Opioid Use in Patients With Inflammatory Bowel Disease

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Background: Data on opioid use in patients with inflammatory bowel disease and the relationship between disease, opioid use, and healthcare resource utilization are needed.

Methods: This analysis of real-world data from IBM Watson Health Commercial Claims and Encounters Database included patients with the first claim of inflammatory bowel disease (IBD) between 2007 and 2014.

Results: Opioid use was higher in patients with IBD than in the matched non-IBD cohort. Adjusted for age, gender, and Charlson Comorbidity Index score, inpatient and emergency room visits risk was higher in opioid users than non-users in both IBD cohorts.

Conclusions: Opioid use could be a potential surrogate for inadequate disease control manifested by increased inpatient and emergency room visit risks. These results suggest a need exists for better disease management and the development of an outcomes measurement tool for IBD pain.

Lay Summary

Opioid use, inpatient hospital and emergency room visits were higher in patients with inflammatory bowel disease than a matched non-inflammatory bowel disease cohort. Opioid use could be a potential surrogate for inadequate disease control manifested by increased risk for inpatient hospital and emergency room visits.

Key Words: Crohn's disease, pain management, IBM Watson Health Commercial Claims and Encounters Database, ulcerative colitis

INTRODUCTION

Pain is one of the principal concerns among patients with inflammatory bowel disease (IBD); abdominal pain is a component measured directly or indirectly in several disease activity indices.[1,2] Ongoing intestinal inflammation or subsequent complications, such as abscesses or strictures, are common causes of pain. Additionally, extraintestinal manifestations, such as pyoderma gangrenosum,[3] peripheral arthritis,[4] sclerosing cholangitis,[5,6] and thromboembolic events,[7,8] are thought to be inflammatory sources of pain in patients with IBD.[6]

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase type-2 (COX-2) inhibitors have been employed to alleviate abdominal pain in some cases, but NSAIDs may exacerbate IBD symptoms and COX-2 inhibitors have cardiovascular risks.[9,10] Opioids have been prescribed for pain management; however, information about the prevalence of their use among individuals with IBD is lacking. Long-term opioid use in patients with IBD brings about the risk for addiction, diversion (eg, prescription forgeries, doctor shopping, and medication sharing among friends or family members),[11] and other safety risks. In the 13-year prospective, observational, multicenter, long-term TREAT Registry of North American patients with Crohn's disease (CD), narcotic use at registry entry was a consistent predictor of serious infection risk in patients with CD who were receiving infliximab.[12] Toxic megacolon and stercoral perforation secondary to opioid-induced chronic constipation and narcotic bowel syndrome have also been reported.[6,13]

Recent analysis has shown that from 1999 to 2017, almost 400,000 people in the United States have died from an opioid overdose, delineated in 3 distinct waves beginning with increased opioid prescriptions in the 1990s, heroin overdose deaths beginning in 2010, and synthetic opioid deaths with the introduction of illicitly manufactured fentanyl in 2013.[14–16]

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Our analyses evaluated patients with IBD to identify potential characteristics before disease diagnosis. Given that pain is a component of the disease and opioid use was common, it was important to understand how patients with IBD are utilizing pain medication in the United States. Information on the prevalence of opioid use in patients with IBD is limited. Therefore, our study objectives were to estimate the rates of narcotic opioid use in patients with IBD prior to and after IBD diagnosis and explore the relationship between opioid use and healthcare resource utilization in the United States.

MATERIALS AND METHODS

Data Source and Study Design

This study was a retrospective analysis of the IBM Watson Health Commercial Claims and Encounters (CCAE) Database (formerly known as Truven Marketscan data), which consists of de-identified outpatient, inpatient, and pharmaceutical claims of approximately 40–50 million patients each year representing data from individuals enrolled in US employer-sponsored insurance plans.[17,18] This administrative claims database includes patients' characteristics (eg, age, sex, geographic region–state), enrollment history, medical services information, for instance: diagnoses, procedures, healthcare utilization encounters, outpatient pharmacy-level data (eg, National Drug Code, days' supply, strength, administration method), as well as the cost of each service (eg, inpatient, outpatient, and pharmaceutical costs). From 2000, IBM Watson CCAE contained the data for more than 130 million individual enrollees traveling through the healthcare system and covered by healthcare providers nationwide. Medication and comorbidity codes for IBD are listed in Supplementary Appendix, Tables S1 and S2.

Patients

All patients regardless of age with their first IBD claim between January 1, 2007 and December 31, 2014, 3 years of continuous enrollment [1 year prior to first IBD claim (year 0), first year after first IBD claim (year 1); and second year after first IBD claim (year 2)]; and at least 2 medical claims of CD [ICD-9-CM (International Classification of Disease, Ninth Revision): 555.*, ICD-10-CM: K50.*] or ulcerative colitis (UC) (ICD-9-CM: 556.*, ICD-10-CM: K51.*) during year 1 were included in the analysis (Fig. 1A). The process for identifying patients with CD or UC between January 1, 2007 and December 31, 2014 is illustrated in Fig. 1B.

The date of the first medical claim of CD or UC was used as the study index date, meaning that patients had no medical claim of CD or UC before the identification period. Since the data source of CCAE only includes the patients before Medicare service age as 65 years old, the range of index age is from 0 to 63 years old (with 2 years of continuous enrollment after index date) in this analysis dataset.

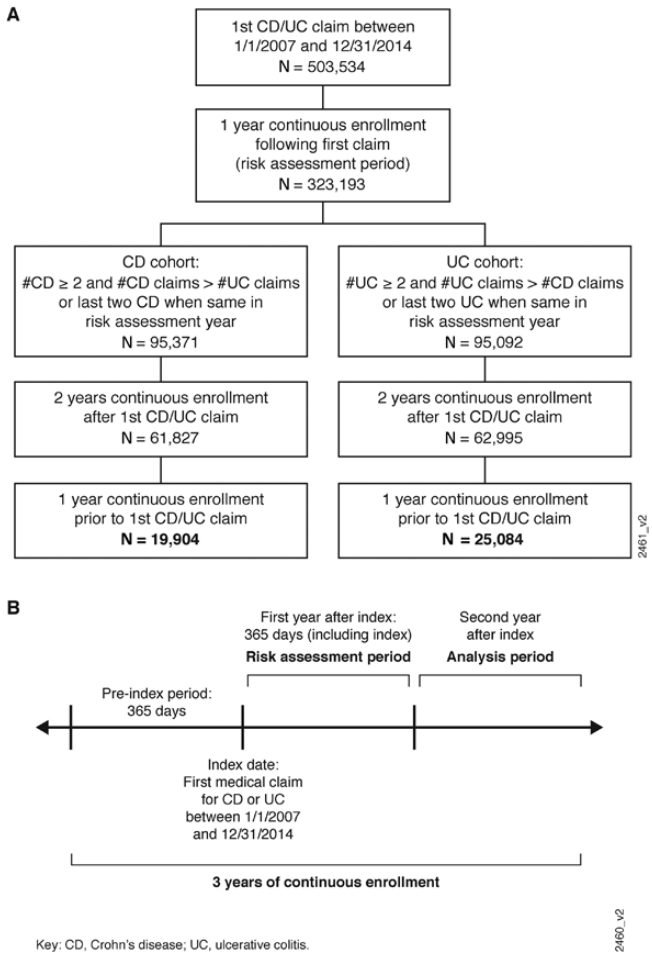


FIGURE 1. Patient identification flowchart (A) and study design (B).

The first year (0–364 days) after the index date was used to classify patients into the CD or UC cohort (risk assessment period). Patients were classified into the CD or UC cohort if the majority of IBD claims were CD or UC by counting the distinctive diagnoses dates. For patients with an even number of CD and UC claims, a cohort was assigned based on the last 2 diagnoses within the risk assessment period. The second year after index date was the analysis period.

A matched non-IBD cohort was created from the database. Patients without any CD or UC claim were matched (1:1 match) to the CD or UC cohorts separately based on age, index date, gender, and state. The index date of the corresponding patient in the CD or UC cohort was used as the index date of the matched patient in the non-IBD cohort. The same 3-year continuous enrollment criteria were applied to the non-IBD cohorts.

Statistical Analysis

Patient demographics and clinical characteristics were obtained for all patients with CD and UC identified during the

TABLE 1. Characteristics of Patients by IBD Cohort

Variable	CD Cohort (*N* = 19,904)	UC Cohort (*N* = 25,084)	*P*
Gender, *n* (%)			0.011
Female	10,933 (54.9)	13,477 (53.7)	
Male	8971 (45.1)	11,607 (46.3)	
Mean (SD) age at first claim, years	39.0 (15.7)	42.9 (13.9)	<0.0001
Distribution by age category, *n* (%), years			<0.0001
<18	2569 (12.9)	1423 (5.7)	
18–29	3296 (16.6)	3234 (12.9)	
30–39	3260 (16.4)	4410 (17.6)	
40–49	4257 (21.4)	6177 (24.6)	
50–59	4897 (24.6)	7314 (29.2)	
60+	1625 (8.2)	2526 (10.1)	
Mean (SD) QCI score during year 1	0.7 (2.0)	0.7 (2.1)	0.6599
Index year of first IBD claim, *n* (%)			0.012
2007	2163 (10.9)	2632 (10.5)	
2008	1982 (10.0)	2593 (10.3)	
2009	2389 (12.0)	3063 (12.2)	
2010	2662 (13.4)	3599 (14.4)	
2011	2917 (14.7)	3709 (14.8)	
2012	2752 (13.8)	3265 (13.0)	
2013	2260 (11.4)	2821 (11.3)	
2014	2279 (14.0)	3402 (13.6)	
Geographic region–state, *n* (%)[a]			<0.0001
Texas	1709 (8.6)	2335 (9.3)	
California	1556 (7.8)	2753 (11.0)	
New York	1323 (6.7)	1554 (6.2)	
Michigan	1179 (5.9)	1599 (6.4)	
Ohio	1100 (5.5)	1199 (4.8)	
Georgia	1096 (5.5)	1377 (5.5)	
Florida	966 (4.9)	1218 (4.9)	
Illinois	894 (4.5)	1033 (4.1)	
Pennsylvania	665 (3.3)	791 (3.2)	
Tennessee	631 (3.2)	763 (3.0)	

CD, Crohn's disease; IBD, inflammatory bowel disease; QCI, Quan-Charlson comorbidity index; SD, standard deviation; UC, ulcerative colitis.
[a]Data for the 10 most common states are summarized.

risk assessment period (1-year period beginning on the date of the first CD or UC diagnosis claim). Covariates were patients' age at the date of first CD or UC claim, gender, index year, geographic region–state, Charlson Comorbidity Index score (or Quan-Charlson Comorbidity Index score; Supplementary Appendix, Table S3), and selected comorbidities (ie, malignancy, anxiety, depression).[19,20] The use of opioid medication [defined as a patient having at least 1 opioid prescription or injection during the time periods (year 0, year 1 after, or year 2 after index date)] was summarized for each patient yearly for 3 periods (1-year period prior to the IBD diagnosis claim, risk assessment period, and analysis period). Outcome measures (ie, inpatient hospital stay and emergency room visit) were obtained for each patient during the risk assessment period (year 1 after index) and analysis period (year 2 after index).

Descriptive statistics were used to summarize patient characteristics. Generalized estimating equations estimated the rates of opioid use over time for all patients and by age category (<18, ≥18), and logistics regression calculated odds ratios (ORs) [95% confidence interval (CI)] [OR (95% CI)] of having an inpatient hospital stay or emergency room visit in year 2 comparing year 1 opioid users and non-users.

TABLE 2. Percent of Patients Receiving IBD Medications During Year 1 in Opioid Users and Non-users by IBD Cohort

	CD Cohort			UC Cohort		
IBD Medication	Opioid Non-user During Year 1 (N = 11,210)	Opioid User During Year 1 (N = 8694)	P	Opioid Non-user During Year 1 (N = 15,701)	Opioid User During Year 1 (N = 9383)	P
Biologic therapies (%)	12.1	18.6	<0.0001	3.8	7.2	<0.0001
Tumor necrosis factor α antagonist						
Adalimumab (Humira)	4.9	9.3	<0.0001	1.3	2.7	<0.0001
Certolizumab pegol (Cimzia)	0.8	1.2	0.0094	0.1	0.1	0.9114
Infliximab (Remicade)	6.8	9.6	<0.0001	2.5	4.7	<0.0001
Golimumab (Simponi)	0.02	0.04	0.4618	0.1	0.2	0.268
α4β7-integrin-antagonist						
Vedolizumab (Entyvio)	0.04	0.1	0.7185	0.04	0.1	0.2205
α4-integrin-antagonist						
Natalizumab (Tysabri)	0.01	0.1	0.0502	0.01	0.03	0.1202
Interleukin-12/23 antagonist						
Ustekinumab (Stelara)	0.0	0.04	0.0492	0.01	0.0	0.2743
Conventional therapies (%)	65.2	70.9	<0.0001	71.9	74.0	0.0003
Immunosuppressants	19.0	20.4	0.0039	9.2	11.7	<0.0001
Azathioprine	8.7	10.4	<0.0001	4.6	6.3	<0.0001
Mercaptopurine	7.7	7.0	0.0909	3.7	3.5	0.2497
Methotrexate	2.9	3.7	0.0029	0.9	1.6	<0.0001
Cyclosporine	0.1	0.1	0.4312	0.1	0.1	0.3693
Tacrolimus	0.4	0.6	0.0727	0.4	0.9	<0.0001
Corticosteroids	38.7	52.9	<0.0001	36.6	50.5	<0.0001
Budesonide	7.0	9.7	<0.0001	3.4	4.5	<0.0001
Hydrocortisone	126.0	2.2	<0.0001	3.7	4.7	<0.0001
Prednisone	28.0	39.5	<0.0001	28.6	38.4	<0.0001
Prednisolone	1.5	0.6	<0.0001	0.6	0.5	0.347
Methylprednisolone	7.6	16.8	<0.0001	8	17.1	<0.0001
5-aminosalicylates	43.3	40.7	0.0002	60.7	55.8	<0.0001
Mesalamine	38.9	36.4	0.0003	52.9	49.8	<0.0001
Sulfasalazine	4.1	4.0	0.8392	6.6	5.9	0.0141
Balsalazide	1.9	2.0	0.75	7.2	5.6	<0.0001
Olsalazine	0.1	0.1	0.0938	0.2	0.1	0.335

CD, Crohn's disease; UC, ulcerative colitis.

RESULTS

Patients

The patient distribution was similar between genders in the CD (N = 19,904) and UC (N = 25,084) cohorts with a higher proportion of females in both cohorts. The mean age at first claim was approximately 40 years in both cohorts, with the highest proportion in age category 50–59 years (Table 1). In both cohorts, the use of IBD medication was higher among opioid users than non-users (Table 2).

TABLE 3. Estimated Proportion of Patients Having At Least 1 Opioid Claim Over Time by IBD Cohort and Age Category

	Estimated Proportion (95% CI) %		
Cohort	Year 0	Year 1	Year 2
<18 years of age			
CD	17.8 (16.3–19.3)	25.7 (24.0–27.4)	21 (19.5–22.7)
UC	14.3 (12.6–16.3)	24.2 (22.0–26.5)	21.9 (19.8–24.1)
Non-IBD[a]	5.9 (5.2–6.7)	8.3 (7.5–9.2)	11.2 (10.3–12.3)
≥18 years of age			
CD	34.1 (33.4–34.8)	46.4 (45.6–47.1)	38.4 (37.6–39.1)
UC	28.5 (27.9–29.1)	38.2 (37.6–38.8)	33.1 (32.5–33.7)
Non-IBD[a]	19.3 (18.9–19.7)	21.2 (20.8–21.6)	22.4 (22.0–22.8)
All patients			
CD	32.0 (31.3–3S2.6)	43.7 (43.0–44.4)	36.1 (35.5–36.8)
UC	27.7 (27.2–28.3)	37.4 (36.8–38.0)	32.5 (31.9–33.1)
Non-IBD[a]	18.1 (17.7–18.5)	20.0 (19.7–20.4)	21.4 (21.0–21.8)

CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; UC, ulcerative colitis.
[a]For a patient in the non-IBD cohort, the index date of the corresponding matched patient with CD or UC was used as the index date for determination of year 0, year 1, and year 2.

Narcotic Opioid Use

The generalized estimating equation estimated percentages of patients with at least 1 opioid claim during year 0, year 1, and year 2 are shown in Table 3. Opioid use was higher in patients with CD or UC than in the matched non-IBD cohort, with the highest rates observed during the first year following IBD diagnosis. Trends for opioid use were generally consistent by IBD cohort within age categories but lower overall for younger patients (Table 3).

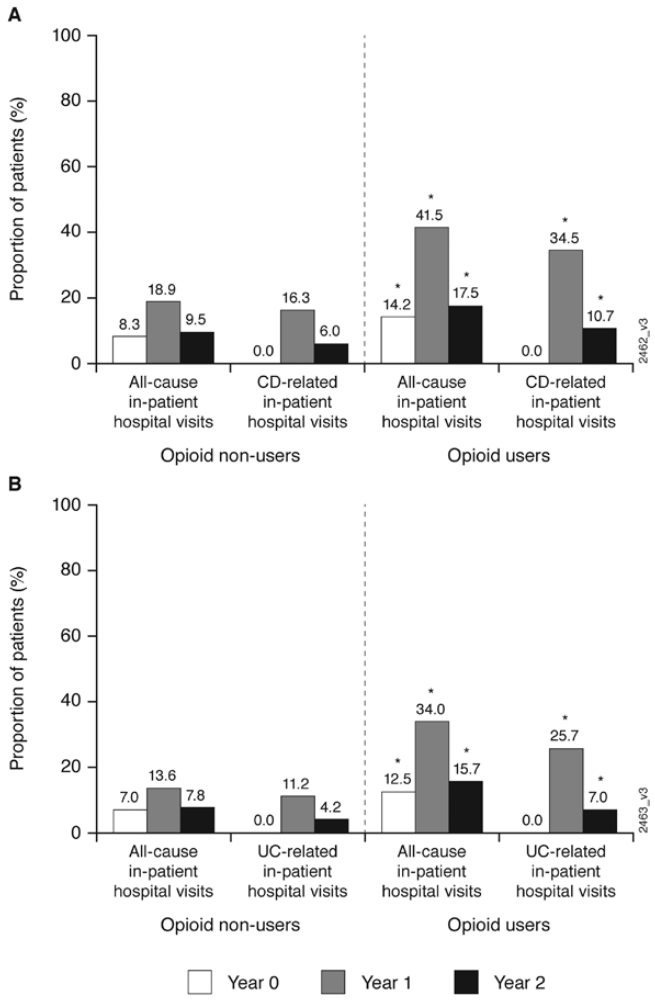
Opioid Use and Healthcare Resource Utilization

Rates of inpatient hospital visits (both all-cause and IBD-related) were higher in opioid users than in non-opioid users in both the CD and UC cohorts (Figs. 2A, B). Likewise, rates of emergency room visits (both all-cause and IBD-related) were higher in opioid users than in non-opioid users in both the CD and UC cohorts (Figs. 3A, B). For the CD cohort, 34.5% of opioid users versus 16.3% of opioid non-users had CD-related inpatient hospital visits during year 1 (Fig. 2A) and 27.4% of opioid users versus 12.2% of opioid non-users had CD-related emergency room visits (Fig. 3A). For the UC cohort, 25.7% of opioid users versus 11.2% of opioid non-users had UC-related inpatient hospital visits (Fig. 2B) and 15.3% of opioid users versus 6.3% of opioid non-users had UC-related emergency room visits (Fig. 3B) during year 1. Based on logistics regression analysis adjusted for age, gender, and Quan-Charlson Comorbid Index score, the risk of inpatient hospital and emergency room visits was higher in opioid users (any opioid claim during year 1) than opioid non-users in both the CD and UC cohorts (Fig. 4). Results were similar when malignancy, anxiety, and depression were included as comorbidity covariates (Supplementary Appendix, Table S4).

DISCUSSION

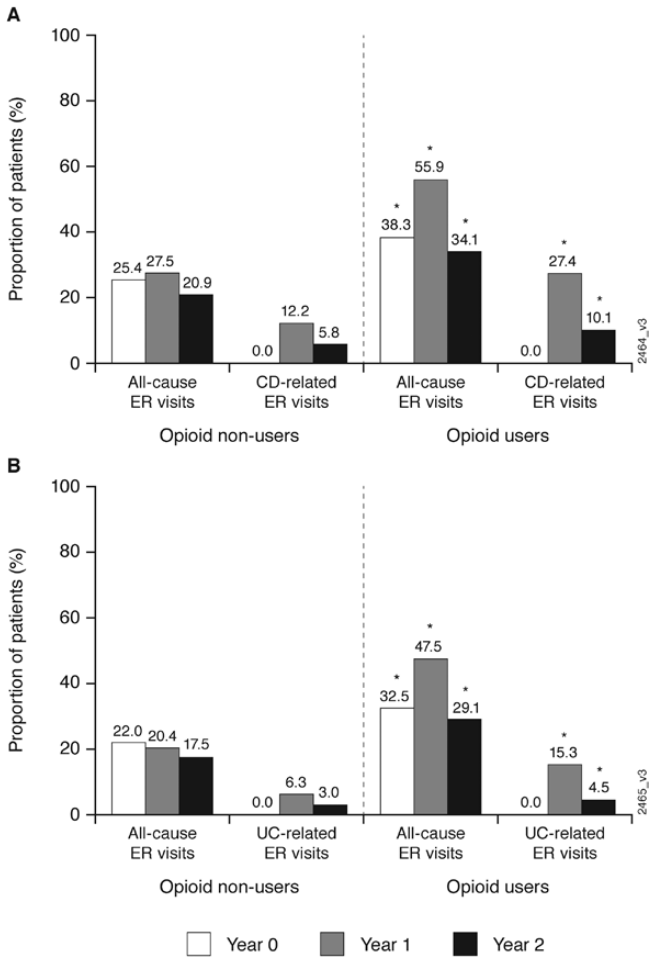
CD and UC are the 2 major forms of IBD and together they affect more than 1 million Americans.[21] Many of these individuals experience pain, and the severity and treatment of their pain has important clinical and economic implications. Our study shows that patients with IBD have higher opioid use compared with patients without IBD. In both the CD and UC cohorts, patients appear to have higher rates of opioid use in the first year following the IBD diagnosis index date than those in the year before diagnosis and the second year after diagnosis. As national healthcare expenditures grow, these findings will be increasingly relevant regarding policy implications for healthcare providers, healthcare organizations, and quality of care for individuals with IBD.

Multiple organizations have developed quality measures for IBD and have included pain or an aspect of pain in their measurement set.[22–25] In 2013, the Crohn's and Colitis Foundation of America developed 10 processes and 10 outcomes measures for IBD.[22] One of the identified IBD outcome measures was the "proportion of patients currently taking narcotic analgesics." In 2016, the International Consortium for Health Outcomes Measurement developed an outcome set for IBD that includes "pain or discomfort."[24] The Canadian "Choosing Wisely" campaign was developed to reduce unnecessary or harmful practices among patients with IBD and recommended physicians to not use opioids for the long-term management of abdominal pain in IBD.[25] Our study provides



Key: CD, Crohn's disease; UC, ulcerative colitis.
* P-values <0.0001 compared to opioid non-users

FIGURE 2. Inpatient hospital visits in opioid users and non-users in the (A) CD and (B) UC cohorts. *P < 0.0001 compared to opioid non-users.



Key: CD, Crohn's disease; ER, emergency room; UC, ulcerative colitis.
* P-values <0.0001 compared to opioid non-users.

FIGURE 3. Emergency room visits in opioid users and non-users in the (A) CD and (B) UC cohorts. *P-value <0.0001 compared to opioid non-users.

real-world evidence of the proportion of patients with IBD who obtain an opioid prescription and, therefore, supports the need for these international quality of IBD care initiatives.

Building on the "Choosing Wisely" campaign recommendation of no opioids for the long-term management of abdominal pain in IBD, there is an opportunity to expand this recommendation further and develop a new clinical trial endpoint that may serve as a quality measure tool, that is, opioid-free remission. Such a measure could be modeled after the current corticosteroid-free remission measure that is not only an endpoint in IBD clinical trials but also is recognized as a quality measure for IBD care.[22–25] As a means to continue moving these IBD quality of care initiatives forward, pharmaceutical clinical development programs could begin incorporating such a measure, opioid-free remission, into their IBD clinical development plans.

An interesting trend was observed with the increasing rate of opiate use in years 1 and 2 in the non-IBD group compared to the rate in year 0. This might be due to the increased opioid prescriptions over time. Recent analysis has shown that from 1999 to 2011 consumption of hydrocodone more than doubled and consumption of oxycodone increased by nearly 500%.[15,26]

Our study has limitations. First, retrospective analyses of claims data are subject to coding errors or incorrectly entered diagnoses that were primarily coded for reimbursement purposes rather than clinical accuracy. Another limitation of claims data is the presence of a diagnosis code on a medical claim that does not guarantee positive presence of a disease, as the diagnosis code may be incorrectly coded or included as a rule-out criterion. Therefore, our results can only present associations and cannot make statements about cause and effect. Variables such as disease severity, over-the-counter medication use, socio-economic

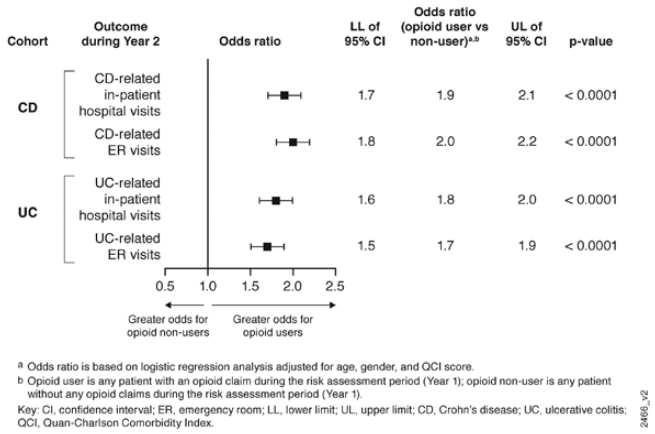


FIGURE 4. Odds ratios and 95% confidence intervals comparing in-patient hospital and emergency room visits among opioid users and non-users by cohort.

status, and patient health behavior are not captured and, therefore, could not be measured and included in our analyses. The presence of a claim for a filled prescription does not indicate whether the medication was consumed or taken as prescribed and, therefore, claims database may not provide a complete representation of medication use in clinical practice. The 1-year evaluation timeframe provides a brief window to observe medication use in patients with IBD and further assessment using a longer follow-up period is necessary to fully understand treatment patterns among patients with IBD. Additionally, this study included adults who have insurance; missing from the analyses are those who do not have insurance and those on Medicaid or Medicare.

CONCLUSIONS

Despite the limitations, this study provides valuable information that opioid use may be associated with inadequate disease control and provides the foundation research for the development of an outcome measure for pain among individuals with IBD.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Crohn's & Colitis 360* online.

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