

Marijuana Consumption in Liver Transplant Recipients

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Marijuana is legalized for either medical or recreational use in over half of the states in the United States and in Canada, but many transplant centers will not list patients who are using marijuana. However, the effect of marijuana on transplant outcomes remains unclear. Thus, we performed a retrospective analysis of all adult (≥ 18 years old) liver transplant patients treated at our center between 2007 and 2017. Patients were grouped according to their marijuana use and tobacco smoking status. We also evaluated tobacco smoking status for the comparative evaluation. Posttransplant morbidity, mortality, and graft survival were evaluated. In total, 316 patients were included: 171 (54%) patients were tobacco smokers (70 current; 101 former), 81 (26%) patients were marijuana smokers (13 current; 68 former), and 64 (20%) patients were both marijuana and tobacco smokers. A total of 136 (43%) reported never smoking marijuana or tobacco. After adjustment, current tobacco users were over 3 times as likely to die within 5 years compared with never users (hazard ratio [HR], 3.25; 95% confidence interval [CI], 1.63–6.46; $P < 0.001$), but no difference was seen between current/former and never marijuana users (HR, 0.52; 95% CI, 0.26–1.04; $P = 0.06$). No significant differences in inpatient respiratory complications, reintubation, or >24 -hour intubation was seen. Overall, pretransplant marijuana use, past or current, does not appear to impact liver transplant outcomes, though tobacco smoking remains detrimental.

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Marijuana is the most commonly consumed illicit drug in the world and in the United States⁽¹⁾; an estimated 8% of the US population ≥ 12 years old was actively consuming marijuana in 2013.⁽²⁾ Though the social and political dynamics surrounding its use are

complicated, it has become more widely accepted in the last few years, and 30% of the adult population now report using it within the last year.⁽²⁾ Recently, marijuana was legalized in some form in 29 states and Washington, DC, as well as in Canada.⁽³⁾

Medical marijuana has been successfully used to treat pruritus, chronic pain, depression, anorexia, sleep disturbance, and nausea, which are all symptoms that are consistently reported by pretransplant patients.⁽⁴⁾ However, neither medical marijuana nor recreational marijuana is regulated for purity or potency, leaving users potentially vulnerable to unpredictable medical efficacy and adverse effects. There is limited evidence that longterm marijuana use can produce chronic obstructive pulmonary disease–like illness, bronchitis, and asthma exacerbations,⁽⁵⁾ and consistent heavy use is related with increased risk of pulmonary complications (though lower compared with tobacco use), increased nausea, and emesis, known as cannabinoid hyperemesis syndrome.^(6,7) Acute intoxication has also been linked with complications in isolated cases, such as myocardial infarction, stroke,⁽⁸⁾ and membranous glomerulonephritis.⁽⁹⁾ Marijuana has also been associated with infections. There are publications showing

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; MVA, motor vehicle accidents; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

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colonization of *Aspergillus*,⁽¹⁰⁾ tuberculosis,⁽¹¹⁾ and mucormycosis.^(12,13) Marijuana can suppress immunity, increasing the risk for infections but conversely, serving as a therapy for ischemia/reperfusion injury.^(14,15)

These varied effects of marijuana use could have significant impacts on both short-term and long-term outcomes after liver transplant. Data regarding the impact of marijuana use on liver transplant candidacy and outcomes are scarce and still emerging.^(16,17) In contrast, cigarette smoking has well-established detrimental health effects for both the general population and transplant recipients. Yet, there are centers that transplant patients who are actively smoking tobacco.⁽¹⁸⁾ With increasing legalization and utilization, more and more transplant centers are going to face the challenge of marijuana-related issues in liver transplantation. Additionally, 7 US states (California, Delaware, Arizona, Illinois, Minnesota, Washington, and New Hampshire) recently introduced legislation explicitly banning denial of transplantation due to marijuana consumption.⁽¹⁷⁾ Thus, the purpose of this analysis was to assess the effect of marijuana and tobacco use on post-liver transplant outcomes.

Patients and Methods

There were 339 consecutive adult (≥ 18 years old) patients who underwent transplantation between July 1, 2007 and July 19, 2017 at our center and were eligible for inclusion. Patients who received multiorgan transplants, retransplants, and patients diagnosed with acute liver failure (ALF) were excluded. Data were obtained by reviewing electronic medical records and were categorized in a similar fashion as prior studies.^(19,20) All patients underwent orthotopic liver transplants with adult cadaveric donors. We accepted both brain death donors and circulatory death donors with a cutoff macrovesicular steatosis of 25%, a cold ischemia time under 8 hours, and a warm ischemia time of < 35 minutes. The recipient technique was piggyback or bicaval anastomosis per surgeon preferences. All patients received standard induction with 500 mg of methylprednisolone intraoperatively, followed by a taper. Tacrolimus and mycophenolic acid were started on postoperative day 1. Patients with a pretransplant creatinine of more than 2 mg/dL received 20 mg of basiliximab intravenously during surgery and on postoperative day 4 with a late tacrolimus start date. Patients were followed clinically and with laboratory testing of serum for graft function periodically, and these data were retrospectively evaluated.

Positive tobacco and/or marijuana use was defined as either reporting use during a direct interview with the patient during the social worker/psychologist visit or by a urine toxicology test prior to transplant. Patients were then classified as current users (use within 6 months of transplant), former users (those who have had a chronic use but no consumption in the previous 6 months), or nonsmokers. Noninhaled forms of tobacco or marijuana use (eg, chewing or edibles) were not included because of small numbers.

Patient characteristics, stratified by marijuana smoking status, were compared using Fisher's exact test. A P value < 0.05 was considered statistically significant. Multivariate logistic regression was used to estimate the effect of tobacco smoking and marijuana smoking on being intubated > 24 hours after surgery, inpatient respiratory complications (pneumonia, progressive respiratory failure, and upper respiratory infections), and reintubation. Models were adjusted for age (categorized as 18-50 and > 50 years), sex, race/ethnicity (categorized as white versus non-white), diabetes status, Model for End-Stage Liver Disease (MELD) score at time of transplant, smoking status, hepatocellular carcinoma (HCC) diagnosis, and primary etiology of cirrhosis. Multivariate Cox proportional hazards regression was used to estimate the effect of tobacco smoking and marijuana smoking on all-cause mortality after adjusting for the same covariates listed above. Interaction terms were used to assess whether potential interaction between tobacco and marijuana smoking on all-cause mortality existed. All analyses were performed using SAS, version 9.4 (SAS Inc., Cary, NC). Institutional review board approval was obtained from the University of North Carolina.

Results

Overall, 316 patients were included, and 81 (26%) reported current or former marijuana use (68 former, 13 current). Median follow-up time was 1582 days (interquartile range, 576-2679 days). Patients reporting marijuana use were more likely to be male (81% versus 63%; $P = 0.002$), be a current (38% versus 17%; $P < 0.001$) or former tobacco smoker (43% versus 28%; $P = 0.01$), be diagnosed with HCC (42% versus 29%; $P = 0.04$), or be diagnosed with either alcoholic cirrhosis (not any patient with acute alcoholic hepatitis) (37% versus 20%; $P = 0.004$) or viral hepatitis (49% versus 29%; $P = 0.001$; Table 1).

TABLE 1. Patient Characteristics Stratified by Marijuana Smoking Status

	Current/Former User (n = 81; 26%)	Never Used (n = 235; 74%)	P Value
Age, years			
18-35 years old	5 (6)	13 (6)	0.79
36-50 years old	12 (15)	53 (23)	0.15
>50 years old	64 (79)	169 (72)	0.24
Sex, male	66 (81)	148 (63)	0.002
Race/ethnicity			
White	64 (79)	177 (75)	0.55
Black	16 (20)	44 (19)	0.87
Hispanic	1 (1)	11 (5)	0.31
Other	0 (0)	3 (1)	0.57
Diabetes	16 (20)	49 (21)	0.87
MELD score			
<10	13 (16)	19 (8)	0.05
10-19	32 (40)	90 (38)	0.90
20-29	24 (30)	79 (34)	0.58
30-39	7 (9)	34 (14)	0.25
≥40	5 (6)	13 (6)	0.79
Tobacco use			
Current	31 (38)	39 (17)	<0.001
Former	35 (43)	66 (28)	0.01
Never	15 (19)	130 (55)	<0.001
HCC diagnosis	34 (42)	68 (29)	0.04
Primary diagnosis			
AIH/PBC/PSC	5 (6)	27 (11)	0.20
Alcoholic cirrhosis	30 (37)	48 (20)	0.004
NASH/cryptogenic	6 (7)	80 (34)	<0.001
Viral hepatitis	40 (49)	67 (29)	0.001
Other	0 (0)	13 (6)	0.04

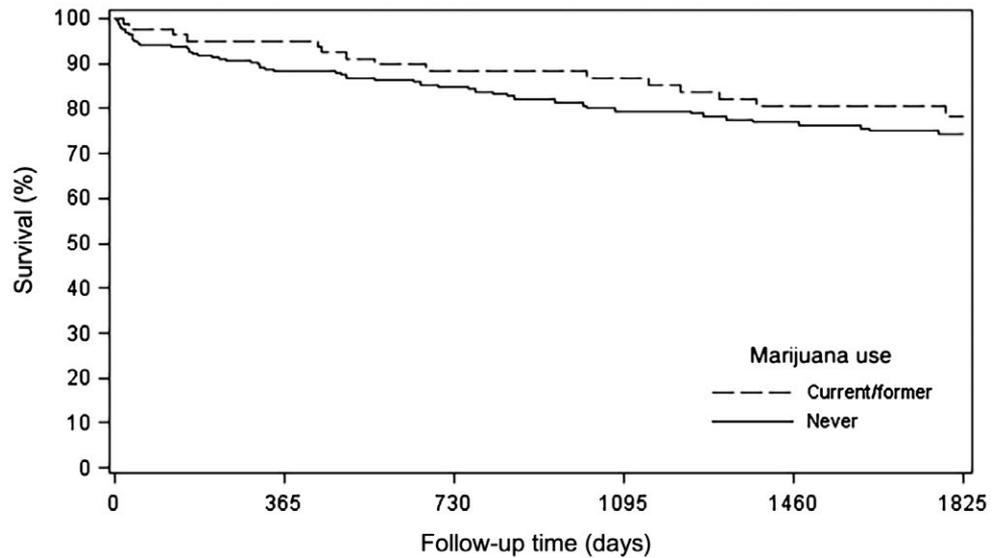
NOTE: Data are given as n (%).

The 1- and 3-year patient survival rates were 92% (n = 93) and 87% (n = 88) for former tobacco smokers, respectively; 85% (n = 60) and 72% (n = 51) for current tobacco smokers, respectively; 96% (n = 66) and 91% (n = 63) for former marijuana smokers, respectively; 100% (n = 13) and 85% (n = 11) for current marijuana smokers, respectively; and 91% (n = 126) and 85% (n = 117) for never smokers, respectively (Figs. 1 and 2). The 1- and 3-year graft survival were 92% (n = 93) and 87% (n = 88) for former tobacco smokers, respectively; 85% (n = 60) and 72% (n = 51) for current tobacco smokers, respectively; 96% (n = 66) and 91% (n = 63) for former marijuana smokers, respectively; 100% (n = 13) and 85% (n = 11) for current marijuana smokers, respectively; and 88% (n = 121) and 81% (n = 112) for never smokers, respectively.

Overall 5-year survival was 75%. No significant difference in 5-year survival was seen between

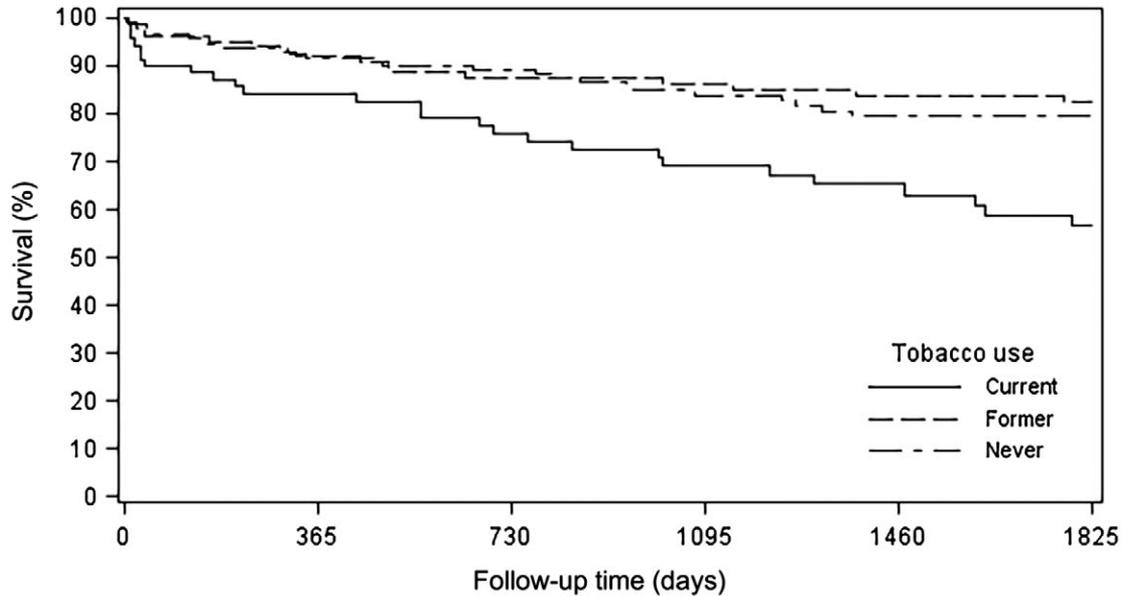
current/former and never marijuana users (78% versus 74%; $P = 0.37$; Fig. 1; Table 2). However, current tobacco users had significantly poorer survival compared with never users (57% versus 79%; $P = 0.006$); no difference was seen between former and never users (82% versus 79%; $P = 0.78$; Fig. 2; Table 2). After adjustment, current tobacco users were still over 3 times as likely to die within 5 years compared with never users (hazard ratio [HR], 3.25; 95% confidence interval [CI], 1.63-6.46; $P < 0.001$). No significant interaction between marijuana and tobacco use was seen on all-cause 5-year mortality ($P = 0.79$).

Overall incidence of being intubated >24 hours after surgery, respiratory complications, and reintubation was 19%, 11%, and 5% for the current/former marijuana smokers and 26%, 20%, and 11% for never smokers respectively. After adjustment, no



Current/former	81	73	62	59	46	37
Never	235	190	164	136	118	102

FIG. 1. The 5-year survival stratified by marijuana use. Overall 5-year survival was 75%. No significant difference in 5-year survival was seen between current/former and never marijuana users (78% versus 74%; $P = 0.37$).



Current	70	53	46	39	31	25
Former	101	87	75	71	65	55
Never	145	123	105	85	68	59

FIG. 2. The 5-year survival stratified by tobacco use. Current tobacco users had significantly poorer survival compared with never users (57% versus 79%; $P = 0.006$). No difference was seen between former and never users (82% versus 79%; $P = 0.78$).

TABLE 2. Crude and Adjusted Effect of Marijuana and Tobacco Use on 5-Year All-Cause Mortality

	Crude		Adjusted*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Marijuana use [†]	0.77 (0.43-1.37)	0.37	0.52 (0.26-1.04)	0.06
Tobacco use [‡]				
Current	2.33 (1.35-4.04)	0.003	3.25 (1.63-6.46)	<0.001
Former	0.85 (0.46-1.60)	0.24	0.95 (0.46-1.98)	0.90

*Adjusted for patient age, sex, race/ethnicity, diabetes, MELD score, tobacco smoking, marijuana use, HCC, and primary diagnosis.

[†]Current or former use compared with never users.

[‡]Compared with never users.

TABLE 3. Incidence and Adjusted Effect of Marijuana Smoking Status on Inpatient Complications

	Current/Formal User (n = 81)	Never Used (n = 235)	OR (95% CI)*	P Value
Intubated >24 hours	15 (19)	61 (26)	0.75 (0.36-1.54)	0.43
Respiratory complications	9 (11)	46 (20)	0.67 (0.28-1.62)	0.38
Reintubation	4 (5)	26 (11)	0.40 (0.13-1.29)	0.13
Any complication	19 (23)	89 (38)	0.62 (0.32-1.21)	0.16

*Adjusted for patient age, sex, race/ethnicity, diabetes, MELD score, tobacco smoking, HCC, and primary diagnosis.

significant differences in the incidence of these outcomes were seen between marijuana users and never users (Table 3).

The cause of death of the current marijuana recipients was acute respiratory distress syndrome, *Cryptococcus* pneumonia, and liver failure without the possibility for retransplant because of marijuana consumption. In the former marijuana-smoking group, 6 patients died of recurrent hepatitis C virus, 4 patients died of sepsis, 2 patients from motor vehicle accidents (MVA), and 1 because of noncompliance.

Discussion

This is a single center study with one of the longest periods of follow-up addressing the issue of marijuana consumption in the liver transplant population. It is unique because it also addresses, compares, and evaluates tobacco smoking in the same cohort. Overall, we found that marijuana users (current or former) were more likely to be male, use tobacco, and be diagnosed with either alcoholic cirrhosis or viral hepatitis. However, marijuana use had no impact on 5-year survival or inpatient complications compared with never users. Current tobacco users compared with never users were more than twice as likely to die within 5 years of

transplant. No interaction between marijuana use and tobacco use was seen on survival.

Recent literature has shown there is no consensus in transplant physicians about marijuana use, and it has been shown in case reports that it can produce complications, such as membranous glomerulonephritis, tachycardia, and tacrolimus toxicity. Nevertheless, the overall survival rates in kidney, liver, lung, and heart transplant patients show no difference from nonusers.⁽¹⁷⁾ Illicit drug use other than marijuana use was found to increase mortality in the liver transplant waiting list.⁽¹⁶⁾

Since California permitted the use of medical marijuana in 1996, followed by recreational legalization in the states of Washington and Colorado in 2012, there have been multiple studies evaluating its safety. Our study has shown, as have others, that marijuana should not be the sole reason to exclude a patient from transplantation because these patients have similar longterm outcomes and graft and patient survival as nonusers in both liver⁽²¹⁾ and kidney⁽⁴⁾ transplantation.

The *Diagnostic and Statistical Manual, 5th edition* defines substance use by the presentation of a pathological set of behaviors to a particular substance in a specific time frame, including impaired control, social impairment, risky use, and pharmacological

indicators.⁽²²⁾ Patients who present with any type of substance use have a higher incidence of poor outcomes and lower graft and patient survival.⁽²³⁾ Differentiating abuse from consumption is imperative in patients using marijuana and other substances, such as opioids, in a responsible manner. In all of these cases, the transplant team's main concern is noncompliance and possible graft loss. Couzi et al.⁽²⁴⁾ found in kidney transplant recipients that substance abuse was not an important part of a patient's noncompliance. The main causes were younger age and complex treatment schedule. We decided to compare marijuana to tobacco because tobacco is a legal substance that can still be consumed by transplant candidates. Currently, liver transplant programs still consider and accept patients for listing who currently use tobacco products, even though there have been multiple studies showing that these patients consistently have poorer outcomes.^(25,26)

Although we did not observe harm with marijuana use in our cohort of patients, marijuana use is not endorsed in our practice. All patients are told to stop smoking marijuana and tobacco (as well as any and all illicit substances) and are subjected to baseline and periodic blood alcohol tests, urine toxicology screens, and testing for nicotine and its metabolites. All patients receive an in-depth interview with a transplant psychologist and social worker, and for those with identified substance use disorders, mandatory enrollment in relapse prevention counseling with monthly toxicology, nicotine, and alcohol testing occurs. No patients are transplanted with active marijuana, tobacco, or alcohol use at the time of transplant. This practice was consistent throughout the study.

In the upcoming years, it will become more common to encounter patients for transplant evaluation who use marijuana, not only for recreational use, but also as treatment to manage symptoms caused by end-stage liver disease and prescribed by a referring physician. As such, it is critical to evaluate and understand the potential risks and benefits of marijuana use in transplant patients. For example, smoking marijuana has been shown to cause chronic inflammatory changes in the airway.⁽²⁷⁾ However, we did not observe any differences in respiratory complications. Alternatively, the health benefits of marijuana include improved pain management, as well as reducing depression, pruritus, nausea, and anorexia, all which are symptoms seen in patients waiting for liver transplant.⁽²⁸⁾ More research

is needed to understand the impact of marijuana in patients with end-stage liver disease and its impending role in the management of symptoms associated with it. Regardless, decisions on the impact of marijuana use on transplant listing should be based on medical evidence on its health effects and outcomes in liver transplant patients and not by the public perception of marijuana use.

Liver transplantation is seen as a scarce resource. Negative public perception of marijuana use and its consumption in liver transplant recipients could affect organ donation. However, the emphasis of this publication is just to report the existing data without any judgment or discrimination to the recipient. In fact, in this study, only 4% of recipients were active marijuana consumers compared with a significant amount of active tobacco smokers, which, to our knowledge, has not made any significant impact on donation.

This study has a few limitations. First, it is a single-center study with a relatively small sample size. Additionally, because marijuana use, recreational or medical, is not legal in North Carolina, it is likely that we may have underestimated the incidence of marijuana use and misclassified some current or former users as never users.

In conclusion, we found that patients who use marijuana (current or former) should not be precluded from liver transplant because they have no significant increase in morbidity or mortality compared with never users. However, patients who currently smoke tobacco should be very carefully considered as candidates, if at all, because they consistently have poorer survival compared with former users and never users.

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