



Original article

Cannabis use may reduce healthcare utilization and improve hospital outcomes in patients with cirrhosis

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ABSTRACT

Introduction and Objectives: Previous studies reveal conflicting data on the effect of cannabis use in patients with cirrhosis. This research evaluates the impact of cannabis on hepatic decompensation, health care utilization, and mortality in patients with cirrhosis.

Material and Methods: A retrospective analysis of the State Inpatient Database (SID) was performed evaluating patients from Colorado and Washington in 2011 to represent pre-cannabis legalization and 2015 to represent post-cannabis legalization. Multivariable analysis was performed to study the impact of cannabis on the rate of admissions with hepatic decompensations, healthcare utilization, and mortality in patients with cirrhosis.

Results: Cannabis use was detected in 370 (2.1%) of 17,520 cirrhotics admitted in 2011 and in 1162 (5.3%) of 21,917 cirrhotics in 2015 (p -value <0.001). On multivariable analysis, cirrhotics utilizing cannabis after its legalization experienced a decreased rate of admissions related to hepatorenal syndrome (Odds Ratio (OR): 0.51; 95% Confidence Interval (CI): 0.34–0.78) and ascites (OR: 0.73; 95% CI: 0.63–0.84). Cirrhotics with an etiology of disease other than alcohol and hepatitis C had a higher risk of admission for hepatic encephalopathy if they utilized cannabis [OR: 1.57; 95% CI: 1.16–2.13]. Decreased length of stay (–1.15 days; 95% CI: –1.62, –0.68), total charges (–\$15,852; 95% CI: –\$21,009, –\$10,694), and inpatient mortality (OR: 0.68; 95% CI: 0.51–0.91) were also observed in cirrhotics utilizing cannabis after legalization compared to cirrhotics not utilizing cannabis or utilizing cannabis prior to legalization.

Conclusion: Cannabis use in patients with cirrhosis resulted in mixed outcomes regarding hospital admissions with hepatic decompensation. A trend towards decreased hospital utilization and mortality was noted in cannabis users after legalization. These observations need to be confirmed with a longitudinal randomized study.

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1. Introduction

After centuries of patients utilizing cannabis for medical ailments, the Food and Drug Administration approved medicinal cannabis in the state of California. This approval allowed physicians to prescribe cannabis to patients for the treatment of chronic pain, cancer, anorexia, migraines, and any other illness in which cannabis could provide relief [1–4]. Since the early 1990s, over 30 states have subsequently passed laws permitting the use of medic-

inal cannabis [5]. While cannabis is now being prescribed for some gastrointestinal diseases, its effect on cirrhosis remains unclear.

The prevalence of cirrhosis is significantly increasing in the United States and it currently affects around 700,000 patients [6]. The rising number of cirrhotics has been linked to the growing obesity epidemic, alcohol abuse, and opioid use leading to surges in hepatitis B and C. Many patients with cirrhosis are unaware of this diagnosis until they develop a feature of hepatic decompensation such as ascites, variceal hemorrhage, or hepatic encephalopathy. Decompensated cirrhotics have a reduced median life expectancy of 2 years compared to 12 years in patients with compensated cirrhosis. Decompensation occurs at a rate of 5–7% annually and accounts for the majority of the hospital admission related to cirrhosis [7]. Once non-surgical options like diuretics, lactulose,

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rifaximin, band ligation, and transjugular intrahepatic portosystemic shunts are no longer effective, the only definitive treatment available for selected patients is liver transplantation [8].

The effectiveness of medicinal cannabis has been noted for many digestive system diseases including cirrhosis. The need to determine the effect of medicinal cannabis on cirrhosis is emerging and conflicting. Rodent models have determined cannabinoid receptors 1 and 2 to be present in hepatocytes and endothelial cells. Pharmacologic manipulation of these receptors has been linked to decreased progression and even reversal of fibrosis in cirrhosis as well as improved neurologic and cognitive function in hepatic encephalopathy [9]. Cannabinoid receptor 1 antagonism has demonstrated vascular effects in patients with cirrhosis. It can cause an increase in vascular resistance and a decrease in portal pressures which may reduce complication from portal hypertension. Endocannabinoids and exocannabinoids are important components of cannabis with mechanistic roles in cirrhosis. They impact fibrosis and the pathophysiology of portal hypertension though the effect has yielded mixed results based on the etiology of liver disease [10–14].

Given the increased use of cannabis after its legalization and conflicting results on its effect on patients with cirrhosis, this study aims to perform a novel evaluation of the effect of cannabis use on admissions with hepatic decompensation, healthcare utilization, and patient outcomes in cirrhotics in the pre-legalization and post-legalization eras of cannabis use.

2. Methods

2.1. Data source

A retrospective analysis of the State Inpatient Database (SID) was performed evaluating patients from Colorado and Washington in 2011 to represent pre-cannabis legalization and 2015 to represent post-cannabis legalization. The SID is part of the Healthcare Cost and Utilization Project (HCUP), which is one of the largest publicly available databases representing 35 million hospitalizations annually. Like other databases provided by HCUP, SID allows patient and hospital demographics, hospital resources, and outcomes to be obtained by participating hospitals [15]. HCUP requires permission to access specific state-based data obtained prior to analysis. Given SID is a publicly available database comprised of de-identified information, The Ohio State University deemed this study exempt from review by the Institutional Review Board.

Utilizing International Classification of Disease (ICD) 9 and 10 codes, admissions including patients with a primary or secondary diagnosis of cirrhosis were included. Patients were excluded if they were under the age of 18.

2.2. Definition of variables

Decompensated cirrhosis was defined as the presence of cirrhosis plus an ICD-9 or ICD-10 code for a feature of decompensation including hepatorenal syndrome, hepatic encephalopathy, active variceal bleeding, or ascites.

Additional variables included age, race, income quartile, and type of insurance. Other comorbidities, as defined by AHRQ-Elixhauser comorbidity scale which was modified to exclude liver disease, were also included. Etiology of cirrhosis was determined with the use of ICD-9 and ICD-10 codes and included alcohol, hepatitis C, hepatitis B, and other etiologies as defined by the presence of cirrhosis but absence of the above codes [16]. Etiology of cirrhosis was determined via a hierarchy model including alcohol, hepatitis C, hepatitis B, and others.

2.3. Outcomes of interest

The primary outcome of interest was to compare the admission rates for hepatic decompensation in cirrhotics utilizing cannabis to cirrhotics not utilizing cannabis. Secondary outcomes included the effect of cannabis use in cirrhotics on healthcare utilization including length of stay, total charges, and patient outcomes. A subgroup analysis was also performed to evaluate the impact of the etiology of cirrhosis with cannabis use on hospital and patient outcomes.

2.4. Statistical analysis

Utilizing chi-square tests or t-tests, patient and hospital demographics, in addition to hospital outcomes, were compared in patients with cirrhosis who received care in 2011 versus 2015. Multivariable regression models were fit for admissions with hepatic decompensation, healthcare utilization, and patient outcomes. All models were adjusted for age, gender, race, income, insurance, Elixhauser comorbidity score, and etiology. In addition, time period (defined as pre- and post-cannabis legalization) and cannabis use were included in the models along with their interaction. The subgroup analyses fit the models described above and included a comparison of the etiology of cirrhosis and cannabis use. This comparison investigated the impact of etiology on cirrhosis on outcomes between patients who used cannabis and those who did not. The etiology of cirrhosis was determined via a hierarchy model including alcohol, hepatitis C, hepatitis B, and others. Data was analyzed using SAS 9.4 (SAS Institute Inc. Cary, NC), and a p-value less than 0.05 was considered significant.

3. Results

A total of 17,520 cirrhotics received inpatient care in Colorado and Washington in 2011 including 370 (2.1%) patients who utilized cannabis. In 2015, a total of 21,971 cirrhotics received inpatient care including 1162 (5.3%) patients who utilized cannabis. There was a significant increase in the number of cirrhotics utilizing cannabis after the legalization in these states (p-value <0.001) (Table 1).

3.1. Features of decompensation

On multivariable analysis, cirrhotics who utilized cannabis after legalization in 2015 had decreased admission rates for specific features of hepatic decompensation including hepatorenal syndrome [Odds Ratio (OR): 0.51; 95% confidence interval (CI): 0.34–0.78] and ascites [OR: 0.73; 95% CI: 0.63–0.84] compared to cirrhotics who did not utilize cannabis. No significant difference in admission rates for hepatic encephalopathy and variceal bleeding was observed between cirrhotics utilizing cannabis after legalization and cirrhotics not utilizing cannabis. There was no significant difference in admission rates for hepatic decompensations in cirrhotics who utilized cannabis in 2011 compared to cirrhotics who did not; however, the impact of legalization on active variceal bleeding could not be assessed, as no patients utilizing cannabis in 2011 experienced variceal bleeding in the data (Table 2).

3.2. Patient and hospital outcomes

On multivariable analysis, cirrhotics utilizing cannabis in 2015 had decreased length of admission [−1.15 days; 95% CI: −1.62, −0.68], total charges for admission [−\$15,852, 95% CI: −\$21,009, −\$10,694] and inpatient mortality [OR: 0.68; 95% CI: 0.51–0.91] compared to cirrhotics who did not use cannabis. However, there was no significant differences in length of stay, total charges, or inpatient

Table 1

Comparison of hospitalized adult patients with cirrhosis in Colorado and Washington before legalization of cannabis (2011) and post legalization (2015).

	2011	(n = 17,520)	2015 (n = 21,971)		p-value
	N	%			
Cannabis use	370	2.1	1162	5.3	<0.001
Female sex	6810	38.9	9092	41.4	<0.001
Age (mean, SD)	57.69	12.0	58.63	12.2	<0.001
Race					<0.001
White	11,819	73.6	15,782	75.0	
Black	648	4.0	765	3.6	
Hispanic	1990	12.4	2667	12.7	
Other	1599	9.9	1821	8.7	
Income quartile					<0.001
First	4001	23.6	4189	19.8	
Second	4115	24.3	5124	24.2	
Third	5418	32.0	7191	34.0	
Fourth	3395	20.1	4644	21.9	
Type of insurance					<0.001
Medicare	6582	37.6	8924	40.6	
Medicaid	3975	22.7	6915	31.5	
Private	4156	23.7	5036	22.9	
Other	2807	16.0	1092	4.9	
AHRQ-Elixhauser Comorbidity $\geq 3^a$	13,390	76.4	18,187	82.8	<0.001
Etiology ^b					<0.001
Alcohol	9389	53.6	11,045	50.3	
Hepatitis C	3094	17.7	3173	14.4	
Hepatitis B	178	1.0	182	0.8	
Other	4859	27.7	7571	34.5	
Outcomes					
Hepatorenal Syndrome	703	4.0	748	3.4	0.001
Hepatic Encephalopathy	3434	19.6	4914	22.4	<0.001
Ascites	5945	33.9	6636	30.2	<0.001
Active Variceal Bleeding	128	0.7	165	0.8	0.815
Mortality	1103	6.3	1515	6.9	0.017
Length of Stay (mean, SD)	5.92	7.2	6.17	7.7	0.001
Total Charges (mean, SD)	\$49,932	\$69,555	\$64,507	\$90,737	<0.001

^a Modified to exclude liver disease.^b Hierarchy Model.**Table 2**Multivariable models analyzing the effect of cannabis in 2011 and 2015 on rates of admission with various hepatic decompensation^a.

Feature of Decompensation	Year	Cannabis Use	Odds Ratio	95% Confidence Interval
Hepatorenal Syndrome	2011	No Cannabis Use	Reference	
		Cannabis Use	0.54	0.29 – 1.03
	2015	No Cannabis Use	Reference	
		Cannabis Use	0.51	0.34 – 0.78
Hepatic Encephalopathy	2011	No Cannabis Use	Reference	
		Cannabis Use	1.004	0.76 – 1.32
	2015	No Cannabis Use	Reference	
		Cannabis Use	0.90	0.77 – 1.05
Ascites	2011	No Cannabis Use	Reference	
		Cannabis Use	0.87	0.69 – 1.09
	2015	No Cannabis Use	Reference	
		Cannabis Use	0.73	0.63 – 0.84
Active Variceal Bleeding	2011 and 2015	No Cannabis Use	Reference	
		Cannabis Use	0.84	0.44 – 1.60

^a All models adjusted for age, gender, race, income, insurance, Elixhauser comorbidity, and etiology.**Table 3**Multivariable models analyzing the effect of cannabis in 2011 and 2015 on healthcare utilization and patient outcomes^a.

Outcome	Year	Cannabis Use	Odds Ratio/Days/ \$	95% Confidence Interval
Inpatient Mortality	2011	No Cannabis Use	Reference	
		Cannabis Use	1.11	0.72 – 1.70
	2015	No Cannabis Use	Reference	
		Cannabis Use	0.68	0.51 – 0.91
Length of Stay	2011	No Cannabis Use	Reference	
		Cannabis Use	-0.56 days	-1.38 – 0.25
	2015	No Cannabis Use	Reference	
		Cannabis Use	-1.15 days	-1.62 – -0.68
Total Charges	2011	No Cannabis Use	Reference	
		Cannabis Use	-\$8673	-\$17,608 – \$261
	2015	No Cannabis Use	Reference	
		Cannabis Use	-\$15,852	-\$21,009 – -\$10,694

^a All models adjusted for age, gender, race, income, insurance, Elixhauser comorbidity, and etiology.

Table 4Multivariable models analyzing the impact of cannabis on rate of admissions with various cirrhosis decompensation according to its etiology^a.

Outcomes	Cannabis Use	Etiology of Cirrhosis	Odds Ratio	95% Confidence Interval
Hepatorenal Syndrome	No Cannabis Use	Alcohol	Reference	
		Other	0.53	0.47 – 0.60
		Alcohol	Reference	
Hepatic Encephalopathy	Cannabis Use	Other	0.21	0.08 – 0.61
		Alcohol	Reference	
		Hepatitis C	0.17	0.15 – 0.19
	No Cannabis Use	Other	0.87	0.82 – 0.92
		Alcohol	Reference	
		Hepatitis C	0.24	0.14 – 0.40
Ascites	Cannabis Use	Other	1.57	1.16 – 2.13
		Alcohol	Reference	
		Hepatitis C	0.61	0.57 – 0.65
	No Cannabis Use	Other	0.55	0.52 – 0.58
		Alcohol	Reference	
		Hepatitis C	0.48	0.35 – 0.66
Active Variceal Bleeding	Cannabis Use	Other	0.20	0.13 – 0.30
		Alcohol	Reference	
		Other	0.93	0.72 – 1.19
	No Cannabis Use	Alcohol	Reference	
		Other	0.17	0.02 – 1.35

^a All models adjusted for age, gender, race, income, insurance, Elixhauser comorbidity, and etiology.**Table 5**Multivariable models analyzing the effect of cannabis according to etiology of cirrhosis on healthcare utilization and patient outcomes^a.

Outcomes	Cannabis Use	Etiology of Cirrhosis	Odds Ratio / Day / Cost	95% Confidence Interval
Mortality	No Cannabis Use	Alcohol	Reference	
		Hepatitis C	0.76	0.67 – 0.87
		Other	0.83	0.75 – 0.92
	Cannabis Use	Alcohol	Reference	
		Hepatitis C	0.15	0.05 – 0.49
		Other	0.85	0.47 – 1.54
Length of Stay	No Cannabis Use	Alcohol	Reference	
		Hepatitis C	–0.14	–0.37 – 0.09
		Hepatitis B	–0.38	–1.24 – 0.47
	Cannabis Use	Other	–0.12	–0.31 – 0.07
		Alcohol	Reference	
		Hepatitis C	0.10	–0.91 – 1.12
Total Charges	No Cannabis Use	Hepatitis B	8.69	2.64 – 14.73
		Other	0.21	–0.82 – 1.25
		Alcohol	Reference	
	Cannabis Use	Hepatitis C	\$3016	\$472 – \$5560
		Hepatitis B	\$1917	–\$7469 – \$11,304
		Other	\$2925	\$868 – \$4982
	No Cannabis Use	Alcohol	Reference	
		Hepatitis C	\$1741	–\$9432 – \$12,913
		Hepatitis B	\$17,597	–\$48,706 – \$83,901
	Cannabis Use	Other	\$1214	–\$10,143 – \$12,571

^a All models adjusted for age, gender, race, income, insurance, Elixhauser comorbidity, and year.

mortality between cirrhotics who utilized cannabis and cirrhotics who did not use cannabis in 2011 (Table 3).

3.3. Subgroup analysis based on etiology of cirrhosis

Of the total 17,520 cirrhotics admitted in 2011 and 21,971 cirrhotics admitted in 2015, the majority of patients had alcoholic cirrhosis (53.6% and 50.2% respectively) followed by other etiologies, hepatitis C, and hepatitis B (Table 1).

On multivariable analysis, the admission rate of hepatic decompensation varied based on the etiology of liver disease and cannabis use. The risk of admission for ascites and hepatorenal syndrome varied based on etiology regardless of cannabis use. However, patients with etiologies of cirrhosis other than alcohol and hepatitis C had a reduced risk of admission with hepatic encephalopathy if they did not utilize cannabis [OR: 0.87; 95% CI: 0.82–0.92] and an increased risk if they did utilize cannabis [OR: 1.57; 95% CI: 1.16–2.13] (Table 4).

On multivariable analysis of hospital outcomes, patients with a hepatitis C cirrhosis diagnosis who utilized cannabis had a decreased risk of mortality compared to patients with alcoholic cirrhosis and other etiologies of cirrhosis [OR: 0.15; 95% CI 0.05–0.49]. Length of stay and total charges were not significantly different between the etiologies of cirrhosis regardless of cannabis use (Table 5).

4. Discussion

As the medicinal properties of cannabis become more recognized and subsequently prescribed throughout the United States, it is crucial to understand its effect on patients with cirrhosis. Research published thus far has yielded conflicting results on reversal of fibrosis and reduction of portal hypertension related complications. This study revealed mixed results regarding the effect of cannabis use on the incidence of hospital admissions due to hepatic decompensation. Improved healthcare utilization and patient outcomes in cirrhotics utilizing cannabis after the legal-

ization of medicinal cannabis were noted. Improved outcomes in cirrhotics utilizing cannabis may be related to decreased portal hypertension shown in previous studies.

The secondary analysis, which evaluated hospital admission for decompensation based on the etiology of liver disease and cannabis use, continues to highlight mixed results in regard to the effect of cannabis on admissions due to hepatic decompensation [17]. Cirrhotics with etiologies other than alcoholic liver disease who utilize cannabis have a lower risk of admission due to specific factors of hepatic decompensation specifically ascites and hepatorenal syndrome. However, an increase in admissions due to hepatic encephalopathy based on the etiology of liver disease and the utilization of cannabis was noted. Utilizing medications or substances like cannabis that have known psychotropic effects can result in alterations of mental status and can potentially aggravate hepatic encephalopathy. While cannabis use may reduce admissions due to other factors of decompensation, it is crucial to highlight that it may worsen hepatic encephalopathy, one of the leading indications for admission in patients with decompensated cirrhosis.

As significantly improved outcomes were noted after the legalization of cannabis compared to pre-legalization, it can be assumed that the prescribed, regulated dose of cannabis influenced outcomes. In 2011, strict laws regarding administration, dosing, duration of therapy, and quality control of cannabis were not in effect, which allowed patients to take inconsistent, unregulated dosing. Since legalization, further research has been completed emphasizing recommended daily dosing based on underlying components and appropriate titration and administration in order to provide medicinal benefit and avoid side effects like psychogenic complications [18]. If medicinal cannabis is utilized in liver disease, this study highlights the need for it to be regulated by a trained medical professional.

While this study highlights an association between some improvement in hospital utilization and mortality in cirrhotics utilizing cannabis, the long-term effects of cannabis in cirrhotics is much more controversial, especially in patients who are liver transplant candidates. Many transplant centers consider a patient who is using cannabis to be ineligible for a transplant despite mixed data on its effect on transplant outcomes. Recent studies have determined cannabis users do not have increased risk of mortality or delisting while waiting for a liver transplant compared to transplant candidates who do not use cannabis [19]. However, the increased risk of infectious complications, like aspergillosis, in immunocompromised transplant recipients who utilize cannabis has been cited. [20,21]. Before medicinal cannabis is considered in cirrhotics, the timing and progression of disease should be considered. Those with compensated disease who are not currently undergoing transplant evaluation may be the ideal patient population for this intervention, although further research is required.

Multiple strengths and weaknesses should be noted while considering the data presented. First, this is one of the largest evaluations to date attempting to assess the effect of cannabis use on cirrhotics. This number of patients could not be obtained with a single or multicentered analysis. While associations between cannabis use and outcomes could be determined, this study highlights the need for prospective trials to further clarify the effect of cannabis on cirrhosis, as the number of cannabis users continues to increase in the United States. Given this study was performed with a large national database, there are limitations that should be noted. Confirmation of the ICD-9 and ICD-10 coding on an individual patient basis was unable to be confirmed, although these codes have been verified in previous studies. The utilization of the State Inpatient Database does not allow each patient's MELD score to be evaluated given laboratory values are not recorded. Information on medications cannot be collected, and the dose, length of utilization, and medical prescription data is unknown.

5. Conclusion

In summary, medicinal cannabis is associated with improved patient and hospital outcomes in cirrhotics, but yields mixed results in the reduction of hospital admission for hepatic decompensation, specifically those with hepatic encephalopathy. Improvement in outcomes is noted after the legalization of cannabis, when patients are more likely to be taking consistent, regulated doses. While an association in improved short-term outcomes is demonstrated, the long term effects of cannabis use and subsequent complications in transplant patients remain unclear at this time. Additional research in the form of prospective trials should be performed to further clarify the effect of medicinal cannabis on liver disease prior to the acceptance of this as an appropriate intervention.

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