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Cannabis Use and Outcomes in Patients with Chronic Pancreatitis: A National Inpatient Sample Analysis

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ABSTRACT

Background & Aims: Cannabis is a commonly used recreational and medicinal substance and has been shown to have anti-inflammatory and analgesic effects. Previous studies have shown that cannabis may reduce disease severity of pancreatitis. We aim to use nationally available data to further investigate the impact of cannabis on outcomes among patients with chronic pancreatitis (CP).

Methods: Nationwide Inpatient Sample (NIS) 2016-2020 was used to identify patients with CP. Patients were stratified based on the presence of cannabis use. Data was collected regarding patient demographics, comorbidities, and Charlson Comorbidity Index (CCI). The outcomes assessed were sepsis, acute kidney injury (AKI), deep vein thrombosis (DVT), pulmonary embolism (PE), intensive care unit (ICU) admission, acute pancreatitis (AP), pancreatic cancer, total charges, and length of stay. The relationships were analyzed using multivariate logistic regression.

Results: Out of 907,790 hospitalized patients in this study; 52,360 (5.8%) were cannabis users. After adjusting for confounding factors, cannabis use was associated with decreased odds of mortality (aOR=0.47, p<0.001), DVT (aOR=0.71, p<0.001), PE (aOR=0.622, p=0.002), ICU admission (aOR=0.705, p<0.001), pancreatic cancer (aOR=0.730, p=0.021). There was no difference in odds of AKI, sepsis or AP between the two groups.

Conclusions: Our study found that cannabis use is associated with reduced disease severity and better outcomes among patients hospitalized with CP. Further studies are needed to confirm our findings and explore the role of cannabinoids in pancreatitis.

Key words: cannabis – chronic pancreatitis – health care costs – hospital mortality – cannabinoids.

Abbreviations: AKI: acute kidney injury; AP: acute pancreatitis; CB: canabinoid; CBD: cannabidiol; CP: chronic pancreatitis; CCI: Charlson Comorbidity Index; DVT: deep vein thrombosis; ECS: endocannabinoid system; ICU: intensive care unit; PE: pulmonary embolism; THC: Δ9-tetrahydrocannabinol.

INTRODUCTION

Chronic pancreatitis (CP) is a debilitating chronic disease which commonly presents as severe, constant, dull postprandial pain in the mid-epigastric region radiating to the back, which can significantly worsen patients' quality of life [1, 2]. Prescription and over-the-counter pain medications have been the mainstay of treatment for pain associated with CP. With the increasing use of cannabis post-legalization, studies have been undertaken to understand the analgesic and anti-inflammatory effects of cannabinoids (CB) as an alternative to opioids or other analgesics. While the evidence is mixed, some patients have described a decreased need for prescription opioids after starting cannabis regimens, though these findings have been primarily anecdotal in nature. Bach-huber et al. [3] described that states with medical cannabis laws have significantly lower annual opioid overdose mortality rates compared to states without medical cannabis. A recent examination of Medicare claims data also showed that the use of prescription pain medications was significantly reduced in states following the implementation of medical cannabis laws [4]. Bicket et al. [5] investigated adults with chronic pain in states with medical cannabis laws and found that 3 in 10 persons reported using cannabis to manage their pain. Interestingly, more than half of those adults who used cannabis to manage pain, reported that use of cannabis led them to decrease the use of prescription and over-the-counter

pain medications, and less than 1% reported that use of cannabis increased their use of these medications [5].

Cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC) are the two primary CBs found in cannabis. Cannabis exerts its effects through its widely distributed receptors within the endocannabinoid system (ECS), which is composed of receptors, endogenous ligands, and ligand metabolizing enzymes. Cannabinoid receptors are abundant within the pancreatic tissue, with CB1 receptors primarily in the alpha cells and CB2 receptors in the delta cells [6]. Their presence facilitates cannabis-induced acute pancreatitis [7, 8]. Also, CB1 and CB2 receptors have a potential role in reducing gastric acid secretions and intestinal secretions [9]. However, studies have suggested cannabis was associated with better outcomes in patients with acute pancreatitis [10]. Furthermore, cannabinoids evidently reduce markers of inflammation and fibrosis in pancreatic stellate cells, which may decrease disease severity in CP, as it is characterized by persistent and prolonged inflammation in the pancreas [11]. While existing literature shows the significant role of the ECS in providing an analgesic and anti-inflammatory effect and its potential use in CP, our study aimed to use national data to assess the impact of cannabis use on additional outcomes among hospitalized patients with CP [12].

METHODS

Data Source

A retrospective cohort analysis was done utilizing the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) from 2016 to 2020. It is the nation's largest database of inpatient hospital stays. It collects data from a 20% stratified sample of hospitals in 37 states of the United States and has been reliably used to estimate disease burden and outcomes [13]. Each hospitalization is de-identified and maintained in the NIS as a unique entry. Institutional review board (IRB) approval was not required as data is de-identified.

Study Population

The International Classification of Diseases 10th Version, Clinical Modification (ICD-10 CM) diagnosis codes were used to identify all patients with chronic pancreatitis (K86.0, K86.1). Patients aged less than 18, those with missing demographics and mortality data were excluded from the analysis. The 907,790 cases who met the inclusion criteria, were stratified into two groups, those with and without cannabis use, based on the presence of ICD-10 code F12 (Fig. 1).

Study Variables

We collected information on patient demographics such as age (three groups: < 44 years, 45–64 years, and > 65 years), gender, race, primary insurance, and median income quartile. Hospital characteristics such as region, bed size, and rural/urban location, pre-specified by HCUP, were also collected. We further collected information regarding comorbidities and used the Charlson Comorbidity Index (CCI) to assess the comorbidity burden. CCI is a well-validated index based on ICD 10-CM codes meant to be used in large administrative data to predict mortality and hospital resource use (14).

Study Outcomes

The outcomes assessed were in-hospital mortality, sepsis, acute kidney injury (AKI), deep vein thrombosis (DVT), pulmonary embolism (PE), intensive care unit (ICU) admission, acute pancreatitis and pancreatic cancer.

Statistical Analysis

Hospital-level discharge weights were used to generate national estimates. Chi-square was used to compare categorical variables, and an independent sample t-test was used to measure continuous variables. Univariate and Multivariate logistic regression was performed. We adjusted for patient demographics, hospital comorbidities, CCI, tobacco smoking, and etiology of chronic pancreatitis. The multivariate logistic regression model included only variables with a p <0.1 on

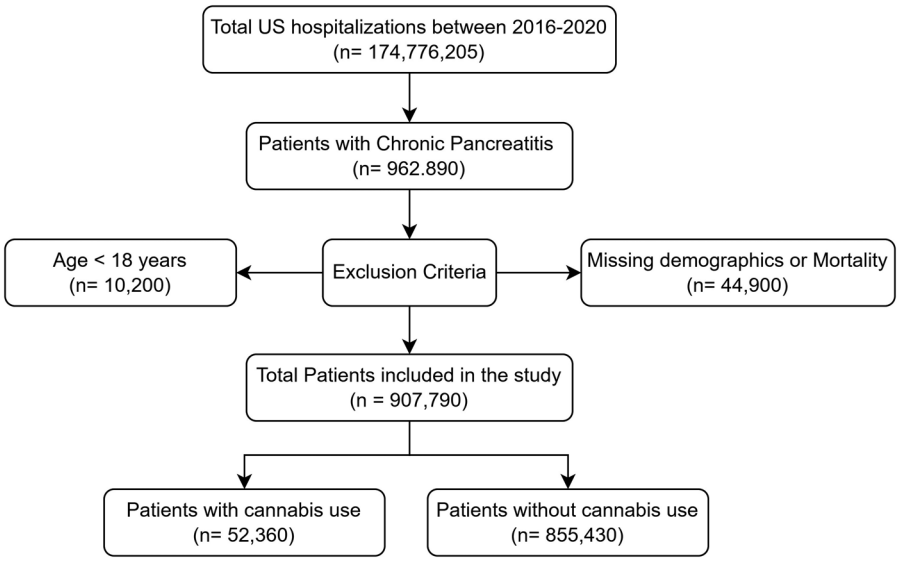

Fig. 1. Inclusion flow diagram for the study

univariate analysis. The unadjusted and adjusted odds ratios were calculated with a 95% confidence interval. A type I error of <0.05 was considered statistically significant. Data analysis was performed using STATA 17.0 (Texas).

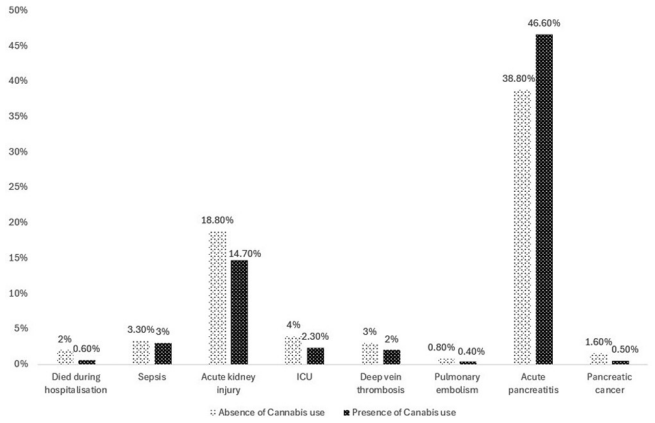

Fig. 2. Outcomes of Chronic Pancreatitis patients, stratified by presence of cannabis use.

RESULTS

Patient Demographics and Hospital Characteristics

Out of 907,790 hospitalized patients with CP, 52,360 (5.8%) were cannabis users. A higher proportion of cannabis users were 18-44 years old (48.4%), male (66.0%), white (57.0%), had medicaid insurance (45.5%), and were in the lowest income quartile (43.1%). A complete list of patient demographics and hospital characteristics included in the study can be seen in Table I.

Patient comorbidities and etiology of cannabis use

Patients who used cannabis had greater prevalence of alcohol-related CP, tobacco use, mild liver disease, and metastatic cancer compared to patients who did not use cannabis. A comprehensive list of comorbidities with cannabis use is presented in Table II.

In-hospital mortality

The incidence of in-hospital mortality was 0.58% in cannabis users and 2.0% in non-cannabis users. Information regarding the outcomes is presented in Fig. 2. After adjusting for confounding factors, cannabis users had a statistically significant lower likelihood of death during hospitalization (aOR=0.47, 95%CI: 0.62-0.82, p<0.001). The results of the multivariate logistic analysis are presented in Table III.

Sepsis

The incidence of sepsis was 3.0% in cannabis users vs. 3.3% in non-cannabis users. After adjusting for confounding factors, no association was noted between the two groups (aOR=0.92, 95%CI: 0.82-1.04, p=0.17).

Acute Kidney Injury

The incidence of AKI in cannabis users was 15% vs. 19% in non-cannabis users. After adjusting for confounding factors, no association was noted between the two groups (aOR=1.01, 95%CI: 0.95-1.07, p=0.83).

ICU admission

The incidence of ICU admission in cannabis users was 2.3% vs. 4.0% in non-cannabis users. After adjusting for confounding factors, cannabis users had a lower likelihood of ICU admission (aOR=0.71, 95%CI: 0.62-0.81, p<0.001).

Deep Vein Thrombosis

The incidence of DVT was 2% in cannabis users vs. 3.0% in patients without cannabis use. After adjusting for confounding factors, cannabis users had a statistically significant decrease in odds of having DVT (aOR=0.71, 95%CI: 0.62-0.82, p<0.001).

Pulmonary Embolism

The incidence of PE in cannabis users was 0.4% vs. 0.8% in patients who did not use cannabis. After adjusting for confounding factors, cannabis users had a statistically significant lower likelihood of PE (aOR=0.62, 95%CI: 0.46-0.84, p=0.002).

Acute Pancreatitis

The incidence of AP was 46.6% in cannabis users, vs. 39% in patients who did not consume cannabis. After adjusting for confounding factors, there was no difference between the two groups (aOR=1.00, 95%CI: 0.96-1.04, p=0.92).

Pancreatic Cancer

The incidence of pancreatic cancer was 0.5% in cannabis users, vs. 1.6% in patients without cannabis use. After adjusting for confounding factors, cannabis users had a statistically significant lower likelihood of pancreatic cancer (aOR=0.73, 95%CI: 0.56-0.95, p=0.021).

DISCUSSION

Our study, using nationally available data, reports that hospitalized patients with CP and cannabis use had a lower risk of in-hospital mortality, ICU admission, thromboembolic events, and pancreatic cancer. A higher incidence of AP was noted in these patients, however, after adjusting for confounding factors, the relationship was not significant.

Our study found that cannabis use was associated with lower odds of in-hospital mortality among patients hospitalized with CP. Patients with CP are at a higher risk of complications due to their compromised immune system, tissue damage, and long-standing pancreatic inflammation. The protective effect of cannabis may be due to the effect of the ECS on immune response, inflammation and redox activity [15]. This may also explain the lower incidence of sepsis in cannabis users. CBD/THC has been reported to reduce sepsis by decreasing endothelial inflammation, cytokine production, and free radical formation [16-18]. Several animal and human studies have reported cannabis use modulates inflammatory response by reducing the pro-inflammatory cytokines interleukine (IL)-1, IL-2, IL-6, IL-12 and tumor necrosis factor (TNF)-α [19-21].

Table I. Patient demographics stratified by the presence of cannabis use

	Absence of cannabis use, n(%)	Presence of cannabis use. n(%)	
Age categories			
18-44	237,020 (28.0)	25,350 (48.4)	**<0.001**
45-65	420,165 (49.1)	24,555 (47.0)	**<0.001**
>65	198,245 (23.2)	2,455 (4.7)	**<0.001**
Gender			
Male	475,600 (56.0)	34,390 (66.0)	**<0.001**
Female	379,830 (44.4)	17,970 (34.3)	**<0.001**
Race			
White	558,770 (65.3)	29.630 (57.0)	**<0.001**
African American	184,285 (22.0)	16,875 (32.2)	**<0.001**
Hispanic	73,965 (8.6)	3,975 (7.6)	**<0.001**
Asian/pacific Islander	12,635 (1.5)	270 (0.5)	**<0.001**
Native American	6,745 (0.8)	670 (1.3)	**<0.001**
Other	19,030 (2.2)	940 (1.8)	**<0.001**
Insurance			
Medicare	340,775 (39.8)	12,620 (24.1)	**<0.001**
Medicaid	237,870 (27.8)	23,815 (45.5)	**<0.001**
Private	188,455 (22.0)	8,055 (15.4)	**<0.001**
Uninsured	56,835 (7.0)	5,460 (10.4)	**<0.001**
Income			
Lowest quartile	300,855 (35.2)	22,590 (43.1)	**<0.001**
Second quartile	227,785 (26.6)	13,655 (26.1)	**<0.001**
Third quartile	190,120 (22.2)	10,180 (19.4)	**<0.001**
Highest quartile	136,670 (16.0)	5,935 (11.3)	**<0.001**
Region of hospital			
Northeast	152,715 (18.0)	7,865 (15.0)	**<0.001**
Midwest	206,260 (24.1)	15,015 (29.0)	**<0.001**
South	348,585 (41.0)	19,245 (37.0)	**<0.001**
West	147,870 (17.3)	10,235 (20.0)	**<0.001**
Urban	788,855 (92.2)	48,530 (93.0)	**0.1171**
Teaching hospital	622,505 (73.0)	39,050 (75.0)	**<0.001**
Bed size of hospital			
Small	176,320 (20.6)	11,305 (22.0)	**0.0195**
Medium	240,595 (28.1)	15,070 (29.0)	**0.0195**
Large	438,515 (51.3)	25,985 (49.6)	**0.0195**
CCI			
0	188,010 (22.0)	15,665 (29.9)	**<0.001**
1	214,310 (25.1)	14,585 (28.0)	**<0.001**
2	145,830 (17.1)	8,625 (16.5)	**<0.001**
3 or more	307,280 (35.9)	13,485 (25.8)	**<0.001**

Cannabis also has an antimicrobial effect on gram-positive and gram-negative organisms [22-24]. It also reduces bacterial LPS-induced sepsis by reducing the number of adherent leukocytes [25]. A retrospective cohort study by Shover et al. [26] suggested that active cannabis users hospitalized with COVID-19 had better clinical outcomes compared with non-users, which is consistent with the findings of our study.

The relationship between cannabis and AP has shown conflicting results in previous literature. A 10-year analysis of the NIS reported cannabis users to have lower mortality, morbidity, and hospitalization cost than non–cannabis-exposed patients [27]. A systematic review by Barkin et al. [28] investigating cannabis-induced AP reported recurrent AP related temporally to cannabis use. Goyal et al. [29] found that the concomitant use of cannabis and alcohol may reduce the severity of AP. Additionally, an NIS study from 2012-2014 by Adejumo et al. [30] found that the concomitant use of alcohol and cannabis reduces the incidence of AP. Conversely,

Table II. Comorbidities and etiology among patients with chronic pancreatitis, stratified by the presence of cannabis use

Comorbidities	Absence of cannabis use n(%)	Presence of cannabis use n(%)	p
Alcohol-related chronic pancreatitis	172,250 (20.1)	15,815 (30.2)	<0.001
Tobacco use	343,360 (40.1)	35,200 (67.2)	<0.001
Acute mocardial ischemia	59,435 (6.9)	2,860 (5.5)	<0.001
Congestive heart failure	114,280 (13.4)	4,355 (8.3)	<0.001
Peripheral vascular disease	55,655 (6.5)	2,455 (4.7)	<0.001
Cerebrovascular disease	29,605 (3.5)	1,025 (2.0)	<0.001
Dementia	22,330 (2.6)	300 (0.6)	<0.001
Chronic obstructive pulmonary disease	218,300 (25.5)	12,225 (23.4)	<0.001
Rheumatoid disease	26,470 (3.1)	930 (1.8)	<0.001
Peptic ulcer disease	30,505 (3.6)	1,745 (3.3)	0.2122
Mild liver disease	164,750 (19.3)	11,965 (23.0)	<0.001
Diabetes	216,015 (25.3)	10,460 (20.0)	<0.001
Diabetes+complications	152,595 (17.8)	6,830 (13.0)	<0.001
Hemiplegia/Paraplegia	7,030 (0.8)	260 (0.5)	<0.001
Renal disease	150,675 (17.6)	5,900 (11.3)	<0.001
Cancer	34,530 (4.0)	920 (1.8)	<0.001
Moderate/severe liver disease	59,410 (7.0)	3,040 (5.8)	<0.001
Metastatic cancer	16,205 (2.0)	395 (7.5)	<0.001
AIDS	5,870 (0.7)	550 (0.1)	<0.001

Matsuda et al. [31] using a murine model of cerulein-induced severe AP, demonstrated that endocannabinoids can worsen the course of the disease and that the administration of an exogenous CB1 antagonist (AM251) ameliorated the disease [31]. Furthermore, Dembiński et al. [32] demonstrated that a natural endogenous ligand for the CB1 receptor (anandamide) increased the severity of AP, while administration of an exogenous CB1 receptor antagonist AM251 was associated with a reduced pancreatic tissue inflammation [32]. In contrast, Michalski et al. [10] demonstrated that AP patients showed an up-regulation of cannabinoid receptors and increased levels of endo- cannabinoids in the pancreas. The administration of a synthetic agonist of CB1 and CB2 receptors (HU210) in mice with induced AP led to a reduction in tissue pancreatic inflammation [10]. Further studies are needed to identify the mechanisms responsible for these conditions.

Our study found that cannabis use was associated with lower odds of DVT and pulmonary embolism among hospitalized patients with CP. Literature has shown mixed results regarding the role of cannabinoids in thromboembolic events. Desai et al. [34] reported cannabis use to be associated with lower odds of pulmonary embolism admissions in young adults. Other studies have reported cannabis users to have higher rate of thromboembolic events in trauma, geriatric, and post-operative patients [34-36]. Mendizabal et al. [37] suggested that chronic marijuana use may lead to cycles of vasoconstriction and vasodilation independent of skeletal muscle activity. Cannabis has been shown to exert a procoagulant effect by acting on the

Table III. Multivariate logistic model results identifying association between cannabis use and various complications

Outcomes	Adjusted Odds Ratio	95% Confidence Interval	p
Died during hospitalization	0.47	0.62-0.82	<0.001
Sepsis	0.92	0.82-1.04	0.17
Acute kidney injury	1.00	0.95-1.07	0.83
ICU	0.71	0.62-0.81	<0.001
Deep vein thrombosis	0.71	0.62-0.82	<0.001
Pulmonary embolism	0.62	0.46-0.84	0.002
Acute pancreatitis	1.00	0.96-1.04	0.92
Pancreatic cancer	0.73	0.56-0.95	0.021
	Adjusted Coefficient	**95% Confidence Interval**	**p**
Length of stay	-0.56	-0.67 - -0.45	<0.001
Total hospitalization charges	-6991.32	-8384.22 - -5598.43	<0.001

CB1, CB2 receptors, which are present on the surface of the platelets, thus increasing the expression of surface glycoprotein IIb-IIIa and P-selectin on human platelets in a dose-dependent manner [38]. Some authors report an inhibiting effect of large concentrations of THC on ADP-induced platelet aggregation in a dose-dependent manner; others found increased irreversible platelet aggregation independently of an added inducer in the presence of THC [39-40]. The reduction in pro-inflammatory cytokines in cannabis users may also play a role in reduced incidence of DVT and pulmonary embolism, which was noted in our study. In vitro coagulation studies reveal that cannabis and two of the major cannabinoids, THC and cannabinol (CBN), displayed inhibition of thrombin activity and thrombin-induced clot formation [41]. Further studies are needed to clarify the mechanisms responsible for our findings and the complex interplay between cannabis, pancreatitis, and thromboembolism.

Our study notes that even after adjusting for confounding factors, cannabis use was associated with lower odds of developing pancreatic cancer. Cannabinoid receptors are highly expressed in pancreatic cancer compared with normal pancreatic tissue [42)]. Furthermore, CBD and THC appear to have antiproliferative and proapoptotic effects in a dose-dependent manner, which can potentially explain our findings [43-44]. Cannabidiol modulation has also been shown to be beneficial in improving survival in a clinically relevant pancreatic cancer model when combined with gemcitabine [45].

We acknowledge that our study has several limitations. The NIS database relies on ICD-10 coding, which is subject to human error. Additionally, this is an observational study, and NIS does not provide data regarding pharmacologic agents, radiographic findings, and outpatient visits. NIS tracks hospitalizations rather than individual patients; therefore, a single patient can account for multiple hospitalizations. Other limitations include self-reporting of cannabis use and lack of information regarding the amount and frequency of substance use. Furthermore, NIS lacks data regarding the duration and the amount of cannabis used by the patient. Further studies with more granular data will be beneficial in studying the effect of varying doses of cannabis on the pancreas. Our study strengths include the large sample size and lack of regional bias, which we feel helps to mitigate the limitations.

CONCLUSIONS

Our study reports cannabis use among hospitalized patients with chronic pancreatitis to be associated with improved in-hospital outcomes as well as lower odds of developing pancreatic cancer. Our findings should be interpreted with caution, as although cannabis may have some beneficial effects in chronic pancreatitis patients, its impact on other pancreatic disorders and organ systems needs to be taken into account. Future research with more granular data, aiming to identify the exact mechanism by which cannabis exerts its effects on the pancreas and other organ systems is required.

Conflicts of interest: None to declare.

Authors' contribution: A.S., N.T, H. S.B., V.K. and H.I. contributed to the conceptualization, methodology, formal analysis, and writing of the original draft and editing. R.M. and A.S. contributed to data curation, formal analysis, and editing. A.S. and J.Y. contributed to the supervision, editing, conceptualization, and final approval of the study.

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