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ABOUT COVER

Associate editor of *World Journal of Hepatology*, Dr. Yong-Ping Yang is a Distinguished Professor at Peking University Health Science Center in Beijing, China. Having received his Bachelor's degree from Yanbian University in 1985, Dr. Yang undertook his postgraduate training at PLA Medical College, receiving his Master's degree in 1992. He rose to Chief Physician in the Hepatology Division of the Fifth Medical Center of the Chinese PLA General Hospital in 2003 and has held the position since. His ongoing research interests involve liver fibrosis, cirrhosis and hepatocellular carcinoma, with a particular focus on cryoablation and cryo-immunotherapy for hepatocellular carcinoma. Currently, he serves as Chairman of the Department of Liver Disease of the Chinese PLA General Hospital and as President of the Chinese Research Hospital Association for the Study of the Liver Disease. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Cannabis use history is associated with increased prevalence of ascites among patients with nonalcoholic fatty liver disease: A nationwide analysis

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Abstract

BACKGROUND

Recent studies have revealed the endocannabinoid system as a potential therapeutic target in the management of nonalcoholic fatty liver disease (NAFLD). Cannabis use is associated with reduced risk for NAFLD, we hypothesized that cannabis use would be associated with less liver-related clinical complications in patients with NAFLD.

AIM

To assess the effects of cannabis use on liver-related clinical outcomes in hospitalized patients with NAFLD.

METHODS

We performed a retrospective matched cohort study based on querying the 2014 National Inpatient Sample (NIS) for hospitalizations of adults with a diagnosis of NAFLD. The NIS database is publicly available and the largest all-payer inpatient database in the United States. The patients with cannabis use were selected as cases and those without cannabis were selected as controls. Case-control matching at a ratio of one case to two controls was performed based on sex, age, race, and comorbidities. The liver-related outcomes such as portal hypertension, ascites, varices and variceal bleeding, and cirrhosis were compared between the groups.

consultant for Bayer, and Eisai. The other authors have no potential conflicts of interest to report.

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RESULTS

A total of 49911 weighed hospitalizations with a diagnosis of NAFLD were identified. Of these, 3820 cases were selected as the cannabis group, and 7625 non-cannabis cases were matched as controls. Patients with cannabis use had a higher prevalence of ascites (4.5% *vs* 3.6%), with and without cannabis use, $P = 0.03$. The prevalence of portal hypertension (2.1% *vs* 2.2%), varices and variceal bleeding (1.3% *vs* 1.7%), and cirrhosis (3.7% *vs* 3.6%) was not different between the groups, with and without cannabis use, all $P > 0.05$. Hyperlipidemia, race/ethnicity other than White, Black, Asian, Pacific Islander or Native American, and higher comorbidity score were independent risk factors for ascites in the cannabis group. Among non-cannabis users, obesity and hyperlipidemia were independent protective factors against ascites while older age, Native American and higher comorbidity index were independent risk factors for ascites.

CONCLUSION

Cannabis was associated with higher rates of ascites, but there was no statistical difference in the prevalence of portal hypertension, varices and variceal bleeding, and cirrhosis.

Key Words: Nonalcoholic fatty liver disease; Fatty liver; Cannabis; Marijuana use; Liver diseases; Hospitalization

Core Tip: Recent studies showed the lower prevalence of nonalcoholic fatty liver disease (NAFLD) among cannabis users compared to non-cannabis users, therefore suggestive of cannabis's modulatory role in the development of NAFLD. However, our case-control matching analysis, based on sex, age, race, and comorbidity, showed cannabis use as independently associated with higher rates of ascites in patients with NAFLD. A conceivable explanation for the finding is the dominant effect of cannabinoid receptor type 1 through its hepatic profibrotic effects in patients with NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is now one of the most common liver diseases worldwide, and its global burden is growing[1]. Weight loss remains the primary treatment for NAFLD, and other treatment modalities have been actively studied, including the use of cannabinoids. Emerging evidence suggests that cannabis may play an important role in the management of various chronic liver diseases[2]. A retrospective population study by Adejumo *et al*[3] has shown a dose-dependent reduction in the prevalence of NAFLD with cannabis use, and cannabis has been suggested to suppress or even reverse the development of NAFLD.

The prevalence of NAFLD parallels that of the obesity pandemic, and NAFLD is considered a metabolic disorder where its pathogenesis involves the complex interplay among hormonal, nutritional, and genetic factors[4]. Aside from a significant weight loss, another cornerstone of the management is to reduce cardiovascular, oncologic, and hepatic risk factors for mortality[4,5]. Perhaps, cannabis use can modulate effects on the development and progression of NAFLD through its metabolic risks and its impact on hepatic steatosis.

Cannabis use is associated with increased appetite and calorie consumption, but paradoxically it is associated with reduced risk of obesity and diabetes[6]. In a cross-sectional data by Kim *et al*[6], active cannabis use provided a protective effect against

NAFLD, independent of metabolic risks. Yet, there has been conflicting evidence whether or not cannabis induces the progression of chronic liver diseases, but a systemic review by Farooqui *et al*[7] showed that when confirmed by liver biopsy, there was no association between cannabis use and prevalence of hepatic fibrosis. This lack of association is contrary to initial cross-sectional studies by Hézode *et al*[8] and Ishida *et al*[9] who suggested increased fibrosis in patients who use marijuana.

Here, we aimed to measure clinical outcomes of cannabis use at the national level among hospitalized patients with NAFLD. Given the previously demonstrated correlation between cannabis use and reduced prevalence of NAFLD, we hypothesized that cannabis would be associated with fewer liver-related complications in patients than in individuals who did not use cannabis. This is the first database study to investigate cannabinoids' effects on liver-related outcomes in hospitalized patients with NAFLD. With our study, we hope to alert clinicians of the possible relevance of ascertainment of cannabis use, which in turn might alter future routine assessments to further probe about cannabis use, especially in light of trends showing recent increases in use in the United States.

MATERIALS AND METHODS

Data source and study population

This study is a retrospective analysis of the 2014 Healthcare Cost and Utilization Project-National Inpatient Sample (HCUP-NIS). The HCUP-NIS is the largest all-payer inpatient database in the United States, comprising more than 40 states with more than 7 million annual hospital discharges[3]. Results were extracted from the NIS database by identifying hospitalized patients older than 18 years with a diagnosis of NAFLD, by using the corresponding International Classification of Diseases codes: 571.8 (other chronic nonalcoholic liver disease). We excluded common secondary causes of intrahepatic fat accumulation by excluding alcoholic liver disease, hemochromatosis, viral hepatitis B and C, primary biliary cirrhosis, autoimmune hepatitis, and toxic liver disease. The HCUP-NIS is publicly accessible, de-identified database, and it is considered a limited database. Under Health Insurance Portability and Accountability Act, a limited database does not require a review by the institutional review board (IRB). Therefore, Rutgers IRB approval was deemed not required in our study.

Model design

Patients with NAFLD with cannabis use were selected as cases, and those without cannabis use were used to produce the control group through case-control matching at a ratio of one case to two controls, on the basis of sex, age, race, and comorbidities. Sex was binary (women or men), race was categorical (White, Black, Hispanic, Asian or Pacific Islander, Native American, and other), and obesity was binary (no obesity or obesity). The age was converted into eight categorical variables for different age groups: 18-27, 28-37, 38-47, 48-57, 58-67, 68-77, 78-87, and 88 or older. The elixhauser comorbidity index (ECI) was used to assess comorbidities in patients. ECI is a method of categorizing comorbidities on the basis of the International Classification of Diseases, which calculates a weighted sum of each of the presence of 29 binary comorbidities[10]. ECI uses 29 of the Agency for Healthcare Research and Quality comorbidity indicators to predict hospital use and in-hospital mortality[11,12]. In our study, the ECI score ranged from -21 to 44, with a mean score of 3. ECI was converted into four groups: ECI ≤ 0, 1-5, 6-10, and ≥ 11.

Outcomes and predictive variables

The primary outcomes of the study were inpatient mortality, advanced liver disease-related complications including portal hypertension, ascites, varices and variceal bleeding, cirrhosis, and spontaneous bacterial peritonitis (SBP), as presented in Table 1. SBP and inpatient mortality were not included in our final analysis as it was not possible to conduct meaningful analysis due to their small sample sizes. For each hospitalization, baseline demographics and hospital characteristics were obtained. To address potential confounding factors, we added diabetes, hyperlipidemia, and obesity in Table 1 to compare their baseline prevalence between the case control groups.

Statistical analyses

A biomedical statistical expert (SHW) reviewed statistical analysis. All data analyses

Table 1 Patient demographics, hospital characteristics, and outcomes among patients with nonalcoholic fatty liver disease, by history of cannabis use

	Cannabis users, *n* = 3820	Non-cannabis users, *n* = 7625	*P* value
Sex			NS[1]
Female	36.0%	36.1%	
Male	64.0%	63.9%	
Patient age, mean (SD)	41.4 (12.9)	42.0 (12.9)	0.03[2]
Patient age, in 10 years age groups[3]			NS[4]
18-27	16.8%	16.6%	
28-37	25.3%	25.3%	
38-47	20.4%	20.5%	
48-57	25.8%	25.8%	
58-67	11.0%	11.0%	
68-77	0.8%	0.8%	
Race/ethnicity			NS[4]
White	60.6%	60.7%	
Black	21.6%	21.6%	
Hispanic	13.9%	13.9%	
Asian or pacific islander	0.4%	0.4%	
Native American	0.9%	0.9%	
Others	2.6%	2.4%	
ECI, mean (SD)	2.1 (9.4)	3.6 (8.1)	< 0.01[2]
ECI, by category			NS[4]
≤ 0	47.6%	47.7%	
1-5	15.8%	15.9%	
6-10	19.6%	19.5%	
11 or higher	16.9%	16.9%	
Insurance			< 0.05[4]
Medicare	16.6%	17.2%	
Medicaid	42.8%	30.5%	
Private	21.9%	42.6%	
Self-Pay	13.4%	6.0%	
Others	5.4%[5]	3.7%	
Cannabis abuse			
Non-dependent use	94.1%	0 (by definition)	
Dependent use	5.9%	0 (by definition)	
Length of stay (days)	5.1	4.9	0.18[2]
Total hospitalization charges	$42503	$43183	NS[2]
Comorbidities			
Diabetes	29.2%	34.8%	< 0.05[5]
Obesity	29.5%	49.4%	< 0.05[5]
Hyperlipidemia	24.2%	32.4%	< 0.05[5]
Clinical outcomes			

Portal hypertension	80 (2.1%)	165 (2.2%)	NS[5]
Ascites	170 (4.5%)	275 (3.6%)	0.03[5]
Varices and variceal bleeding	50 (1.3%)	130 (1.7%)	0.11[5]
Cirrhosis	140 (3.7%)	275 (3.6%)	NS[5]

[1]Chi-square, 2-tailed.
[2]Student *t*-test, 2-tailed.
[3]Patient ages ranged from 18 to 73, there was no one over 78.
[4]Chi-square, 2-tailed, for 2 by *n* table: Statistical significance demonstrates that the two groups differ.
[5]Condition absent *vs* present in the 2 groups, chi-square, 2-tailed. NS: Not statistically significant; ECI: Elixhauser comorbidity index.

were conducted using SPSS, version 26 (IBM Corp, Armonk, NY, United States). NIS is based on a complex sampling design that includes stratification, clustering, and weighting. Weighting of patient-level observations was implemented to obtain estimates for the entire population in the United States of hospitalized patients with NAFLD. All statistical analyses were two-tailed, with $P < 0.05$ considered statistically significant. Chi-squared tests were performed to compare categorical data, and Student *t*-tests were performed for continuous data. Univariate linear (continuous outcomes) or logistic (dichotomous outcomes) regression analysis were used to calculate unadjusted odds ratios for the primary outcomes. Subsequently, multivariate regression analysis was used to adjust the results for potential confounders. The final multivariate logistic regression model was built by including those factors associated with the outcome in univariate analysis with $P < 0.20$.

RESULTS

Patient characteristics and demographics

A total of 3820 patients with NAFLD who had a history of cannabis use were identified in our study. 7625 patients with NAFLD and without cannabis use were matched and placed in the control group. Table 1 summarizes the patients' baseline characteristics. There was no statistical difference of age, sex, race, ethnicity, and ECI between the groups ($P > 0.05$); therefore, these variables were successfully matched. Yet, patients who used cannabis were slightly younger (mean age: 41.4 *vs* 42.0, $P = 0.03$), and had fewer comorbidities (ECI mean: 2.1 *vs* 3.6, $P < 0.01$), with and without cannabis use. However, the differences in the mean age and mean ECI were not clinically different between the groups.

There were statistical differences in types of insurance in the case group compared with the control group. The proportion of Medicare holders was lower in the cannabis group (16.6% *vs* 17.2%), and a proportion of patients with private insurance was also less in cannabis group (21.9% *vs* 42.6%), with and without cannabis use; all $P < 0.05$. Detailed patient demographics and hospital characteristics are presented in Table 1.

There were fewer patients with metabolic derangement such as diabetes (29.2% *vs* 34.8%), obesity (29.5% *vs* 49.4%), and hyperlipidemia (24.2% *vs* 32.4%) in the cannabis group compared to the non-cannabis group. Of note, 94.1% of the cannabis users were coded under non-dependent use, and due to such a high proportion of non-dependent cannabis use, dose-dependent effects of cannabis on different liver-related complications were not able to be explored.

Liver disease-related complications

The cannabis group had a higher prevalence of ascites [4.5% *vs* 3.6%, OR 1.25; 95% confidence interval (CI): 1.02-1.51]. There was no statistical difference in the prevalence of portal hypertension [2.1% *vs* 2.2%, not statistically significant (NS)], varices and variceal bleeding (1.3% *vs* 1.7%, $P = 0.11$), and cirrhosis (3.7% *vs* 3.6%, NS), with and without cannabis use. There was a small sample size, less than 10 in one of the groups for spontaneous bacterial peritonitis and inpatient mortality, and therefore not included in the analysis. Detailed chronic liver disease-related complications are presented in Table 1.

Healthcare resource utilization associated with index admission

The mean length of stay was longer for those who used cannabis compared to those

who did not use cannabis (5.1 d *vs* 4.9 d), but this difference was not statistically different, $P = 0.18$. Total hospitalization charges were lower for patients who used cannabis ($42503) compared with those who did not use cannabis ($43183), but this difference was also not statistically different either.

Independent predictors of ascites

The variables found to be independent predictors of ascites among cannabis users were hyperlipidemia (aOR 1.53; 95%CI: 1.08-2.17), racial group other than White, Black, Hispanic, Asian, Pacific Islanders or Native American (aOR 2.57; 95%CI: 1.24-5.31), and higher comorbidity index (aOR 1.08; 95%CI: 1.07-1.10), all $P < 0.05$. Among patients who did not use cannabis, older age (aOR 1.02; 95%CI: 1.01-1.03), Native Americans (aOR 2.60; 95%CI: 1.03-6.61), and higher comorbidity index (aOR 1.05; 95%CI: 1.04-1.06) were independent predictor of ascites. However, in the same group, obesity (aOR 0.61; 95%CI: 0.46-0.81) and hyperlipidemia (aOR 0.59; 95%CI: 0.44-0.80) were independent protective factors against ascites, all $P < 0.05$. The univariate and multivariate logistic regression analysis for ascites is further delineated in Table 2.

DISCUSSION

Cannabis is produced from *Cannabis sativa*, known as the marijuana plant, which contains more than 60 active chemical compounds called cannabinoids[3,13]. The primary effects of cannabinoids come from activation of cannabinoid receptors: The two types of G-protein coupled cannabinoid receptors, cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2)[7,14]. CB1 is primarily expressed in the brain while CB2 in immune tissue, and under normal physiologic conditions both CB1 and CB2 are very weakly expressed by the liver[15]. However, an upregulation of these receptors are markedly induced in the human liver with cirrhosis[16,17]. The levels of CB1 are six times greater in patients with chronic hepatitis C compared to control while twice greater in patients with cirrhosis compared to those at a lower fibrosis state[18-20]. CB1 and CB2 exert opposite effects on the liver; CB1 has profibrogenic properties while activation of CB2 in mice has been associated with antifibrotic and anti-inflammatory properties[7].

The most active and best-studied cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD)[7,13]. Both THC and CBD act on CB-1 and CB2, but they have different affinities for the receptors. CB1 activation has been shown to have pro-inflammatory effects and to be involved in hepatic fibrosis and steatosis[3,21]. For instance, in CB1 null mice, CB1 blockers increase fatty acid oxidation and decrease hepatic inflammation and lipogenesis[22]. In contrast, CB2 exerts anti-inflammatory effects. CB2 activation has also been shown to suppress obesity and steatohepatitis and to protect the liver from ischemia-reperfusion injury[3]. THC preferentially activates the CB1 pathway, whereas CBD triggers the dominant activation of CB2[3]. The clinical impact of receptor expression and the ratio of activated CB1 and CB2 are unclear among patients with NAFLD. Given the previous evidence of opposite hepatic effects of CB1 and CB2, it is conceivable to suspect the overall cannabinoid effects from both receptors. Ascites is the only liver-related complication that was significantly different between cannabis and non-cannabis groups out of the complications tested in our study, (OR 1.25; 95%CI: 1.02-1.51). Therefore, a possible explanation for higher prevalence of ascites is the dominant hepatic effects of activated CB1 compared to CB2.

Because marijuana use remains illegal in many states in the United States, most marijuana consumed is often not produced under a controlled setting. Therefore, marijuana varies in its contents and has a risk of containing other chemical contaminants, and it also varies in the amounts of active cannabinoids[23]. Different modes of administration along with dynamic pharmacokinetic processes of cannabinoids lead to different bioavailabilities of active cannabinoids ingested. The most common administration route is smoking through cigarettes, pipes, or water pipes[24]. Smoking is the principal route of cannabis administration as it provides a rapid and efficient delivery to the brain, and the ability to titrate dose to the desired effect[25]. The different inhalation methods lead to inconsistent delivery of cannabinoids in the body, thus making control of the dose of active cannabinoids difficult[23]. Oral administration of cannabis involves a slower absorption, and therefore it has a slower, more-delayed peak of THC, one of the primary psychoactive components of cannabis[25]. Wall *et al*[26] reported oral THC bioavailability as 10%-20%. Therefore, many cannabis users prefer smoking due to a quick onset of effects, but smoking is generally not recommended for therapeutic use[25]. Unfortunately, the mode of

Table 2 Independent predictors of ascites among patients with nonalcoholic fatty liver disease, stratified by cannabis use history

Cannabis users (*n* = 3820)					Non-cannabis users (*n* = 7625)				
Ascites	**OR (95%CI)**	***P* value**	**aOR (95%CI)**	***P* value**	**Ascites**	**OR (95%CI)**	***P* value**	**aOR (95%CI)**	***P* value**
	Univariate logistic regression		Multivariate logistic regression[1]			Univariate logistic regression		Multivariate logistic regression[1]	
Diabetes	1.17 (0.84-1.62)	NS			Diabetes	1.16 (0.91-1.49)	0.23		
Obesity	1.00 (0.71-1.40)	NS			Obesity	0.41 (0.31-0.53)	< 0.01	0.61 (0.46-0.81)	< 0.01
Hyperlipidemia	1.32 (0.94-1.85)	0.11	1.53 (1.08-2.17)	0.02	Hyperlipidemia	0.57 (0.43-0.77)	< 0.01	0.59 (0.44-0.80)	< 0.01
Age (continuous)	0.99 (0.98-1.01)	0.22			Age (continuous)	1.02 (0.01-1.03)	< 0.01	1.02 (1.01-1.03)	< 0.01
Race/ethnicity (categoric)					Race/ethnicity (categoric)				
White	Reference				White	Reference			
Black	1.13 (0.78-1.64)	NS			Black	0.80 (0.58-1.10)	0.16		
Hispanic	0.87 (0.53-1.42)	NS			Hispanic	1.00 (0.70-1.42)	NS		
Asian or pacific islander	[1]				Asian or pacific islander	[1]			
Native American	[2]				Native American	1.96 (0.78-4.92)	0.15	2.60 (1.03-6.61)	0.04
Others	2.46 (1.24-4.87)	0.01	2.57 (1.24-5.31)	0.01	Others	0.71 (0.29-1.74)	NS		
Comorbidity (continuous)	1.08 (1.07-1.10)	< 0.01	1.08 (1.07-1.10)	< 0.01	Comorbidity (continuous)	1.06 (1.05-1.07)	< 0.01	1.05 (1.04-1.06)	< 0.01
Sex (female)	0.80 (0.58-1.09)	0.15			Sex (female)	0.99 (0.77-1.27)	NS		

[1]Univariate analysis with screening $P < 0.02$ was used to determine variables to include in the final multivariate analysis. Hyperlipidemia, Race/ethnicity, comorbidity index, and sex included in the regression.
[2]Univariate analysis with screening $P < 0.02$ was used again, and obesity, hyperlipidemia, age, race/ethnicity, and comorbidity index were included in the multivariate regression. NS: Not statistically significant.

cannabis use is not systematically recorded in the NIS, and our retrospective study would be unlikely to reliably capture mode data to compare different modes in the cannabis group. A large prospective study in which mode and dose of cannabis would be ascertained and monitored would be of interest to study the effects of dose and mode on the clinical outcomes.

The patients who used cannabis had higher prevalence of ascites compared to non-cannabis group (OR 1.25; 95%CI: 1.02-1.51). Possible explanations for this finding can be related to 1) hypoalbuminemia due to the toxicity of cannabis use or 2) lower body mass, which is a potential indicator for inadequate nutritional status. Hypoalbuminemia was described as a spectrum of toxic reactions from intravenous cannabis use along with fulminant gastroenteritis, toxic hepatitis, acute renal failure, electrolyte disturbances, leukocytosis, anemia, and relative thrombocytopenia from a study of 4 cases of intravenous cannabis use by Payne *et al*[27] in 1975. Serum albumin is the most abundant plasma protein and therefore binding to albumin is a key determinant of the drug efficacy, distribution and possible toxicity of cannabinoids[28]. The increase in plasma albumin may reduce the unbound fraction of cannabinoids, which further reduces the efficacy of the drug[28]. Along the same reasoning, it is conceivable to hypothesize more cannabinoid toxicity in patients with hypoalbuminemia due to more unbound cannabinoids. A study by Blüml *et al*[29] showed an inverse relationship between body mass index (BMI) and illicit drug use including cannabis use among young males, and therefore along with the toxicity of high-dose cannabis use, hypoalbuminemia from poor nutritional status may explain higher rate of ascites in cannabis users due to the low oncotic pressure from hypoalbuminemia. The forementioned explanation for hypoalbuminemia can partly explain the isolated finding of higher rates of ascites in cannabis users without higher rates of portal hypertension, varices and variceal bleeding and cirrhosis. Another explanation of such finding can be related to a lack of long-term follow-up. As the NIS is limited to hospitalized data, a spectrum of clinical presentations of decompensated

cirrhosis such as varices and variceal bleeding and actual clinical diagnosis of cirrhosis outside of hospital may not be captured in our study design. Further studies with a long-term follow-up investigating cannabis use in patients with NAFLD are warranted to further evaluate the rates of clinical manifestations of decompensated cirrhosis.

The patients with cannabis group had a higher rate of ascites compared to the non-cannabis group despite higher baseline rates of metabolic risks in non-cannabis group such as diabetes, hyperlipidemia, and obesity. This suggests that cannabis may not be a magic bullet for the management of NAFLD. In cannabis group, higher comorbidity index was an independent risk factor for ascites, and this is expected as older patients with more comorbidity are associated with worse prognosis in patients with chronic liver diseases. In non-cannabis group, age and higher comorbidity were again independent risk factors for ascites. However, strikingly obesity (aOR 0.61; 95%CI: 0.46-0.81) and hyperlipidemia (aOR 0.59; 95%CI: 0.44-0.88) were independent protective factors against ascites in patients with NAFLD who did not use cannabis. A possible explanation for this finding can be related to nutritional status in patients with ascites. Metabolic derangements such as obesity and insulin resistance predispose to NAFLD[30], and therefore they are risk factors for development of NAFLD. However, at terminal stage of liver disease with evidence of decompensation such as ascites, the increased BMI and appropriate albumin levels can be protective against developing ascites. Previous studies showed that muscle wasting was worse in obese patients[31] with cirrhosis, and these patients are at high risk for fat-and water-soluble vitamin depletion[32]. Therefore, our finding of the association between obesity and reduced prevalence of ascites is surprising. However, a study by Li *et al*[33] showed that patients with higher BMI had lower rates of liver-related mortality compared to lower BMI among patients with cirrhosis and hepatocellular carcinoma. We were not able to measure nutritional status in our study; therefore although obesity often co-exists with malnutrition, we can speculate that our study population with an obesity diagnosis may have better nutrition than those without obesity.

Patients with cirrhosis are at higher risk for poor tolerance of fasting, and therefore aggressive energy restriction is avoided in these patients[34]. Due to the risk of sarcopenia with weight loss, patients who are advised to lose weight should be monitored for changes in body muscle mass and muscle strength[34]. Therefore, increased BMI in the setting of end-stage liver disease may suggest better nutritional status compared to non-obese patients. In the meantime, sarcopenic obesity is associated with a higher rate of mortality in patients with cirrhosis, and therefore further distinction between sarco obesity and obesity is warranted. The impairment of liver lipogenesis is prominent in decompensated NAFLD, and subsequently low levels of cholesterol in advanced NAFLD is not surprising. Therefore, in patients with decompensated NAFLD as seen with ascites, hyperlipidemia and obesity can be associated with less prevalence of ascites due to a better nutritional status in this vulnerable population with advanced liver disease.

Among cannabis users, hyperlipidemia was an independent risk factor for ascites (aOR 1.53; 95%CI: 1.08-2.17). Previous few studies showed significantly diminished level of serum high-density lipoprotein, low-density lipoprotein, and total cholesterol in liver cirrhosis[35,36]. Similarly, some studies showed a decrease in triglyceride in cirrhosis[36]. Liver biosynthesis is reduced with the progression of cirrhosis[37]. Although there were mixed findings of the relationship between cholesterol values and cirrhosis, our findings are compatible with the abovementioned relationship.

This is the national retrospective study to evaluate the clinical effects of cannabis among hospitalized patients with NAFLD at the national level. Strengths of our manuscript are a large sample size as well as the use of case-control matching analysis, where the groups are matched on age, sex, race, comorbidity. To address potential confounding factors, we also examined diabetes, hyperlipidemia, obesity as co-variates in multi-variate analysis.

Despite these strengths, our study has some limitations that are mainly associated with the nature of large population database studies, in which patients are typically not routinely tested for cannabis use upon admission, and the diagnosis of cannabis use is often made from patient reports. Therefore, unless patients are forthcoming with their caregivers regarding cannabis use, cannabis use may be missed or under-coded. The NIS also relies on accurate billing by clinicians to accurately record diseases and complications, which may lead to an underestimate of diagnosis. In addition, monitoring long-term clinical outcomes, such as liver-related complications not recorded in NIS, remains challenging.

Another limitation of this study is the inability to characterize different concentrations or modes of cannabis administration. 94.1% of the cannabis users were coded under non-dependent use, and due to the limited sample size, we could not

provide dose-dependent data. A possible explanation for the low baseline percentage of dependent cannabis use is a lack of available data, limited current routine clinician assessment, or truly low number of patients who abuse cannabis. We were unable to characterize the concentrations and effects of each cannabinoid, as well as the dose-dependent effects of these cannabinoids. Long-term randomized controlled studies with different levels of cannabinoid types and amounts are warranted to better understand each cannabinoid's effects on the cannabinoid system in the body.

CONCLUSION

In conclusion, this was the first database study investigating progressive liver disease-related clinical outcomes in hospitalized patients with NAFLD. Cannabis was associated with higher rates of ascites, but there was no statistical difference in the prevalence of portal hypertension, varices and variceal bleeding, and cirrhosis. In the cannabis group, hyperlipidemia was an independent risk factor for ascites but in non-cannabis group hyperlipidemia and obesity were independent protective factors against ascites. A large prospective study in which mode and dose of cannabis would be ascertained and monitored would be of interest.

ARTICLE HIGHLIGHTS

Research background

The impact of cannabis on the progression of chronic liver diseases has been unclear in prior studies. Systemic reviews showed no association between the increased prevalence of hepatic fibrosis and cannabis use, but cannabis use was still associated with a reduced prevalence of nonalcoholic fatty liver disease.

Research motivation

Because of the modulatory effects of cannabis on risk factors for the development of nonalcoholic fatty liver disease (NAFLD), we wanted to measure the correlation between cannabis use and clinical outcomes related to chronic liver diseases. Without clear evidence between the cannabis use and progression of established NAFLD, it is critical for clinicians to educate the patients on the use of cannabis due to limited evidence on cannabinoid effects. Therefore, our study is motivated to alert clinicians of the possible relevance of ascertainment of cannabis use, which in turn might alter future routine assessments to further probe about cannabis use, especially in light of trends showing recent increases in use in the United States.

Research objectives

Our study aimed to assess the association between cannabis use and clinical liver-related outcomes among hospitalized patients with NAFLD.

Research methods

In our study, we performed a retrospective matched cohort study for hospitalized adult patients with NAFLD. Case-control matching at a ratio of one case to two controls was performed based on sex, age, race, and comorbidities to adjust for confounders. The liver-related complications including portal hypertension, ascites, varices and variceal bleeding, and cirrhosis were measured and compared between two groups.

Research results

The cannabis group had a higher prevalence of ascites compared to patients with NAFLD who did not use cannabis. Obesity and hyperlipidemia were independent protective effects against ascites in the non-cannabis group.

Research conclusions

Cannabis use was associated with higher rates of ascites despite higher rates of metabolic risks in the non-cannabis group such as diabetes, hyperlipidemia, and obesity. This suggests that cannabis may not be a magic bullet for the management of NAFLD, and therefore judicious use of cannabis in advanced NAFLD is warranted.

Research perspectives

A large prospective study in which mode and dose of cannabis use would be warranted to further explore the effects of administration mode and dose of cannabis on the liver-related clinical complications.

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