821 (9.1%)		981 (10.2%)	35298 (11.3%)	
Hispanic	370 (6.3%)	13526 (7.4%)		454 (4.7%)	13602 (4.3%)	
Others	222 (3.8%)	8625 (4.7%)		273 (2.8%)	10275 (3.3%)	
Age at hospitalization			<0.001			<0.001
18-44 years	2312 (36.1%)	64127 (31.1%)		4835 (45.1%)	141834 (40.0%)	
45-64 years	2125 (33.1%)	63874 (31.0%)		3701 (34.5%)	120696 (34.0%)	
65-84 years	1660 (25.9%)	64228 (31.2%)		1896 (17.7%)	79923 (22.5%)	
>85 years	315 (4.9%)	13677 (6.6%)		285 (2.7%)	12088 (3.4%)	
BMI (kg/m <sup>2</sup> )			<0.001			<0.001
19 or less	87 (9.6%)	2504 (8.1%)		166 (10.6%)	6288 (12.0%)	
20-29	75 (8.2%)	1574 (5.1%)		76 (4.8%)	2192 (4.2%)	
30-39	202 (22.2%)	4772 (15.4%)		331 (21.1%)	7332 (14.0%)	
40 or greater	546 (60.0%)	22182 (71.5%)		997 (63.5%)	36599 (69.8%)	
Length of stay and hospital charges per admission						
Length of stay (days) (mean±SD)	5.6±5.7	6.0±7.5	<0.001	5.1±5.5	5.3±6.4	<0.001
Total charges per admission (\$) (mean±SD)	40418.2±54422.1	48413.7±83495.2	<0.001	33712.8±41208	39017.6±62790	<0.001

BMI, body mass index; SD, standard deviation; UC, ulcerative colitis; CD, Crohn's disease; IBS, irritable bowel syndrome

**Table 2** Complications

Variable, n (%)	UC+IBS	UC	P-value	CD+IBS	CD	P-value
Fistulation or abscess	159 (2.5%)	5354 (2.6%)	0.55	539 (5.0%)	29168 (8.2%)	<0.001
Bowel obstruction	407 (6.4%)	15958 (7.8%)	<0.001	1449 (13.5%)	60605 (17.1%)	<0.001
Stricture	89 (1.4%)	3769 (1.8%)	0.009	587 (5.5%)	22839 (6.4%)	<0.001
Malnutrition	370 (5.8%)	12270 (6.0%)	0.53	528 (4.9%)	20411 (5.8%)	<0.001
Anemia	1997 (31.1%)	61737 (30.0%)	0.046	2609 (24.3%)	85754 (24.2%)	0.71
Perianal disease	31 (0.5%)	1095 (0.5%)	0.60	106 (1.0%)	5205 (1.5%)	<0.001
Hypovolemia	59 (0.9%)	2144 (1.0%)	0.35	91 (0.9%)	2876 (0.8%)	0.67
Electrolyte abnormality	1565 (24.4%)	45564 (22.1%)	<0.001	2270 (21.2%)	70906 (20.0%)	0.003

UC, ulcerative colitis; CD, Crohn's disease; IBS, irritable bowel syndrome



**Figure 1** Increase in prevalence of irritable bowel syndrome (IBS) from 2007-2015 in patients with ulcerative colitis (UC) and Crohn's disease (CD)

stays (5.6 vs. 6.0 for UC and 5.1 vs. 5.3 for CD,  $P < 0.001$ ) than patients who had IBD alone.

The IBD-IBS group had a lower prevalence of complicated IBD. In particular, complications specific to CD, such as fistulation, strictures, intra-abdominal abscess, perianal disease and malnutrition, were significantly less common in the CD-IBS group compared to the CD group (Table 2). Among comorbidities, anxiety, depression, bipolar disorder and opioid abuse were significantly more frequent in the IBD-IBS group than the IBD group (Table 3). While 17.1-21.1% of the IBD-IBS group had anxiety, only 9.7-11.8% of the IBD group had the diagnosis of anxiety.

## Discussion

This is the first large-scale study that has attempted to determine the frequency and study the epidemiology

**Table 3** Comorbidities

Variable, n (%)	UC+IBS	UC	P-value	CD+IBS	CD	P-value
Generalized anxiety disorder	1095 (17.1%)	19973 (9.7%)	<0.001	2258 (21.1%)	41962 (11.8%)	<0.001
Major depressive disorder	111 (1.7%)	2210 (1.1%)	<0.001	223 (2.1%)	4674 (1.3%)	<0.001
Bipolar disorder	272 (4.2%)	4501 (2.2%)	<0.001	642 (6.0%)	12692 (3.6%)	<0.001
Opioid use	118 (1.8%)	2283 (1.1%)	<0.001	335 (3.1%)	8066 (2.3%)	<0.001

UC, ulcerative colitis; CD, Crohn's disease; IBS, irritable bowel syndrome

of IBS among hospitalized IBD patients. In this national cohort of hospitalized patients, the estimated age-adjusted frequency of IBS among IBD patients increased over the years, which underlines the importance of understanding this subpopulation (Fig. 1). In our study, the average prevalence of IBS co-diagnosis in hospitalized IBD patients was 3%. As of today, there has been no study that evaluated the incidence and prevalence trend of IBS in IBD inpatients. However, a recent meta-analysis that assessed IBS-like symptoms in a non-hospitalized IBD population stated that the prevalence was about 35% [5].

Our theory regarding the large disparity between the rates of IBS in inpatients vs. outpatients with IBD is that IBS-IBD patients tend to have relatively low symptom severity, which does not lead to frequent hospital admission. Our data seem to further support this theory, showing a shorter length of inpatient stay, a lower hospital cost, a less complicated IBD disease course, and fewer elective admissions in IBD-IBS patients. Our findings are similar to those reported by Gracie *et al* in 2018, that hospitalizations due to disease activity were significantly fewer in IBD-IBS patients compared to IBD patients without IBS [15]. Another possible explanation of the shorter hospital stays and lower costs in the IBD-IBS group, despite the overall increasing frequency of hospitalization, could be that these patients are hospitalized to rule out possible IBD flare, but are soon discharged with an unremarkable inflammatory laboratory workup and without undergoing GI procedures, which can be both costly and time consuming.

No prior studies have revealed any significant age difference between IBD-IBS and IBD patients [16]. However, studies that attempted to investigate any association of age with IBS diagnosis among IBD patients found that diagnosis of IBD at a younger age increased the risk of developing IBS [17,18]. We also found that, while patients in both groups were mostly obese, IBS patients had relatively lower body weights. Recent studies have shown a positive association between BMI and symptom severity in both IBS and IBD, and patients with a BMI >30 kg/m<sup>2</sup> experienced more frequent flare ups requiring hospitalizations, which is consistent with our inpatient demographic data of both groups [19,20].

The IBD-IBS group had a lower prevalence of complicated IBD, which was anticipated as IBS in IBD patients is diagnosed by ruling out active inflammation. CD patients with a co-diagnosis of IBS were less likely to have complications secondary to CD, such as bowel obstruction, strictures, fistulas, intra-abdominal abscess, perianal disease and malnourishment (Table 2). Based on our analysis of the demographics, comorbidities and

complications of this population, the IBD-IBS group differs significantly from the IBD-alone group, which supports the theory that they may be mutually exclusive [11].

The IBD-IBS group had higher rates of major depressive disorder, bipolar disease and opioid use disorder than the IBD group. The current literature suggests that anxiety is more common, and the quality of life significantly lower, in IBD-IBS patients than in IBD patients [21,22]. More importantly, generalized anxiety disorder was found to be twice as prevalent in the IBD-IBS group. Considering that the prevalence of anxiety disorder and depressive disorder for IBS and IBD are similar, we can hypothesize that the higher rates of anxiety and depressive disorder in our inpatient IBD-IBS group may have been due to cumulative psychological effects from both IBD and IBS [23].

The strong association of depression and anxiety with both IBS and IBD has been well established in the literature, as IBS is a functional disease that is influenced by psychological factors, whereas IBD is a disease of autoimmune inflammation with psychiatric problems developing as a consequence and extraintestinal manifestation [24,25]. Studies have shown that IBD patients are at increased risk of developing anxiety and/or depression, and that these patients have more severe disease than those without anxiety and depression [26,27]. Further studies that examine psychological risk factors in the IBD-IBS group would be helpful to evaluate potential contributing factors to the high prevalence of psychological disorder in these patients.

Understanding and identifying the IBS-IBD population could alert physicians to the need for a more appropriate means of workup, including reassurance for patients, psychological counseling, and treatment of any underlying psychiatric disorder. Consequently, appropriate management of these patients could reduce the exposure of IBS patients to unnecessary hospitalization and surgical interventions; a study by Perera *et al* revealed that IBD patients with IBS had greater healthcare utilization, such as frequent hospital visits, and surgeries [17, 28-30].

A limitation of our study is that as a large-scale retrospective study, the use of ICD codes to select the study population and collect data is inevitably less reliable than a small prospective study that has less room for study errors. The large inpatient dataset is a great dataset that allows us to study the inpatient prevalence and epidemiology of this population in the US; however, given it is a large cohort study, we are unable to carry out individual chart reviews to verify the rationale or the timeline for the diagnosis. For example, even though ICD codes for IBD-related adverse

events were rare in IBD-IBS patients, this could be evidence for a study error, a possible misdiagnosis of IBS, or a mistaken ICD code as the discharge and billing diagnosis by a provider. Based on current guidelines, in order to diagnose IBS in IBD patients, imaging, endoscopy or stool biomarkers should be obtained to exclude active disease as the etiology of symptoms in a patient with IBD [12]. Educating providers regarding IBS and IBD would be necessary to reduce the error.

To our knowledge, this is the first large inpatient population cohort study to assess the demographics, complications, comorbidities and hospital utilization of patients with a co-diagnosis of IBS and IBD. This study revealed that IBD patients with IBS tend to be female, younger, of lower weight, have higher rates of psychological disorders, and have less IBD complications compared to IBD patients without an IBS co-diagnosis. Shorter hospital stays and lower hospital charges were also noted in these patients. Our study highlights that these patients differ significantly from IBD-only patients, as IBS is correlated with fewer complications and a shorter length of stay, which indicates that this population has less severe disease. The study's findings may help clinicians and patients gain new insight into our understanding of the disease entity, which will further increase our awareness and lead to better competency in the diagnosis and management of this population.

### Summary Box

#### What is already known:

- Despite treatments for inflammatory bowel disease (IBD), patients in remission may still suffer from gastrointestinal symptoms attributable to overlying irritable bowel syndrome (IBS)
- IBD patients with IBS had greater healthcare utilization, such as frequent hospital visits, and surgeries
- No one has yet explored the differences between IBD-IBS and IBD inpatients to better distinguish this patient population

#### What the new findings are:

- The estimated age-adjusted frequency of IBS among IBD patients has increased over the years
- IBS-IBD patients tend to be female, younger and have lower weight, with more psychological disorders and fewer IBD-specific complications
- They also have shorter hospital stays and lower hospital charges

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## Supplementary material

**Supplementary Table 1** Types of admission, primary payer, and hospital location

Variable, n (%)	UC+IBS	UC	P-value	CD+IBS	CD	P-value
Types of admission			<0.001			<0.001
Non-elective	5434 (84.9%)	164418 (80.0%)		9160 (85.8%)	289891 (82.0%)	
Elective	967 (15.1%)	41004 (12.0%)		1520 (14.2%)	63750 (18.0%)	
Primary payer			<0.001			<0.001
Private	2690 (42.0%)	84052 (40.9%)		4284 (40.1%)	140337 (39.7%)	
Medicare	2414 (37.7%)	85498 (41.6%)		3772 (35.3%)	135358 (38.3%)	
Medicaid	727 (11.4%)	19793 (9.6%)		1691 (15.8%)	47635 (13.5%)	
Other	572 (8.9%)	16202 (7.9%)		944 (8.8%)	30433 (8.6%)	
Hospital location			<0.001			<0.001
Rural	462 (7.2%)	17654 (8.6%)		1033 (9.7%)	36489 (10.3%)	
Urban teaching	3504 (54.9%)	116900 (57.0%)		5726 (53.6%)	193334 (54.8%)	
Urban non teaching	2420 (37.9%)	70605 (34.4%)		3929 (36.8%)	123205 (34.9%)	

UC, ulcerative colitis; CD, Crohn's disease; IBS, irritable bowel syndrome