

RESEARCH LETTER

# Cannabis use and postoperative outcomes in patients undergoing hepatectomy

## Introduction

The increasing use of cannabis following its increasing legalization has raised concerns about its impact on liver function, particularly in regard to elevated hepatic transaminases seen with FDA-approved cannabidiol (CBD) for the treatment of seizure disorders.<sup>1</sup> However, the implications for hepatic surgery remain unclear. We sought to better understand the association of self-reported cannabinoid use with transaminase levels and surgical outcomes in patients undergoing hepatectomy. We hypothesized that there would be no significant difference in hepatic enzymes in cannabis users when compared to non-users and that there would be no difference in clinical outcomes.

## Methods

We performed a retrospective review of prospectively collected clinical data maintained in the University of Colorado liver surgical database. Patients 18 years or older who underwent hepatectomy between 2019 and 2022 were included. Clinical data contained in the database includes patient demographics, comorbidities, oncologic diagnosis and treatment, operative metrics and morbidity, details of hospitalization, and postoperative outcomes.

Cannabis use status was self-reported and documented in the electronic health record. Cannabis use was defined as any current or previous cannabis use prior to the date of surgery. The primary outcomes were pre- and postoperative hepatic enzyme levels, as well as postoperative complications. Complications were defined using the Clavien-Dindo system and were considered minor for grades 1–2 and major for grades 3–5.<sup>2</sup> Chemotherapeutic regimens were classified as hepatotoxic if they included fluorouracil and/or platinum-based agents.

Descriptive statistics were generated comparing cannabis users and non-users. We specifically assessed tobacco use and moderate or greater alcohol use (greater than 7 drinks per week) for concomitant cannabis use. Multivariable regression model was used to determine factors associated with increased hepatic enzymes and postoperative complications. Statistical significance was defined as  $p \leq 0.05$ . Statistics were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### Demographics and treatment

Of the 363 consecutive patients included, 149 (41.0%) underwent major hepatectomy ( $\geq 3$  segments) and 214 (59.0%) minor hepatectomy ( $< 3$  segments) (Table 1). Sixty-four patients (17.6%) reported cannabinoid use, with most reporting recreational use ( $n = 25/64$ , 39.1%). Cannabinoid users were younger (52 vs 61 years,  $p < 0.001$ ) and more commonly current tobacco users (50.0% vs 36.8%,  $p = 0.050$ ) than non-users.

### Hepatic enzymes

In univariate analysis, cannabinoid use was not associated with differences in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin levels preoperatively, as well as on postoperative days 1, 3, and 5. On multivariable analysis, including sex, major hepatectomy, tobacco use, ECOG score, surgical approach, and hepatotoxic chemotherapy, these findings persisted, with the exception of POD5 AST, which was lower in cannabinoid users (37 vs 46,  $p = 0.02$ ).

### Postoperative complications

There were 126 patients (34.7%) who experienced complications within 90 days of surgery, categorized as grade 1–2 ( $n = 79/126$ , 62.7%) and grade 3–5 ( $n = 47/126$ , 37.3%). On univariable analysis, there was no significant difference in all complication rates between cannabinoid users and non-users (34.4% vs 34.8%,  $p = 0.67$ ). Detailed complication information is presented in Table 2. There was no difference in grade 1–2 (16/22 vs 63/104,  $p = 0.79$ ) or grade 3–5 (6/22 vs 41/104,  $p = 0.79$ ). On multivariable analysis, including age, sex, major hepatectomy, tobacco use, ECOG score, surgical approach, and hepatotoxic chemotherapy, findings related to cannabinoid use persisted for all complications, as well as grade 1–2, and grade 3–5 complication subsets. Major hepatectomy (OR 2.30, 95% CI (1.40–3.79),  $p = 0.001$ ) and hepatotoxic chemotherapy (OR 1.74, 95% CI (1.06–2.84),  $p = 0.03$ ) were associated with increased complications.

## Discussion

This retrospective analysis of a prospectively maintained institutional clinical database evaluated the association of self-reported cannabis use with laboratory and clinical outcomes after hepatic surgery. We found no significant differences in pre- and postoperative hepatic

**Table 1** Baseline demographic information

Variable	Control (N = 299)	Experimental (N = 64)	P-Value
Sex - Female	169 (56.5%)	30 (46.9%)	0.16
Age at Surgery	61 (50–69)	52 (36–65)	<b>0.0001</b>
BMI	26 (23–31)	25 (22–28)	<b>0.01</b>
Diagnosis Type			
Colorectal Liver Meta	81 (42.6%)	19 (46.3%)	n/a
NET Meta to Liver	2 (1.1%)	0 (0.0%)	
HCC/Other Primary	17 (9.0%)	1 (2.4%)	
Non-colorectal	27 (14.3%)	9 (22.0%)	
Benign	21 (11.1%)	3 (7.3%)	
Intra-Hepatic Chol	18 (9.5%)	6 (14.6%)	
Extra-Hepatic Chol	4 (2.1%)	0 (0.0%)	
Other	7 (3.7%)	1 (2.5%)	
Gallbladder Cancer	12 (6.4%)	2 (4.9%)	
Smoker (Current vs None)	109 (36.8%)	32 (50.0%)	<b>0.050</b>
Caucasian	256 (85.6%)	59 (92.2%)	0.16
Hispanic Ethnicity	39 (13.2%)	2 (3.2%)	<b>0.02</b>
Previous Abdominal Surgery	121 (40.6%)	16 (25.0%)	<b>0.02</b>
ECOG			
0	218 (79.3%)	43 (75.4%)	0.63
1	49 (17.8%)	11 (19.3%)	
2-4	8 (2.9%)	3 (5.3%)	
Insurance Status			
Private	147 (49.2%)	34 (53.1%)	0.80
Medicare	106 (35.5%)	20 (31.3%)	
Other	46 (15.4%)	10 (15.6%)	
History of COPD	8 (2.7%)	2 (3.1%)	0.69
History of CHF	1 (0.3%)	0 (0.0%)	1.0
Hypertension	126 (42.1%)	22 (34.4%)	0.25
Stroke	9 (3.0%)	0 (0.0%)	0.37
Previous PCI	10 (3.3%)	1 (1.6%)	0.70
Ascites	1 (0.3%)	0 (0.0%)	1.0
CKD	22 (7.4%)	1 (1.6%)	0.09
History of DVT/PE	25 (8.4%)	9 (14.1%)	0.16
Diabetes	47 (15.7%)	6 (9.4%)	0.19
ETOH (Current)	6 (2.2%)	2 (3.7%)	0.62
Cirrhosis present	9 (3.0%)	1 (1.6%)	1.0
Chronic Liver Disease	24 (8.0%)	5 (7.8%)	0.95
Anti-HCV	11 (8.3%)	3 (11.1%)	0.71
Hepatotoxic Chemo	136 (46.0%)	34 (53.1%)	0.30
Radiation	6 (2.1%)	2 (3.3%)	0.63
Surgical Approach			
Open	199 (66.6%)	38 (59.4%)	0.43
Minimally Invasive	100 (33.4%)	25 (39.1%)	
Procedure converted to Open	3 (3.0%)	2 (8.0%)	0.26
Major Hepatectomy ( $\geq 3$ segments)	126 (42.1%)	23 (35.9%)	0.36

(continued on next column)

**Table 1** (continued)

Variable	Control (N = 299)	Experimental (N = 64)	P-Value
Hepatectomy Location			
Right	57 (45.2%)	10 (43.5%)	0.54
Left	45 (35.7%)	7 (30.4%)	
Extended Right	10 (7.9%)	4 (17.4%)	
Extended Left	14 (11.1%)	2 (8.7%)	
ASA Class			
1: Healthy	5 (1.7%)	0 (0.0%)	0.66
2: Mild Systemic	66 (22.1%)	17 (26.6%)	
3: Severe Systemic	216 (72.2%)	46 (71.9%)	
4: Threat to life	12 (4.0%)	1 (1.6%)	

Bold font indicates statistical significance.

**Table 2** Surgical complications following hepatectomy

Variable	Control (N = 299)	Experimental (N = 64)	P-Value
Bile Leak			
No	247 (92.2%)	59 (93.7%)	0.50
Grade 1	5 (1.9%)	2 (3.2%)	
Grade 2	3 (1.1%)	1 (1.6%)	
Grade 3	13 (4.9%)	1 (1.6%)	
Hernia	3 (1.1%)	0 (0.0%)	1.0
Facial Dehiscence	0 (0.0%)	0 (0.0%)	n/a
Hemorrhage	17 (6.4%)	3 (4.8%)	0.78
Liver Failure	13 (4.9%)	3 (4.8%)	1.0
Postoperative Ascites	7 (2.6%)	3 (4.8%)	0.41
PV/SMV Thrombosis	2 (0.8%)	0 (0.0%)	1.0
Pneumonia	4 (1.5%)	2 (3.2%)	0.32
UTI	6 (2.2%)	0 (0.0%)	0.60
Sepsis	5 (1.9%)	1 (1.6%)	1.0
Septic Shock	5 (1.9%)	1 (1.6%)	1.0
Intra Abdominal Abscess	11 (4.1%)	0 (0.0%)	0.23
Bacteremia	3 (1.1%)	2 (3.2%)	0.24
Superficial Wound Infection	3 (1.1%)	1 (1.6%)	0.57
Deep Wound Infection	3 (1.1%)	0 (0.0%)	1.0
Postop MI	0 (0.0%)	0 (0.0%)	n/a
Postop DVT	2 (0.8%)	0 (0.0%)	1.0
Pulmonary Embolism	5 (1.9%)	0 (0.0%)	0.59
Postop Intubation	4 (1.5%)	1 (1.6%)	1.0
Mechanical Ventilation	2 (0.8%)	1 (1.6%)	0.47
Renal Dialysis	2 (0.8%)	0 (0.0%)	1.0
Postop Stroke	1 (0.4%)	0 (0.0%)	1.0
Surgical Complication	104 (34.8%)	22 (34.4%)	0.95
Surgical Complication Type $\leq$ 2	63 (60.6%)	16 (72.7%)	0.28
Surgical Complication Type $\leq$ 3	78 (75.0%)	18 (81.8%)	0.50

enzymes between cannabis users and non-users, with the exception of lower AST in cannabinoid users on POD 5 (37 vs 46,  $p = 0.02$ ), which likely has no clinical relevance. These findings align with

previous work, where elevations in hepatic enzymes associated with high-dose CBD use were attributed to interactions with antiepileptic medications.<sup>1,3</sup> More recent research has shown no significant

increase in transaminase levels in patients not on concurrent anti-epileptics or using lower CBD doses.<sup>4</sup>

Additionally, there was no difference in postoperative complications between cannabinoid users and non-users, consistent with our previous work evaluating cannabinoid use and pancreatic surgery.<sup>5</sup> The effect of cannabinoid use on surgical outcomes remains understudied. The existing literature on cannabinoid use in the perioperative setting shows mixed results, including studies that report increased incidence of myocardial infarction, increased composite morbidity, or no difference depending on the surgical procedure.<sup>6–8</sup> However, these studies have assessed these outcomes in the setting of cannabis use disorder, whereas cannabinoids are often used by oncology patients for management of anorexia, nausea, and pain.<sup>9</sup> Given this, it may not be appropriate to generalize outcomes in patients with cannabis use disorder to the oncology patient population.

Our study has limitations, primarily related to its retrospective nature. Additionally, given that this is a single-center study in a state that was an early adopter of both medical and recreational use of cannabinoids, these results may not be generalizable to other institutions in other states. We relied on patients self-reporting cannabinoid use, which is known to underestimate the true prevalence of cannabinoid use.<sup>10</sup> This, in addition to the lack of standardized dosing or methods of consumption, makes true assessment of the effects of cannabinoids challenging to assess and highlights the need for better methods to quantify use.

While the use of cannabinoids did not appear to affect outcomes in this study, its growing prevalence underscores the need for better understanding its impact on patients undergoing liver surgery. This is particularly important as cannabinoids are often marketed for conditions such as nausea, pain, anorexia, weight loss, and even for treating malignancies. Prospective studies evaluating the route, dosage, and frequency of use are necessary to validate these findings and develop evidence-based guidelines for managing cannabinoid users being evaluated for surgery.

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#### Conflicts of interest

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