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Leading Off

The Impact of Cannabis Use on Clinical Outcomes in Inflammatory Bowel Disease: A Population-based Longitudinal Cohort Study

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Background: Cannabis use is common in inflammatory bowel disease (IBD). Recent studies demonstrated that use of cannabis may relieve symptoms; however, it is still unclear how safe cannabis and its derivatives are for IBD patients. We performed this study to evaluate the impact of cannabis use on several key clinical outcomes in IBD.

Methods: We performed a retrospective study using the TriNetX Diamond Network. Cannabis use and noncannabis use subcohorts were identified for 3 patient groups: (1) IBD, (2) Crohn's disease (CD), and (3) ulcerative colitis (UC). Baseline differences between subcohorts for each group were controlled by propensity score matching. In each group, we compared relative incidence of emergency department (ED) visits, hospitalization, corticosteroid use, opioid use, IBD-related surgery, and death between cannabis users and noncannabis users.

Results: Inflammatory bowel disease cannabis users demonstrated an increased risk for corticosteroid use (risk ratios [R],1.095; 95% CI, 1.021-1.174; $P = .011$), ED visits (RR, 2.143; 95% CI, 2.034-2.257; $P < .001$), hospitalizations (RR, 1.925; 95% CI, 1.783-2.079; $P < .001$) and opioid use (RR, 1.35; 95% CI, 1.14-1.6); $P < .001$), but not an increased risk of IBD-related surgery or death. The CD and UC groups exhibited similar outcomes, except only CD demonstrated an increased risk for corticosteroid and opioid use.

Conclusions: Cannabis use in IBD patients is associated with several poor clinical outcomes, including increased risk of corticosteroid and opioid use, ED visits and hospitalization, though not IBD-related surgery or death. It is not clear what drives these risks or whether they are directly related to IBD-associated disease activity or other factors. Further prospective studies are warranted to more carefully investigate these relationships.

Key Words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, cannabis

Introduction

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are idiopathic inflammatory disorders of the gastrointestinal tract. Inflammation associated with IBD can have a significant and detrimental impact on patient quality of life.[1,2] Even when IBD appears to be in remission, patients frequently exhibit one or more problematic symptoms, including abdominal pain, bowel habit changes, fatigue, and a variety of extraintestinal manifestations involving the joints, skin, or eyes.[3–5] Patients and their providers are frequently challenged by these symptoms and how to effectively and/or safely manage them.[6,7] In these instances, IBD patients commonly utilize cannabinoids (in addition to standards of care) seeking symptomatic relief.[8,9]

Cannabis and its components have been used for thousands of years for therapeutic purposes in human beings.[10] In modern times, cannabis has been utilized to address refractory conditions or symptoms associated with a wide variety of conditions, including cancer-related nausea and pain, as well as epilepsy.[11,12] Indeed, several pure cannabinoids (THC [dronabinol], nabilone, and cannabidiol (CBD) [Epidiolex]) have been FDA approved for treatment of varying medical diagnoses.[13] Given the apparent positive impact that cannabis use has demonstrated in a number of conditions, including symptoms associated with the gut, there has been significant interest in the potential application of these agents in treating major digestive disorders, including IBD. In fact, recent studies have found that cannabis use is associated with IBD-associated symptom relief, particularly abdominal pain, diarrhea, and nausea.[9,14,15]

However, it is still unclear how safe crude cannabis is in IBD, in part because of differences in study methodologies and the fact that many previous investigations focused on this topic utilized relatively small patient cohorts. For example, a small observational study (involving 30 patients) demonstrated that the likelihood of corticosteroid use is reduced in cannabis users with CD.[16] Two separate retrospective case control studies found that cohorts of several hundred CD and UC inpatients who used cannabis leading up to their admissions were each less likely to require surgery (eg, colectomy), develop complications (eg, bleeding, bowel obstruction), and had shorter mean hospital stays.[17,18] However,

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Key Messages

- **What is already known?** Cannabis use in inflammatory bowel disease may relieve symptoms.
- **What is new here?** Patients with IBD who use cannabis may be at risk for poor clinical outcomes including increased risk for hospitalization, emergency department visits, corticosteroids, and opioid use.
- **How can this study help patient care?** The results from this research bring attention to potential risks associated with cannabis use in the setting of IBD and encourages future research in order to better understand the relationship between cannabis use and clinical outcomes in IBD.

in a different retrospective case control study involving 1401 IBD patients, the relative rate of visiting the ED was higher in cannabis users.[19] A separate observational study of 313 IBD patients compared clinical outcomes in IBD patients who did and did not use cannabis.[20] They found that cannabis users, while demonstrating significant symptom improvement, were significantly more likely to eventually require bowel surgery. These discrepancies can be confusing for both provider and patient to interpret. Thus, it is imperative that larger scale, high-quality clinical studies evaluating the impact of cannabis on clinical outcomes in IBD are completed.

Notably, previous legal restrictions and/or societal taboos have changed over the last several years. With increasingly widespread legalization of medicinal cannabis use in the United States, along with associated changes in public perception, more patient data related to cannabis utilization are becoming available. Here, we undertake a population-based, retrospective cohort study to evaluate the impact of cannabis use in IBD in relation to several key clinical outcomes (including those previously investigated) in order to further clarify the relative safety of cannabis use in these patient populations.

Methods

Study Design and Participants

This retrospective cohort study was completed using data from the TriNetX Diamond Network (www.trinetx.com) database. TriNetX is a global, federated research network that allows real-time access to de-identified data and is compliant with the HIPAA Privacy Rule. The Diamond Network within TriNetX consists of over 212 million patients from 92 health care organizations and provides access to the electronic medical record (EMR) data from community-based primary and specialty care settings and medical and pharmacy claims.

Inclusion criteria

The Diamond Network was queried for patients with IBD recorded in EMRs between January 1, 2016, and December 31, 2016, using the International Classification of Diseases Tenth Revision, Clinical Modification (ICD-10-CM) codes K50 (Crohn's disease) and K51 (ulcerative colitis).

Patients with IBD were then divided into 2 cohorts, a cannabis user cohort and a nonuser cohort. Patients were included in the cannabis user cohort if the following terms appeared in the EMR between 6 months after and 2 years after the IBD diagnosis in the previously mentioned timeframe: Cannabis-related disorders (ICD-10 F12), Cannabinoids, natural (Current Procedural Terminology [CPT] code 80349), or Cannabinol (RXNorm 1976). Of note, we attempted to use medication codes for cannabis and/or cannabis derivatives, but our initial searches returned no patients, so we opted against including this. The nonuser cohort consisted of IBD patients who did not have the cannabis-related terms in their EMR any time after the (2016) IBD diagnosis (Supplemental Figure 1). The same query strategy was then performed separately on both IBD subtypes (eg, CD, ICD-10 K50 and UC, ICD-10 K51).

Exclusion criteria

Patients were excluded if their EMR contained references to cancers (where cannabinoid use might be unrelated to the IBD diagnosis): (1) malignant neoplasms of lip, oral cavity, and pharynx (ICD-10 C00-C14); (2) malignant neoplasms of digestive organs (ICD-10 C15-C26); (3) malignant neoplasms of respiratory and intrathoracic organs (ICD-10 C30-C39); (4) malignant neoplasms of bone and articular cartilage (ICD-10C40-C41); (5) melanoma and other malignant neoplasms of skin (ICD-10 C45-C49); (6) malignant neoplasm of breast (ICD-10C50); (7) malignant neoplasm of female genital organs (ICD-10-CM C51-C58); (8) malignant neoplasm of male genital organs (ICD-10C60-C63); (9) malignant neoplasm of urinary tract (ICD-10-CM C64-C68); (10) malignant neoplasms of eye, brain, and other parts of central nervous system (ICD-10C69-C72); (11) malignant neoplasms of thyroid and other endocrine glands (ICD-10 C73-C75); (12) malignant neoplasms of ill-defined, other secondary and unspecified sites (ICD-10 C68-C80); (13) malignant neuroendocrine tumors (ICD-10C7A); (14) or secondary neuroendocrine tumors (ICD-10C7B). Patients who had a record of both UC and CD diagnoses were also excluded from the cohorts.

Data Collection and Outcomes

The TriNetX Diamond Network was accessed on March 3, 2023, to provide a de-identified set of patients with an IBD diagnosis within the date range January 1, 2016, and December 31, 2016. The cannabis cohort was defined as adults (18 years of age or older) with IBD who had cannabis use recorded in the electronic medical record between 6 months after and 2 years after the (2016) IBD diagnosis. The control cohort was defined as adults with IBD who had no recorded cannabis use or related diagnosis in the EMR any time after the (2016) IBD diagnosis.

We compared the relative rates of the following clinical outcomes in the cannabis using and noncannabis using cohorts: (1) emergency department (ED) visits (CPT code 1013711); (2) hospitalizations (CPT codes 1013659, 1013729, and 1013699 and TriNetX code visit type: short stay, inpatient encounter, inpatient nonacute); (3) corticosteroid use (prednisone [RXNorm 8640], methylprednisolone [RXNorm 6902], budesonide [RXNorm 19831], hydrocortisone [RXNorm 5492]); (4) new opioid use (opioid analgesics [VA National Formulary code CN101], fentanyl [RXNorm 4337], morphine [RXNorm 7052], oxycodone [RXNorm 7004], meperidine [RXNorm 6754], hydrocodone [RXNorm 5489]); (5) IBD-related surgery (colectomy, partial [CPT 1007455], colectomy, total abdominal

without proctectomy [CPT 1007463], colectomy, total abdominal with proctectomy [CPT 1007468] proctectomy [CPT 1007599], enterectomy, resection of small intestine [CPT 1007438], ileostomy [ICD-9-CM 46.2], colostomy [SNOMED 398740003 and ICD-9-CM 46.1], enterostomy [SNOMED 87150006]); and (6) mortality (TriNetX: deceased). The outcomes listed here were measured between 1 day after the index event up to 1 year after the index event (IBD diagnosis in the noncannabis user cohort and the date cannabis use first reported in the electronic medical record in the cannabis user cohort).

Statistical Analysis

All analyses were completed using the statistical applications available on TriNetX. Balanced cohorts were generated with 1:1 propensity score matching using logistic regression for the following demographics, baseline clinical characteristics, and medication use: age, sex, IBD type (CD [ICD-10 K50] vs UC [ICD-10 K51]), infliximab use (RxNorm 191831), chronic ischemic heart disease (ICD-10 I25), diabetes mellitus (ICD-10 E08-E13), chronic kidney disease (ICD-10 N18), chronic obstructive pulmonary disease (ICD-10 J44), cerebrovascular accident (ICD-10 I63), generalized anxiety disorder (ICD-10 F41.1), and IBD-related complications (eg, other and unspecified intestinal obstruction [ICD-10 K56.6], and fistula of intestine [ICD-10 K63.2]; Tables 1-3). Of note, after evaluating the relative use of several medical therapies (including biologic and immunomodulator medications), we decided to use only infliximab because it was by far the most commonly employed biologic agent described within our study period (ie, there were more patients on infliximab than all other biologic agents combined). Additionally, when using infliximab as the sole therapeutic agent-matching variable, we were able to evaluate the largest study cohorts. We also left out other relatively newer therapeutic agents for the study period (eg, vedolizumab, ustekinumab, etc.) in an effort to avoid other potential biases (including possible financial factors related to access to newer medications).

Following propensity score matching, none of these variables demonstrated a statistically significant difference between cannabis user and noncannabis user cohorts in the IBD or IBD subtype groups ($P > .05$), with the exception of fistula of intestine (ICD-10 K63.2), which was found to be more likely in the whole IBD cohort ($P = .040$). These specific variables were selected due to their importance to the overall health of each patient, their relevance to IBD severity, and/or their significant influence on the clinical outcomes being evaluated in this study.

Risk ratios (RRs) with 95% confidence intervals (CIs) in addition to Kaplan-Meier survival curves with hazard ratios, log-rank, and χ^2 tests were calculated for each outcome of interest. An alpha level of 0.05 was used to determine statistical significance of the results. Logistic regression provided these analyses.

Ethics Statement

Due to the fact that TriNetX contains no patient identifying information as a federated network, research studies that use TriNetX do not require informed consent from patients or ethical approval.

Results

Clinical Characteristics of the Whole IBD Cohort

After propensity score matching, we identified 5075 individuals in each cohort (ie, IBD cannabis users and IBD without cannabis use) who met the study criteria (Table 1). Cannabis users demonstrated an increased likelihood of corticosteroid use (RR, 1.095; 95% CI, 1.021-1.174; $P = .011$), ED visitation (RR, 2.143; 95% CI, 2.034-2.257; $P < .001$), hospitalization (RR, 1.925; 95% CI, 1.783-2.079; $P < .001$), and opioid use (RR,1.35; 95% CI, 1.138-1.6); $P < .001$). There was no statistically significant difference in the relative risk of IBD-related surgery (RR, 0.682; 95% CI, 0.354-1.313; $P = .249$) or death (RR, 1.362; 95% CI, 0.936-1.98; $P = .105$; Figure 1).

Table 1. Patient characteristics after propensity score matching in IBD cohorts.

Characteristics	IBD Cohorts After Propensity Score Matching (n = 5075)		
	IBD Cannabis Use	IBD No Cannabis Use	*P*
Age at Index	5075 (100%)	5075 (100%)	0.408
Female	2545 (50.15%)	2523 (49.71%)	0.662
Crohn's disease [regional enteritis]	3494 (68.85%)	3492 (68.81%)	0.966
Ulcerative colitis	1581 (31.15%)	1583 (31.19%)	0.966
Generalized anxiety disorder	994 (19.59%)	1016 (20.02%)	0.584
Diabetes mellitus	747 (14.72%)	778 (15.33%)	0.389
Other chronic obstructive pulmonary disease	746 (14.70%)	778 (15.33%)	0.374
Other and unspecified intestinal obstruction	694 (13.68%)	684 (13.48%)	0.772
Chronic ischemic heart disease	434 (8.55%)	435 (8.57%)	0.972
Chronic kidney disease (CKD)	310 (6.11%)	312 (6.15%)	0.934
Fistula of intestine	176 (3.47%)	140 (2.76%)	***0.040***
Cerebral infarction	138 (2.72%)	122 (2.40%)	0.315
Infliximab	276 (5.44%)	260 (5.12%)	0.478

Table 2. Patient characteristics after propensity score matching in Crohn's disease cohorts.

Characteristics	CD Cohorts After Propensity Score Matching (n = 3495)		
	CD Cannabis Use	CD No Cannabis Use	*P*
Age at Index	3495 (100%)	3495 (100%)	0.460
Female	1786 (51.10%)	1773 (50.73%)	0.756
Generalized anxiety disorder	699 (20%)	706 (20.20%)	0.835
Diabetes mellitus	462 (13.22%)	478 (13.68%)	0.575
Other chronic obstructive pulmonary disease	493 (14.11%)	514 (14.71%)	0.474
Other and unspecified intestinal obstruction	611 (17.48%)	618 (17.68%)	0.826
Chronic ischemic heart disease	260 (7.44%)	280 (8.01%)	0.370
Chronic kidney disease (CKD)	206 (5.89%)	197 (5.64%)	0.644
Fistula of intestine	162 (4.64%)	143 (4.09%)	0.266
Cerebral infarction	84 (2.40%)	80 (2.29%)	0.752
Infliximab	238 (6.81%)	223 (6.38%)	0.470

Table 3. Patient characteristics after propensity score matching in ulcerative colitis cohorts.

Characteristics	UC Cohorts After Propensity Score Matching (n = 1578)		
	UC Cannabis Use	UC No Cannabis Use	*P*
Age at Index	1578 (100%)	1578 (100%)	0.674
Female	759 (48.10%)	760 (48.16%)	0.972
Generalized anxiety disorder	294 (18.63%)	312 (19.77%)	0.416
Diabetes mellitus	284 (18.00%)	300 (19.01%)	0.463
Other chronic obstructive pulmonary disease	252 (15.97%)	252 (15.97%)	1
Other and unspecified intestinal obstruction	82 (5.20%)	70 (4.44%)	0.318
Chronic ischemic heart disease	172 (10.90%)	173 (10.96%)	0.955
Chronic kidney disease (CKD)	103 (6.53%)	98 (6.21%)	0.716
Fistula of intestine	12 (0.76%)	12 (0.76%)	1
Cerebral infarction	53 (3.36%)	47 (2.98%)	0.542
Infliximab	37 (2.35%)	38 (2.41%)	0.907

Clinical Characteristics of the CD Cohort

After propensity score matching, we identified 3495 individuals in each CD cohort who met the study criteria (Table 2). Cannabis users demonstrated an increased likelihood of corticosteroid use (RR, 1.16; 95% CI, 1.067-1.261; $P < .001$), ED visitation (RR, 1.924; 95% CI, 1.815-2.04; $P < .001$), hospitalization (RR, 1.884; 95% CI, 1.72-2.064; $P < .001$), and opioid use (RR, 1.446; 95% CI, 1.18-1.773; $P < .001$). There was no statistically significant difference in the relative risk of IBD-related surgery (RR, 1.083; 95% CI, 0.495-2.371; $P = .841$) or mortality (RR, 1.222; 95% CI, 0.789-1.89; $P = .368$; Figure 2).

Clinical Characteristics of the UC Cohort

After propensity score matching, we identified 1578 individuals in each CD cohort who met the study criteria (Table 3). Cannabis users demonstrated an increased likelihood of ED visitation (RR, 2.375; 95% CI, 2.145-2.631; $P < .001$) and hospitalization (RR, 2.146; 95% CI, 1.852-2.485; $P < .001$). There was no statistically significant difference in relative risk of corticosteroid use (RR, 1.105; 95% CI, 0.967-1.263; $P = .141$), IBD-related surgery (RR, 1; 95% CI, 0.417-2.396; $P = 1$), mortality (RR, 1.167; 95% CI, 0.624-2.181; $P = .6288$), or opioid use (RR, 1.117; 95% CI, 0.82-1.523; $P = .4837$; Figure 3).

Discussion

This investigation is important because it represents one of the largest and, to date, the only population-based study to examine health-related impacts of cannabis use in IBD patients, including evaluations of both CD and UC cohorts. We found that IBD patients who use cannabis are at increased risk for several negative clinical outcomes including corticosteroid use, opioid use, ED visitation, and hospitalization, even after controlling for key demographic and clinical factors including patient age, sex, IBD type, severity, and treatment. Notably, we also demonstrated that cannabis use in IBD is not associated with an increased risk for IBD-related surgery or mortality.

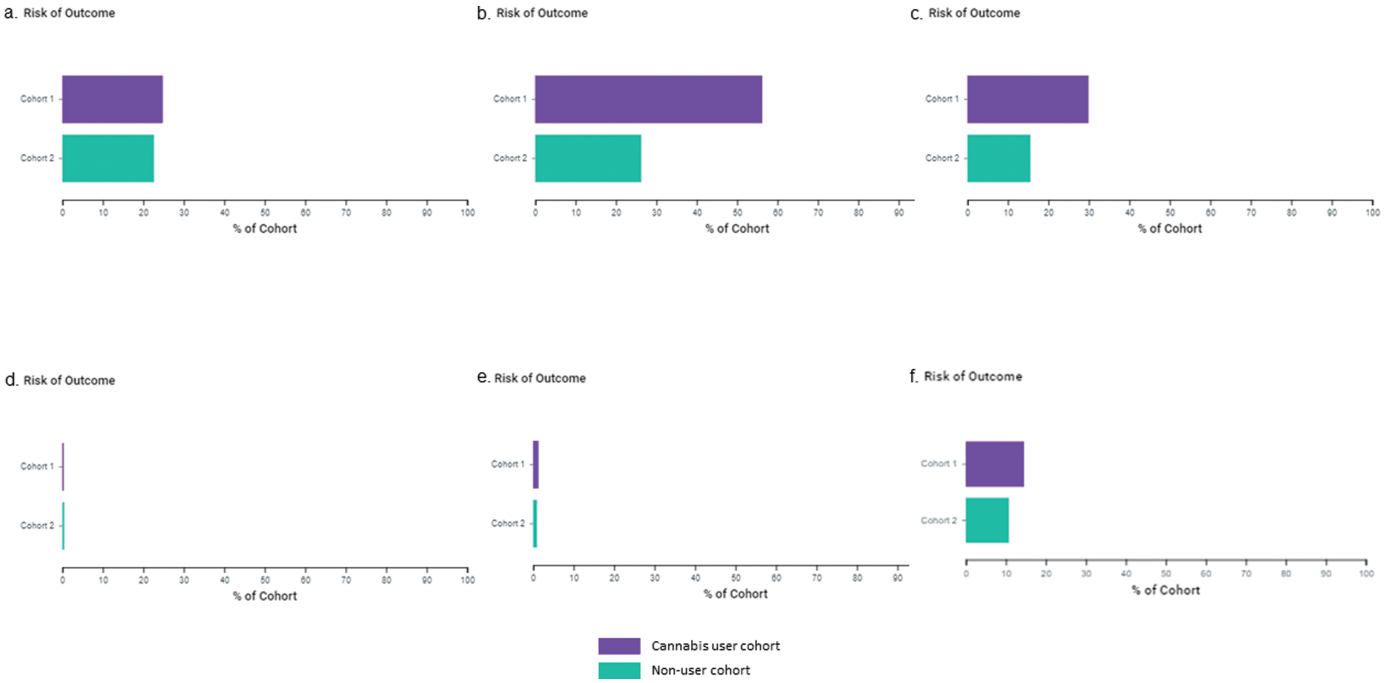

Figure 1. Risk of Outcome analysis in IBD cohort comparisons. A, Corticosteroid use. B, Emergency department services. C, Hospitalization. D, IBD related surgery. E, Mortality. F, Opioid Use.

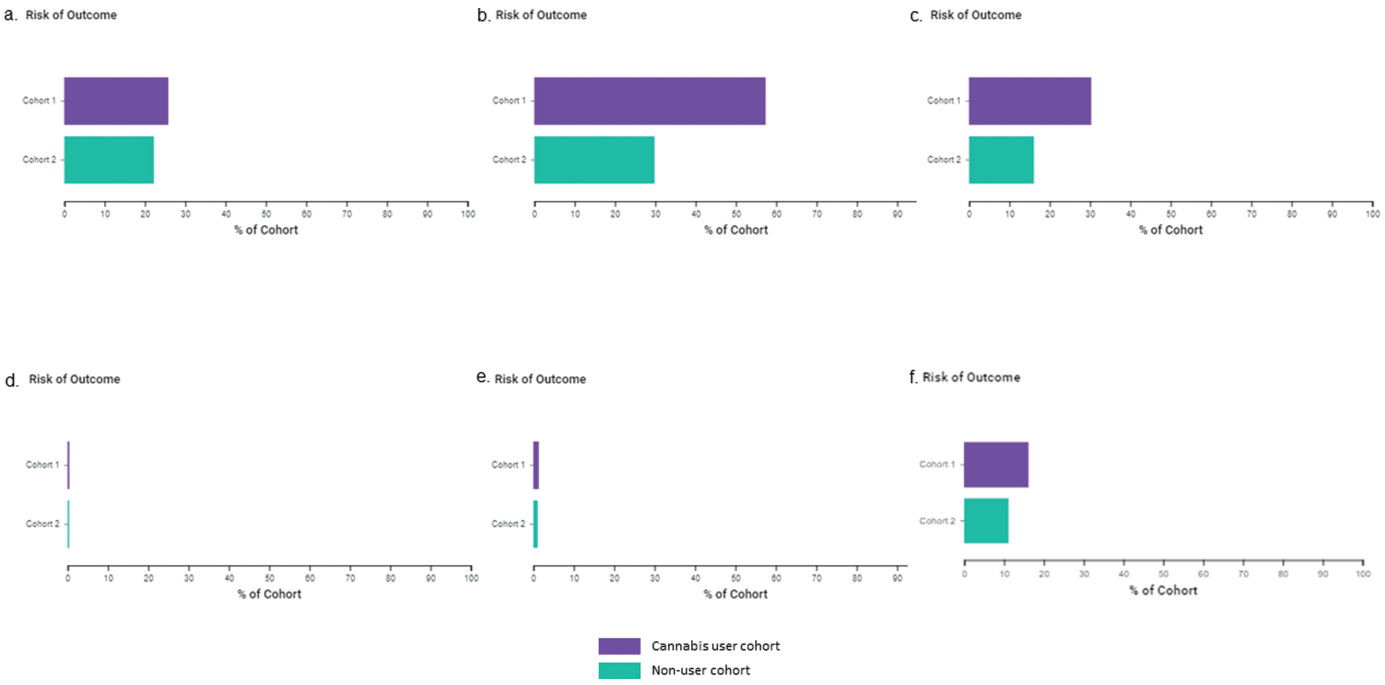

Figure 2. Risk of Outcome analysis in Crohn's disease cohort comparisons. A, Corticosteroid use. B, Emergency department services. C, Hospitalization. D, IBD related surgery. E, Mortality. F, Opioid Use.

This study is notable for several reasons. Some of the results are consistent with or similar to those of previous studies. This includes demonstrating an increased risk of ED visits.[19] At least one previous study demonstrated an association between outpatient cannabis use and inpatient opioid use.[21] Additionally, at least 2 prior investigations reported reduced risk of both IBD-related surgery and complications in cannabis users,[17,18] while we demonstrated no significant relative risk of IBD-related surgery or complications in this cohort (eg, intestinal obstructions, fistulae). There were also discrepancies when compared with some previous studies. One previous publication reported that cannabis use decreases the risk for corticosteroid use,[9] whereas we demonstrated a significant increased risk in this setting. Additionally, at least one prior investigation found that cannabis use in IBD was associated with increased risk for

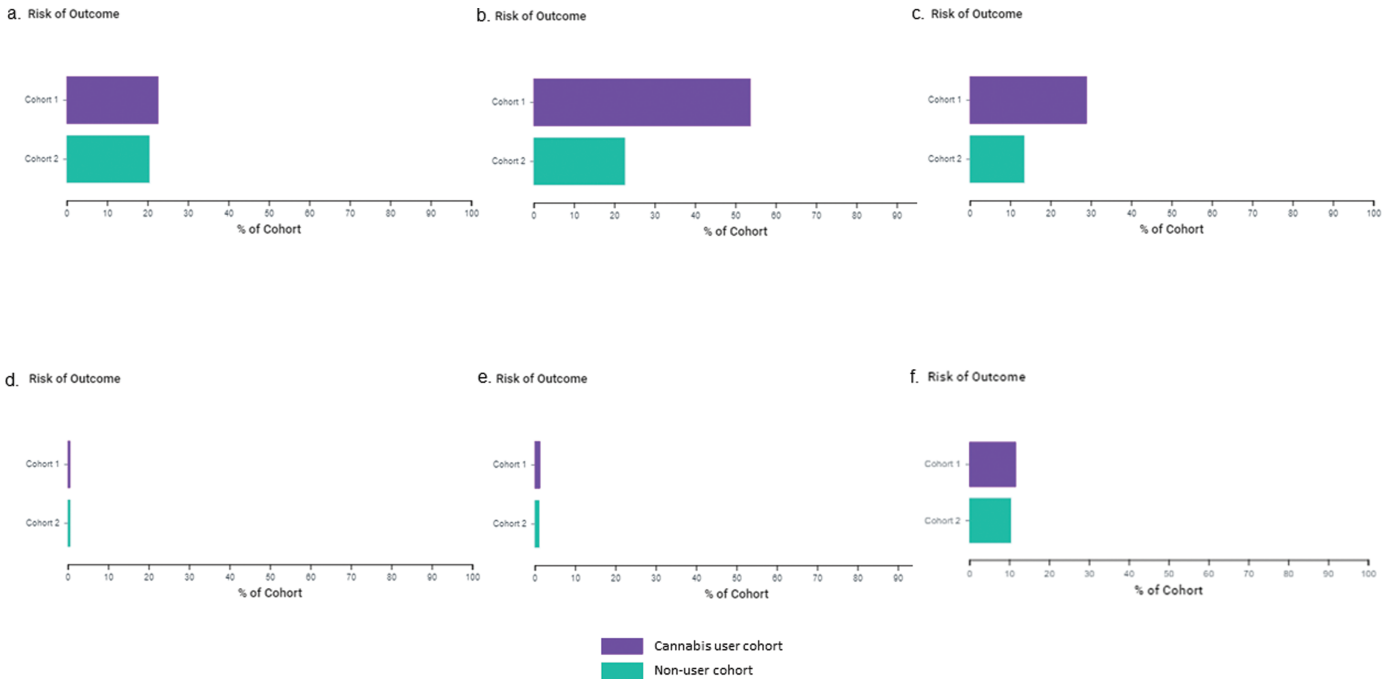

Figure 3. Risk of Outcome analysis in ulcerative colitis cohort comparisons. A, Corticosteroid use. B, Emergency department services. C, Hospitalization. D, IBD related surgery. E, Mortality. F, Opioid Use.

IBD-related surgery,[20] but we did not. We also report at least one major outcome that has not been specifically evaluated in a large IBD cohort: mortality. We found no evidence of increased all-cause mortality risk in IBD patients who use cannabis. This finding is significant because no investigation of this size has evaluated risk of death from cannabis in IBD. Additionally, prior studies of all-cause mortality risk related to cannabis in other populations have been inconsistent.[22–25] Finally, this is one of the few investigations to evaluate the impact of cannabis use in both CD and UC cohorts, and we demonstrated similar relative outcomes in each patient group (with the exception of corticosteroid use).

There are a variety of potential explanations for the findings of this investigation. Concerns have been raised that cannabis use may mask key symptoms indicating the presence of active IBD.[9,15,20] It is possible that cannabis-using IBD patients may be at increased risk of missing important signals indicating that damage is occurring in the gastrointestinal tract. If true, this could explain at least part of the increased risks of corticosteroid use, ED visits, and hospitalization demonstrated in IBD cannabis users. Notably though, there was no evidence of an increase in the risk of IBD-related complications or surgery. Part of this may be explained by the shorter relative follow-up period in our study when compared with previous studies. However, there may also be alternative factors driving risk for the poor outcomes described previously. Other explanations for the increase in ED and hospital visits in IBD cannabis users may include direct effects of the cannabis products themselves. Acute cannabis intoxication and cannabis poisoning are independently associated with increased risk of ED visitation and hospitalization.[26,27] One specific gastrointestinal-related adverse reaction related to chronic and higher dose cannabis use is cannabinoid hyperemesis syndrome (CHS).[28] Cannabinoid hyperemesis syndrome is an overlooked diagnosis associated with severe and recurrent nausea, vomiting, and abdominal discomfort. This constellation of symptoms can lead to repeated visits to the ED.[9,28] Considering each of this study's findings, while cannabis appears to impart risk for certain poor outcomes, it is not clear how specific these risks are to IBD itself.

This investigation has several potential weaknesses. It was a retrospective cohort study and so was at risk of a variety of errors, including recall and selection biases. While efforts were made to limit these weaknesses, it was impossible to control for every potential influential comorbidity and/or confounding factor. For example, patients may have simply neglected to tell their providers about their cannabis use (particularly if they felt there was a social stigma associated with it). Additionally, although we initially attempted a variety of approaches to screen for use of cannabis and its derivatives (including evaluation of patient medication lists), the methods we ultimately used to identify cannabis and cannabinoid derivative use (eg, reliance on ICD-10 and CPT codes) could have missed some users. Measures of IBD activity (including laboratory, stool, and endoscopically based testing) were also not consistently available. We were also unable to reliably incorporate concomitant tobacco use or alcohol consumption into our analysis. It will be important to include those factors into future similar studies. In addition, although surgery types could be selected for, it was not possible to determine the specific reason each patient presented to the ED or hospital. This would have been useful in determining whether individuals were presenting as a result of IBD-related complications, cannabis-related factors, and/or other comorbidities. This limited our ability to more definitively evaluate the IBD-specific impact(s) of cannabis use. Finally, the analysis of mortality may not have been as particularly reliable, given the relatively small number of individuals who died during the study. Considering the study design, along with the issues noted herein, no cause and effect relationship can be assigned to any of the findings reported here.

In summary, this study demonstrated that individuals with IBD (including both CD or UC) who use cannabis are at increased risk for corticosteroid use, ED visits, and hospitalization. These associations were revealed even after controlling for key demographic and clinical factors, including several key markers of general health, IBD severity, and complications. We also demonstrated that cannabis use in IBD is not associated with an increased risk for IBD-related surgery or mortality, suggesting that the poor outcomes described here may be driven by factors that are not necessarily primarily related to IBD itself. Further investigation is necessary to refine our understanding of each of these associations and to provide patients and providers clarity regarding the safety of cannabis in this setting.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Conflicts of Interest

None.

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