Received: 27 November 2020 | Revised: 22 March 2021 | Accepted: 2 April 2021

DOI: 10.1111/ctr.14312

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

ORIGINAL ARTICLE

Marijuana use among adult liver transplant candidates and recipients

Alisa Likhitsup[1] | Naba Saeed[1] | Gerald Scott Winder[2,3] | Ammar Hassan[1] | Christopher J Sonnenday[3] | Robert J Fontana[1]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

[2]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

[3]Department of Surgery, University of Michigan, Ann Arbor, MI, USA

Correspondence
Alisa Likhitsup, Division of Gastroenterology and Hepatology, University of Michigan 4320 Wornall Road, Suite 240, Kansas City, MO 64111, USA.
Email: alikhitsup@gmail.com

Abstract

Background: Data regarding marijuana (MJ) use among liver transplant (LT) candidates are limited. We set out to determine the incidence and pre and postLT outcomes of adult LT candidates with a self-reported history of MJ use.

Methods: Baseline clinical characteristics, waitlist, and post-LT outcomes of adult LT candidates from January 2010 to March 2017 were compared.

Results: Among 2690 LT candidates, 630(23%) and 298(11%) reported a history of MJ use and use within the past 12 months, respectively. Although the proportion of MJ users increased over time(β = .76, p = .03), the proportion listed and transplanted did not change. Listing for LT increased with male (OR 1.24, 95% CI 11.01–1.52), MELD score (OR 1.08, 95% CI 1.01–1.15), HCC (OR 1.83, 95% CI 1.39–2.41) but decreased among MJ users (OR 0.67, 95% CI 0.50–0.91, p = .01). The median time to listing was longer among MJ users compared to non-users (115 vs. 87 days, p < .0005). PostLT survival was similar in 83 MJ users and 306 non-users.

Conclusion: The proportion of MJ users among LT candidates is increasing. MJ users have a greater burden of psychosocial issues which may contribute to longer evaluations and lower rate of LT listing. Post-LT survival was not impacted by self-reported MJ use history.

KEYWORDS
liver disease, liver transplantation, marijuana, psychosocial evaluation, substance use disorder

1 | INTRODUCTION

Marijuana (MJ) is the most commonly used illicit drug in the United States with an estimated 10% of US adults reporting active MJ use in the past month.[1] The prevalence of MJ use in the US has significantly increased over the past 15 years.[1] Touted clinical uses of MJ include the treatment of pain, muscle spasticity, refractory epilepsy, and nausea.[2] However, MJ use has also been associated with various adverse effects including infection, cardiopulmonary disease, neuropsychiatric, and behavioral problems.[3]

More than 50% of LT candidates have substance use disorder (SUD) including alcohol-related liver disease (ALD) and injection drug use associated with viral hepatitis.[4] MJ use among solid organ transplant patients is an area of little policy uniformity. Many studies have demonstrated adverse effects of tobacco use in LT candidates and recipients resulting in many US programs prohibiting tobacco use in their LT candidates.[5–7] Only a few studies have investigated the potential harm of MJ use in LT candidates and recipients and risks remain largely unknown. As such, national MJ-related policies and procedures for the evaluation and listing of transplant patients remain highly variable.[8,9]

© 2021 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Marijuana use remains illegal under federal law but state-based decriminalization and legalization of MJ use are increasing. As of January 2020, medical MJ use has been legalized in 33 states, and recreational MJ use is legal in 14 states.[10] In Michigan, medical marijuana was approved in 2008 and recreational MJ in 2018.

A substance use policy at the University of Michigan has proscribed alcohol, tobacco, and other recreational substance use, including MJ, in all adult LT candidates over the past 25 years. No explicit period of MJ abstinence was required but a negative urine drug screen was mandatory for listing. In this study, we aimed to determine 12-month and self-reported lifetime MJ use in consecutive adult LT candidates evaluated between 2010 and 2017. Clinical endpoints of interest included baseline clinical features, time to listing, and listing frequency between self-reported MJ users and never users as well as post-LT outcomes.

2 | METHODS

2.1 | Patient cohort

The University of Michigan Institutional Review Board reviewed and approved this retrospective chart review study. All adult LT candidates over 18 years of age evaluated at the University of Michigan from January 1, 2010, to March 1, 2017, were included. All patients were evaluated by a multidisciplinary team of hepatologists, transplant surgeons, and social workers. Decisions regarding listing for LT versus additional treatment for medical or SUD issues were made via a multidisciplinary selection committee. Living donor recipients, repeat evaluations, and patients with missing data points were excluded.

2.2 | Data collection

Abstracted demographic data included patient age, sex, race, etiology of liver disease, presence of HCC, and Model for End-Stage Liver Disease (MELD) score at evaluation and at transplantation. In addition, marital, insurance, and employment status as well as education levels were determined. Self-reported tobacco, alcohol, MJ, and other substance use history were coded after medical chart review as never used, any prior use, or within the past 12 months. In addition, toxicology test results at LT evaluation, psychiatric histories, past SUD treatment, and substance abuse-related health or legal consequences were collected. Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) scores were assessed in candidates beginning in 2015 and were included in the analysis for these patients.[11]

2.3 | Definitions

Marijuana users included those with use in the last 12 months or at any point in the past per self-report in their medical chart and evaluation notes. Urine drug screens confirmed active MJ use. Serum ethanol and phosphatidylethanol and urine ethyl glucuronide were used as alcohol biomarkers[12] Urine cotinine was used to screen for any nicotine use with urine anabasine and nornicotine confirming tobacco exposure.[13]

2.4 | Outcome measures

The primary outcome of interest was the proportion of MJ users who were listed, transplanted, or de-listed compared to non-users. Secondary outcomes of interest included discrete factors associated with MJ users being listed, and graft and patient survival post-LT.

2.5 | Statistical analysis

Continuous variables were expressed as mean (range). Categorical variables were expressed as percentages. Baseline characteristics at LT evaluation were compared using independent sample *t*-test for continuous variables and chi-squared tests for categorical data. Univariate logistic regression analysis was performed. Multivariable logistic regression analysis included variables with $p < .05$. Variables were tested for co-linearity and multi-step regressions until a good fit was established to assess candidate factors associated with MJ use and LT listing. The proportions of MJ users between 2010 and 2017 were plotted and linear regression was used for time trend analysis; beta coefficient and p-value were reported. Kaplan–Meier analysis was used to assess graft and patient survival. SPSS version 25.0 (IBM Corp) was used for all analyses.

3 | RESULTS

3.1 | Patient characteristics

During the study period, 3045 patients were evaluated for LT at our center with 2690 patients meeting study inclusion criteria (Figure 1). A total of 630 (23%) self-reported MJ use while 298 (11%) had used MJ in the last 12 months. MJ users were significantly younger (OR 0.98, 95% CI 0.97–0.98), male (OR 2.03, 1.67–2.46), and more likely to be diagnosed with ALD (OR 1.52, 95% CI 1.25–1.84), viral hepatitis (OR 2.62, 95% CI 2.17–3.15), or HCC (OR 1.88, 95% CI 1.46–2.43) (Table 1). Self-reported MJ users were also significantly more likely to be unemployed (OR 1.78, 95% CI 1.48–2.15), single (OR 1.39, 95% CI 1.16–1.66), and have Medicaid insurance (OR 2.04, 95% CI 1.66–2.51). As a group, they had lower levels of education (OR 1.42, 95% CI 1.19–1.70). MJ users also reported more prior and last 12-month use of tobacco alcohol, opioids, and illicit substances, substance-related health or legal consequences, prior SUD treatment, underlying psychiatric comorbidities, and use of psychiatric medications compared with non-users (Table 1).

The median SIPAT score was significantly higher in the 102 MJ users compared to the 208 non-users (33 vs. 10; $p = .002$, OR 1.05, 95% CI 1.04–1.07). The SIPAT scores were also more likely to be in

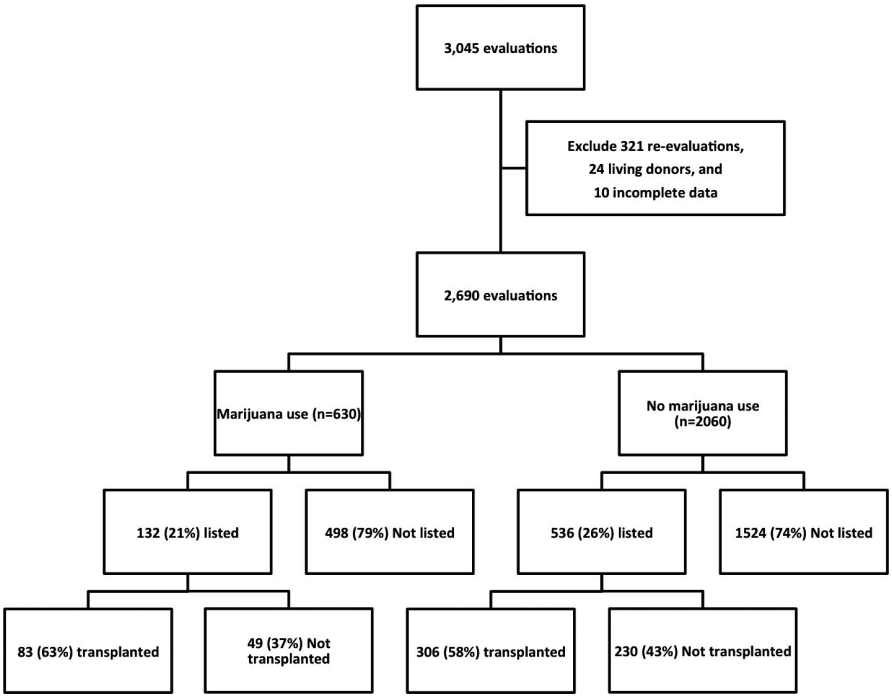


FIGURE 1 Liver Transplant Candidates included in this study. Among the 630 self-reported MJ users, 132 (21%) were listed for LT while 536 (26%) of the 2060 non-users were listed for LT. As of June 1, 2017, 83 and 306 of the self-reported MJ users and non-users have undergone LT, respectively

the poor or high-risk candidate in 36% of the MJ users vs. 13.5% of the non-users. Supplemental Table 1 compares characteristics between the subgroup of MJ users with recent 12-month use and the non-users and the results were similar to Table 1.

3.2 | Toxicology results and SUD treatment

Tobacco, alcohol, MJ, and illicit substance metabolites were significantly more likely to be detected at evaluation in self-reported MJ users compared to non-users (Table 1). In addition, SUD treatment recommendations including local counseling referrals or to intramural psychology or psychiatry were more common in MJ users ($p < .005$). There was no difference between groups in terms of the use of SUD pharmacotherapy. The results were similar in the recent 12-month MJ users (Table S1).

3.3 | Baseline features in self-reported MJ users

Multivariable models were constructed to determine the baseline features associated with MJ use adjusted for age, diagnosis of ALD and viral hepatitis, presence of HCC, insurance status, marital status, employment status, alcohol use history, tobacco use history, substance use history, and SUD health or legal consequences. Self-reported MJ users were more likely to have a diagnosis of viral hepatitis (OR 2.62 95% CI 1.95–3.51), ALD (OR 1.92 95% CI 1.44–2.57), HCC (OR 1.51 95% CI 1.11–2.05), be unemployed (OR 1.32 95% CI 1.06–1.64), and report a history of tobacco (OR 2.11 95% CI 1.68–2.64), alcohol (OR 2.59 95% CI 1.88–3.57), opioid (OR 2.08 95% CI 1.62–2.7), or other illicit substance use (OR 2.74 95% CI 2.06–3.64), and prior history of health or legal consequences (OR 95% 1.96 CI 1.47–2.61) (Table S2).

3.4 | Liver transplant selection outcomes

The proportion of MJ users among LT candidates significantly increased over time (20% in 2010 to 30% in 2017; $\beta = .76$, $p = .03$) (Figure S1). However, the proportion of MJ users being listed or transplanted remained stable over time ($p = .93$ and .65, respectively). The median time from LT evaluation to listing was significantly longer for MJ users compared to non-users (115 vs. 87 days; $p < .005$). In addition, a significantly lower proportion of MJ users were listed for LT compared to non-users (21% vs. 26%, OR 0.75, 95% CI 0.61–0.94, $p = .01$,) (Table 2). The proportion of MJ users not being listed due to active tobacco and MJ use was higher (4.3% vs. 2% and 5.4% vs. 0.6% respectively, $p < .05$. Similarly, the proportion of MJ users not listed due to being too well or having medical contraindications was lower than non-users (19.4% vs. 25%, $p = .002$ and 16% vs. 20%, $p = .07$ respectively (Table 2).

Among 2690 LT candidates, 668 (25%) were listed for LT. Listed patients were more likely to be male (OR 1.36 95% CI 1.13–1.63), have higher MELD at evaluation (OR 1.02, 95% CI 1.01–1.03), less likely to be diagnosed with ALD (OR 0.50, 95% CI 0.40–0.62), but more likely diagnosed with other liver diseases (OR 1.85, 95% CI 1.54–2.22) or HCC (OR 1.96, 95% CI 1.53–2.52) (Table S3). The listed patients were less likely to be single, unemployed, have lower education, no children, and have Medicaid or be uninsured. Prior history of tobacco, MJ, opioid use, psychiatry comorbidities, prior SUD consequences and treatment, positive alcohol, tobacco, MJ metabolites were more frequent in non-listed patients. Marijuana use or use of marijuana within 12 months were less frequent in listed patients (OR 0.75, 95% CI 0.61–0.94 and OR 0.44, 95% CI 0.31–0.62, respectively).

In multivariate models, listed patients were more likely to be male (OR 1.24 95% CI 1.01–1.52), have higher MELD at evaluation

TABLE 1 Characteristics of 2690 patients evaluated for LT stratified by self-reported MJ use

	MJ user	Non-user		
***N* = 2690**	***n* = 630**	***n* = 2060**	**OR (95% CI)**	***p*-Value**
Median age at evaluation (year)	54 (19-75)	57 (18-79)	0.98 (0.97–0.98)	<.005[a]
Male (%)	446 (71)	1122 (55)	2.03 (1.67–2.46)	<.005[a]
Caucasian (%)	518 (82)	1713 (84)	0.94 (0.74–1.19)	.25
Median MELD[b] at evaluation	13 (6-40)	13 (6-40)	0.99 (0.98–1.05)	.23
Diagnosis				
Viral hepatitis (%)	289 (46)	504 (25)	2.62 (2.17–3.15)	<.005[a]
ALD (%)	221 (35)	541 (26)	1.52 (1.25–1.84)	<.005[a]
NASH (%)	20 (3)	287 (14)	0.20 (0.13–0.32)	<.005[a]
Others (%)	100 (16)	728 (35)	0.35 (0.27–0.44)	<.005[a]
Presence of HCC (%)	107 (17)	202 (10)	1.88 (1.46–2.43)	<.005[a]
Insurance status (% Medicaid)	180 (29)	338 (16)	2.04 (1.66–2.51)	<.005[a]
Education level (% K-12 or lower)	302 (48)	810 (39)	1.42 (1.19–1.70)	.01[a]
Employment status (% unemployed)	419 (71)	1086 (57)	1.78 (1.48–2.15)	<.005[a]
Marital status (% single/separate/divorced)	277 (44)	750 (36)	1.39 (1.16–1.66)	.001[a]
Parental status (% has children)	447 (70)	1506 (73)	0.80 (0.66–1.01)	.06
Reported history of (%)				
Marijuana use within 12 months	298 (47)	0	NA	<.005[a]
Tobacco ever use	473 (75)	912 (44)	3.82 (3.12–4.67)	<.005[a]
Tobacco use within 12 months	300 (48)	464 (23)	3.13 (2.60–3.78)	<.005[a]
Alcohol ever use	569 (90)	1313 (64)	5.31 (4.02–7.01)	<.005[a]
Alcohol use within 12 months	257 (41)	523 (25)	2.03 (1.68–2.45)	<.005[a]
Opioid ever use	178 (28)	223 (11)	3.26 (2.61–4.07)	<.005[a]
Opioid use within 12 months	152 (23)	209 (10)	2.83 (2.24–3.56)	<.005[a]
Other illicit substance ever use	193 (30)	130 (6)	6.60 (5.17–8.44)	<.005[a]
Other illicit substance use within 12 months	12 (2)	12 (0.6)	3.33 (1.49–7.45)	.002[a]
SIPAT score available	102 (16)	208 (10)		
Median SIPAT score[c]	33 (0-80)	10 (0-82)	1.05 (1.04–1.07)	<.005[a]
SIPAT score category[c]				
Good or excellent candidate (0–20)	21 (21)	108 (52)	0.64 (0.40–1.04)	.07
Minimal acceptable (21–39)	44 (43)	73 (35)	2.56 (1.72–3.82)	<.005[a]
Poor candidate (40–69)	32 (31)	26 (13)	4.36 (2.56–7.41)	<.005[a]
High risk (>70)	5 (5)	1 (0.5)	8.23 (1.59–42.53)	<.005[a]
Presence of psychiatric comorbidity (%)	266 (42)	498 (24)	2.29 (1.90–2.76)	<.005[a]
On psychiatric medications (%)	175 (28)	352 (17)	1.87 (1.51–2.30)	<.005[a]
Prior SUD health/legal consequences (%)	159 (25)	139 (7)	4.71 (3.67–6.04)	<.005[a]
Prior SUD treatment (%)	175 (28)	196 (10)	3.70 (2.95–4.65)	<.005[a]
Toxicology screen				
Toxicology screening (% completed)	541 (85)	1430 (70)	2.65 (2.07–3.36)	<.005[a]
Alcohol metabolites (% positive)	32 (5)	43 (2)	2.03 (1.27–3.24)	.003[a]
Tobacco metabolites (% positive)	191 (30)	242 (12)	2.68 (2.14–3.35)	<.005[a]

(Continues)

TABLE 1 (Continued)

	MJ user	Non-user		
***N* = 2690**	***n* = 630**	***n* = 2060**	**OR (95% CI)**	***p*-Value**
Marijuana metabolites (% positive)[d]	162 (26)	38 (2)	15.66 (10.80–22.69)	<.005[a]
Opioid metabolites (% positive)	118 (19)	273 (13)	1.18 (0.93–1.51)	.18
Other illicit substances metabolites (% positive)	70 (11)	95 (5)	1.48 (0.78–2.81)	<.005[a]
Counseling/referral	208 (33)	301 (15)	2.96 (2.40–3.70)	<.005[a]
SUD Pharmacotherapy	4 (0.6)	11 (0.5)	1.14 (0.36–3.60)	.82

Abbreviations: ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; MJ, marijuana; NASH, non-alcoholic steatohepatitis; SUD, substance use disorder.

[a]Univariate analysis $p < .05$.

[b]Calculated MELD score, not MELD-Na.

[c]SIPAT score was implemented in LT evaluation process in 2015.

[d]Results did not substantially change if the 38 self-reported non-MJ users with detectable MJ metabolites were recategorized as MJ users (Data not shown)

(OR 1.08, 95% CI 1.01–1.15), with presence of HCC (OR 1.83, 95% CI 1.39–2.41) (Table 3). Marijuana use history was associated with lower likelihood of LT listing (OR 0.67, 95% CI 0.50–0.91, $P = .01$). In addition, a diagnosis of ALD, being single, having Medicaid or being uninsured, and presence of psychiatric disorder were associated with not being listed (Table 3).

3.5 | Liver transplant candidate Waitlist Outcomes

Among the 132 listed MJ users, 83 (63%) underwent LT during follow-up, compared to 306 (58%) listed non-users ($p = .23$; Table 2). Median MELD scores at LT were similar in the two patient groups (22 vs. 23; $p = .68$). Among listed self-reported MJ users, 7 were de-listed due to recurrent MJ use; 5 of them were relisted after MJ abstinence was established while 2 were closed due to non-adherence and active use. In contrast, only 2 of the 536 listed non-users were temporarily de-listed due to active MJ use and both were relisted after receiving counseling and MJ abstinence was confirmed. The reasons for not undergoing LT among MJ users and non-users were similar ($p > .05$). However, SUD-related issues were more frequent among MJ users (10% vs. 4%; $p = .07$).

3.6 | Post-transplant outcomes

Table 4 shows similar 1-year patient and graft survival rates in the 83 MJ users and 306 non-users undergoing LT (OR 1.17, 95% CI 0.38–3.57 $p = .79$ and OR 1.29, 95% CI 0.43–3.91 $p = .6$, respectively). Overall graft and patient survival rates were also similar (OR 0.84, 95% CI 0.36–1.94 $p = .68$ and OR 0.90, 95% CI 0.46–1.77 $p = .77$) between MJ users and non-users during median follow-up times of 1338 days (1–2986) for users and 1156 days (0–3038) for non-users. The OR after adjusting for employment status, history of tobacco use, parental status, and initial toxicology testing demonstrated that the survival outcomes were not different by MJ use (Table 3). In addition, age, gender, and presence of HCC were not associated with post-LT survival. Kaplan-Meier analysis in Figure 2 showed that graft and patient survival was similar between MJ users and non-users (log rank $P = .11$ and 0.65, respectively). Reasons for graft loss were also similar between MJ users and non-users. Graft and patient survival among patient reported using vs. not using MJ within 12 months were compared. Self-reported MJ users within the past 12 months had similar graft survival (Figure S2A) ($p = .10$, log rank) and (Figure S2B) patient survival ($p = .29$, log rank) compared to non-users. However, the data were very limited with only 23 MJ users within 12 months undergoing transplantation.

4 | DISCUSSION

This large retrospective study of a single Midwestern liver transplant center's experience with MJ use reveals the inherent medical and psychosocial complexity of MJ use in this population. Self-reported MJ users in this cohort tended to be younger and male with a higher psychosocial complexity in terms of their psychiatric comorbidity, relationship and socioeconomic status, and comorbid substance use disorders. This complexity correlated with longer evaluation times in the context of an increasing incidence of MJ use in the LT population (**Figure 1**). With an increasing prevalence of MJ use disorders in the United States over the past decade,[14] MJ use will continue to be a challenge for LT centers for the foreseeable future.

In the United States, MJ is still considered an illegal Schedule 1 drug under the Controlled Substances Act,[1] which means its study and the evidence for its use lag behind its burgeoning medical and recreational use. This also means that the MJ laws in the areas where the LT center and patients are located could be widely disparate. Thus far, 8 states have passed laws protecting patients from denial of organ transplantation solely on the basis of MJ use.[15] Nonetheless, MJ policies in organ transplantation are highly

TABLE 2 Liver transplant selection and transplantation outcomes in MJ users and non-MJ users

	MJ users	Non-users		
N = 2690	*n* = 630	*n* = 2060	OR (95% CI)	*p*-Value
Selection results (% listed)[a]	132 (21)	536 (26)	0.75 (0.61–0.94)	.01[b]
Median time to list (days)	115 (0-519)	87 (0-546)	1.003 (1.001–1.006)	<.005[b]
Reason not listed; *n* (%)				
Clinically too well	122 (19.4)	525 (25)	0.62 (0.49–0.78)	.002[b]
Deceased	26 (4.1)	124 (6)	0.62 (0.40–0.96)	.07
Medical issue	101 (16)	411 (20)	0.69 (0.54–0.88)	.03[b]
Alcohol use	64 (10.2)	176 (9)	1.13 (0.83–1.53)	.21
Tobacco use	27 (4.3)	45 (2)	1.88 (1.16–3.07)	.004[b]
Active MJ use	34 (5.4)	12 (0.6)	9.23 (4.74–17.98)	<.005[b]
Other substance use	4 (0.6)	9 (0.4)	1.36 (0.42–4.45)	.53
Others[c]	120 (19)	222 (11)	1.03 (0.76–1.41)	.05
Transplanted (% of listed)	83 (63)	306 (58)	0.79 (0.53–1.16)	.23
Median MELD[d] at LT	22 (13-40)	23 (12-40)	0.99 (0.95–1.04)	.68

Abbreviations: LT, liver transplantation; MELD, model for end-stage liver disease; MJ, marijuana.

[a]Results not substantially changed if the 8 non-users with detectable MJ metabolites were recategorized as MJ user (Data not shown)

[b]Univariate analysis $p < .05$.

[c]Others including insurance concern, transfer care to other facility or patient decline for LT

[d]Calculated or exceptional MELD score, not MELD-Na

TABLE 3 Baseline factors associated with LT listing in 2690 LT candidates

Variable	Odds ratio[a] (95% confidence interval)	*p*-Value
Male	1.24 (1.01–1.52)	.04
Higher MELD	1.08(1.01–1.15)	.02
Presence of HCC	1.83 (1.39–2.41)	<.005
Diagnosis of ALD	0.50 (0.39–0.64)	<.005
Medicaid or uninsured status	0.52 (0.39–0.69)	<.005
Single status	0.64 (0.52–0.78)	<.005
History of marijuana use	0.67 (0.50–0.91)	.01
Underlying psychiatric disorder	0.69 (0.55–0.88)	.002

Abbreviations: ALD, alcohol-related liver disease; CI, confidence interval; HCC, hepatocellular carcinoma; LT, liver transplantation; SUD, substance use disorder.

[a]Adjusted for gender, MELD at evaluation, diagnosis of ALD, presence of HCC, insurance, marital, employment status, history of alcohol, tobacco, marijuana use, psychiatry comorbidities.

heterogeneous between and within institutions and without broad consensus.[9,16] Whether or not MJ use should be considered a relative or absolute contraindication for solid organ transplantation is controversial.[2,17] Uniform national policy will be difficult to develop and adopt given the variability in state regulations and institutional policies. Therefore, it will continue to fall to the judgment of clinicians, teams, and individual centers to evaluate patients with a history of MJ use.

The content, potency, and purity of MJ and other cannabinoid products and preparations are highly variable. How patients use them is also inconsistent (smoking, vaping, eating, etc) and difficult to standardize and quantify.[18] Furthermore, how MJ interacts with the pharmacology, physiology, and psychology of the LT population remains unclear. MJ is increasingly potent in terms of the level of tetrahydrocannabinol (THC) it contains and case reports exist regarding interactions between cannabinoids and immunosuppressants.[3,19–21] Furthermore, MJ products have been contaminated with fungal spores, heavy metals, pesticides, opioids, glass beads, phencyclidine, and tobacco.[16,22–26] Occasional and low-level MJ use has not been associated with worsening pulmonary function or development of lung cancer.[27,28] However, invasive aspergillosis remains a significant cause of morbidity and mortality in transplant recipients including those who use MJ.[29–31] Severe lung injuries in patients using vaping products have been reported including the need for a double lung transplant.[32,33] The increasing prevalence of MJ use in LT patients will require LT clinicians to carefully weigh medical risks and benefits of MJ use.

In our adjusted model, self-reported MJ use was associated with a 33% lower likelihood of LT listing. The median time from LT evaluation to listing was also significantly longer among self-reported MJ users compared to non-users and median SIPAT scores were higher in MJ users compared to non-users likely reflecting this complexity. The results of these analyses also did not substantially change

TABLE 4 Post-transplant outcomes stratified by MJ use history

	MJ users	Non-users			Adjusted OR (95%	
	n = 78	*n* = 291	OR (95% CI)	*p*-Value	CI)[b]	*p*-Value
Median post-LT follow-up (days)	1338 (1-2986)	1156 (0-3038)	1.00	.78		
1-year graft survival (%)[a]	75 (96)	262 (90)	1.17 (0.38–3.57)	.79	1.28 (0.42–3.85)	.66
1-year patient survival (%)[a]	72 (92)	263 (90)	1.29 (0.43–3.91)	.6	1.32 (0.43–4.0)	.64
Overall graft survival (%)	72 (92)	271 (93)	0.84 (0.36–1.94)	.68	0.87 (0.36–2.11)	.76
Overall patient survival (%)	70 (89)	262 (90)	0.90 (0.46–1.77)	.77	0.93 (0.46–1.88)	.85
Total graft loss	6 (8)	20 (7)		.33		
Primary graft non-function	1 (17)	5 (25)				
Acute rejection	1 (17)	3 (15)				
Chronic rejection	0	3 (15)				
HAT or aneurysm	1 (17)	5 (25)				
Biliary stricture	3 (50)	4 (20)				

Abbreviations: HAT, hepatic artery thrombosis; LT, liver transplantation; MJ, marijuana.

[a]Twenty patients were excluded due to incomplete survival data.

[b]Adjusted for employment status, history of tobacco use, parental status, or toxicology test completed at the initial evaluation base on univariate analysis with $p < .05$.

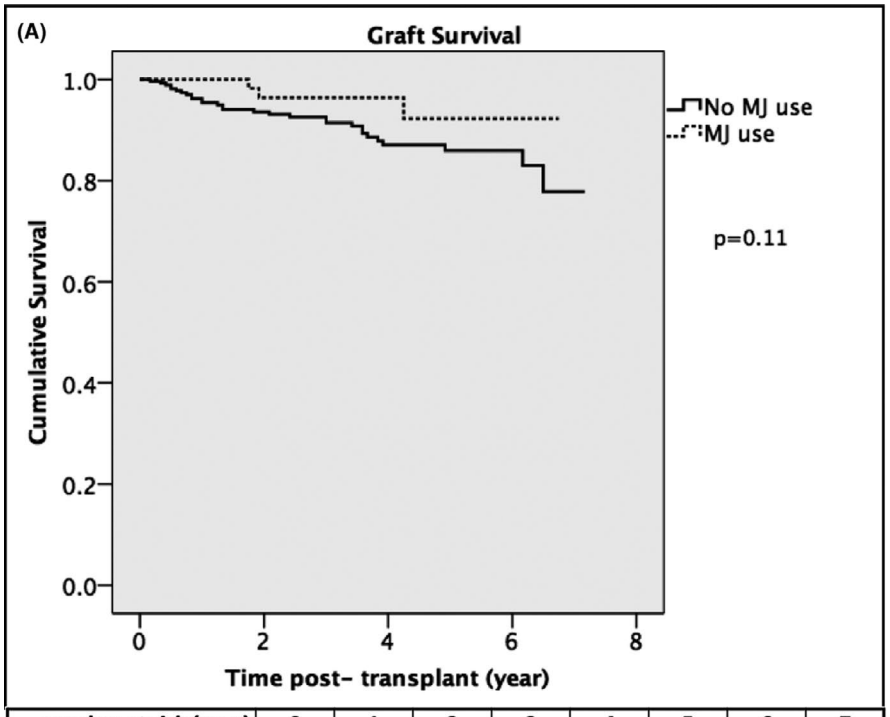
if the 38 and 8 non-MJ users in Tables 1 and 2 with detectable MJ metabolites, respectively, were reclassified as MJ users (Data not shown). Numerous studies document the association of MJ use and mood disorders, psychosis, personality problems, and anxiety.[3] Since pre-transplant substance use has been associated with post-transplant non-adherence to immunosuppression, it is not surprising that cases of graft loss after kidney transplant from immunosuppression non-adherence in the context of high dose MJ use have been reported.[34,35] In the current retrospective series, none of the graft loss cases were attributable to non-adherence. The cognitive risks of MJ and its impact on life satisfaction scores and motivation may be particularly detrimental in a post-LT population returning to life and caring for their grafts. Relevant to LT post-operative pain management, MJ has been linked with lower opioid-related overdoses though this has since been disputed.[36]

Our study did not show differences between self-reported MJ users and non-users in terms of 1-year or overall patient or graft survival rates which is in line with prior studies.[16,37] While tobacco users were 3 times more likely to die within 5 years compared with never users, there was no difference in these outcomes among current, former MJ users, and non-users.[37] In our current study of a more recent cohort of LT candidates, 23% reported a history of MJ use and 11% within the last 12 months. Along with national data, our current study supports the finding that MJ use in the LT population is on the rise. Furthermore, 2% (38patients) of the patients who denied any MJ use had positive MJ metabolites (Table 1). This result reflects potential deceptive reporting of MJ use by these patients. Among patient who denies MJ history of use, 0.6% (12 patients) were not listed due to the detected marijuana metabolites (Table 2).

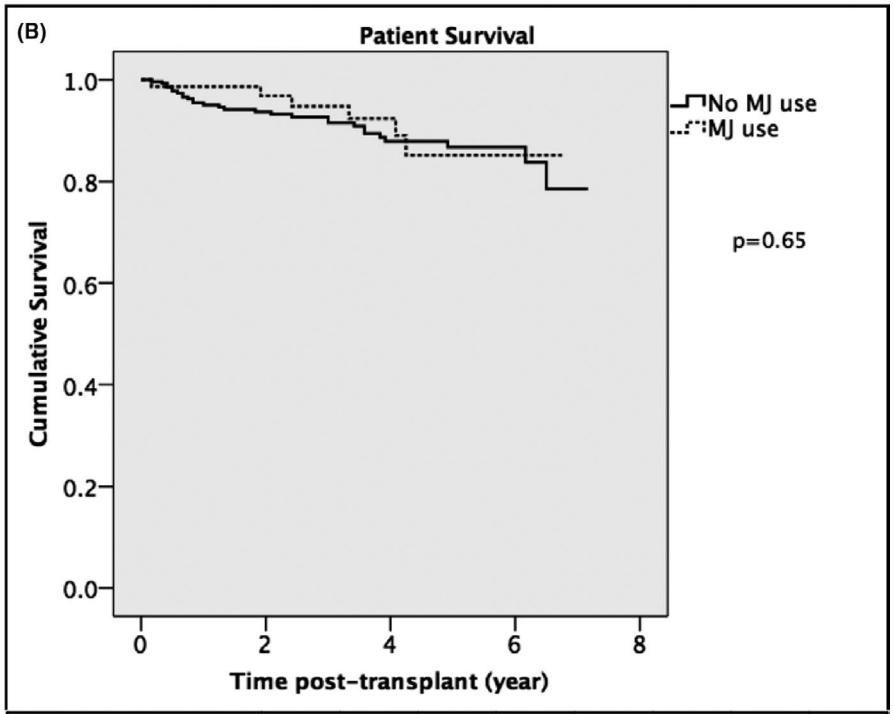
The growing acceptance and legalization of MJ use in society including LT patients mean that LT programs need to have adequate psychosocial personnel and resources to evaluate and treat their patients. The longer evaluation times and lower listing rates identified in our study indicate the need for such psychosocial expansion. As our study identified a higher rate of waitlist removal in MJ users for substance use, a reduction in stigma is also important to improve LT access to MJ users. High levels of collaboration among psychosocial providers and among the broader LT team members may also facilitate working through the substantial MJ-related complexity. Regular and thoughtful use of toxicology testing can be a useful objective tool in these efforts since the nature of the LT environment can motivate some patients to conceal their substance use.[38]

There are several limitations of our study. First, this is a retrospective single-center study wherein the reported history of MJ, tobacco, alcohol, and substance uses were collected from medical records without direct patient interviews. Data regarding whether MJ was used for medical or recreational purposes could not be reliably determined. Second, the amount and route of MJ use could not be reliably quantified. Third, a formal assessment of immunosuppression adherence and psychosocial outcomes post-LT was not feasible in this retrospective study. Finally, the generalizability of our single-center study may be limited; however, our cohort was large and spanned an 8-year period. To address these limitations, future prospective multicenter studies using standardized instruments, definitions, and treatment paradigms in LT candidates are needed. Also, studies looking at "softer" transplant outcomes like mental health metrics, quality of life measures, and SUD treatment engagement both before and after LT are needed.

In conclusion, the proportion of MJ users being evaluated for LT is significantly increasing while the rate of listing and transplantation has remained stable placing an increasing burden of psychosocial nuance on LT teams. Our data and those from others



number at risk (year)	0	1	2	3	4	5	6	7
No MJ use	303	291	287	283	277	276	276	274
MJ use	83	83	81	81	81	80	80	80



number at risk (year)	0	1	2	3	4	5	6	7
No MJ use	303	290	287	283	278	277	277	275
MJ use	83	82	81	80	79	77	77	77

FIGURE 2 Graft and patient survival among self-reported MJ users and non-users. (A) Actuarial graft survival was similar in MJ users and non-users (p = .11) and (B) Actuarial patient survival was also similar between patients with and without a MJ use history (p = .65)

demonstrate that prior MJ use should not uniformly preclude patients from being listed or undergoing LT. Many LT programs may need to invest in additional psychiatric and SUD resources including the incorporation of a transplant psychiatrist and/or psychologist, addiction specialist, and social workers with mental health training. Rates of graft and patient survival are similar in self-reported MJ users and non-users separating the transplant decision from any stigma of use. Going forward, evidence-based,

consensus guidelines may help to standardize the approach to the evaluation and management of LT candidates with a prior or current history of MJ use.

CONFLICTS OF INTEREST

AL, AH, NS, GSW, CJS—none, RJF receives grant support from Abbvie, BMS, and Gilead. He also does consulting for Sanofi pharmaceuticals.

AUTHOR CONTRIBUTION

A Likhitsup designed the study, collected the data, made statistical analysis, and drafted the manuscript; NS collected the data and drafted the manuscript; GSW designed the study and reviewed the manuscript; A Hassan collected the data; CJS supervised the study and reviewed the manuscript; RJF designed the study, made data analysis, supervised the study, and reviewed the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, AL, upon reasonable request.

ORCID

Alisa Likhitsup https://orcid.org/0000-0001-8191-9497

REFERENCES

1. Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, Lyerla R. National estimates of marijuana use and related indicators — national survey on drug use and health, United States, 2002–2014. *MMWR Surveill Summ*. 2016;65(11):1-28. https://doi.org/10.15585/mmwr.ss6511a1
2. Rai HS, Winder GS. Marijuana use and organ transplantation: a review and implications for clinical practice. *Curr Psychiatry Rep*. 2017;19:91.
3. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227.
4. DiMartini A, Crone C, Dew MA. Alcohol and substance use in liver transplant patients. *Clin Liver Dis*. 2011;15:727-751.
5. Likhitsup A, Hassan A, Mellinger J, et al. Impact of a prohibitive versus restrictive tobacco policy on liver transplant candidate outcomes. *Liver Transpl*. 2019;25(8):1165-1176.
6. Cote DR, Chirichella TJ, Noon KA, et al. Abdominal organ transplant center tobacco use policies vary by organ program type. *Transplant Proc*. 2016;48:1920-1926.
7. Fleetwood VA, Hertl M, Chan EY. Liver transplantation to the active smoker: transplant provider opinions and how they have changed: transplantation in smokers: a survey. *J Gastrointest Surg*. 2015;19:2223-2227.
8. Levi ME, Montague BT, Thurstone C, Kumar D, Huprikar SS, Kotton CN. Marijuana use in transplantation: a call for clarity. *Clin transplant*. 2019;33(2):e13456.
9. Zhu J, Chen PY, Frankel M, Selby RR, Fong TL. Contemporary policies regarding alcohol and marijuana use among liver transplant programs in the United States. *Transplantation*. 2018;102(3):433-439.
10. National Conference of State Legislatures. State medical marijuana laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed September 30, 2019.
11. Maldonado JR, Dubois HC, David EE, et al. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT): a new tool for the psychosocial evaluation of pre-transplant candidates. *Psychosomatics*. 2012;53(2):123-132.
12. Webzell I, Ball D, Bell J, et al. Substance use by liver transplant candidates: an anonymous urinalysis study. *Liver Transpl*. 2011;17:1200-1204.
13. Jacob P 3rd, Hatsukami D, Severson H, Hall S, Yu L, Benowitz NL. Anabasine and anatabine as biomarkers for tobacco use during nicotine replacement therapy. *Cancer Epidemiol Biomarkers Prev*. 2002;11:1668-1673.
14. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. *JAMA Psychiatry*. 2015;72(12):1235-1242.
15. Pondrom S. Transplantation and marijuana use. *Am J Transplant*. 2016;16(1):1-2.
16. Ranney DN, Acker WB, Al-Holou SN, et al. Marijuana use in potential liver transplant candidates. *Am J Transplant*. 2009;9:280-285.
17. Greenan G, Ahmad SB, Anders MG, Leeser A, Bromberg JS, Niederhaus SV. Recreational marijuana use is not associated with worse outcomes after renal transplantation. *Clin Transplant*. 2016;30:1340-1346.
18. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medicinal cannabis: rational guidelines for dosing. *IDrugs*. 2004;7(5):464-470.
19. Moadel D, Chism K. Medical marijuana-induced tacrolimus toxicity. *Psychosomatics*. 2019;60(6):603-605.
20. Hauser N, Sahai T, Richards R, Roberts T. High on cannabis and calcineurin inhibitors: a word of warning in an era of legalized marijuana. *Case Rep Transplant*. 2016;2016:4028492.
21. Leino AD, Emoto C, Fukuda T, Privitera M, Vinks AA, Alloway RR. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus. *Am J Transplant*. 2019;19(10):2944-2948.
22. Kagen SL, Kurup VP, Sohnle PG, Fink JN. Marijuana smoking and fungal sensitization. *J Allergy Cini Immunol*. 1983;71:389-393.
23. Kurup VP, Resnick A, Kagen SL, Cohen SH, Fink JN. Allergenic fungi and actinomycetes in smoking materials and their health implications. *Mycopathologia*. 1983;82:61-64.
24. Verweij PE, Kerremans JJ, Voss A, Meis JF. Fungal contamination of tobacco and marijuana. *JAMA*. 2000;284(22):2875.
25. McPartland JM. Contaminants and adulterants in herbal cannabis. In: Grotenhermen F, Russo E, eds. *Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential*. New York, NY: Haworth Press; 2002:337-343.
26. McLaren J, Swift W, Dillon P, Allsop S. Cannabis potency and contaminator: a review of the literature. *Addiction*. 2008;103(7):1100-1109.
27. Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. *JAMA*. 2012;307(2):173-181.
28. Zhang LR, Morgenstern H, Greenland S, et al. Cannabis and Respiratory Disease Research Group of New Zealand, Brhane Y. Cannabis smoking and lung cancer risk: pooled analysis in the International lung cancer consortium. *Int J Cancer*. 2015;136(4):894-903.
29. Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. *Chest*. 1988;94:432-433.
30. Marks WH, Florence L, Lieberman J, et al. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. *Transplantation*. 1996;61(12):1771-1774.
31. Pergam SA. Fungal pneumonia in patients with hematologic malignancies and hematopoietic cell transplantation. *Clin Chest Med*. 2017;38:279-294.
32. United States Department of Health and Human Services. Center of Disease Control (CDC). https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed November 8, 2019.

33. U.S Food and Drug Administration. Vaping Illness Update: FDA Warns Public to Stop Using Tetrahydrocannabinol (THC)-Containing Vaping Products and Any Vaping Products Obtained Off the Street. 2019. https://www.fda.gov/consumers/consumerupdates/vaping-illness-update-fda-warns-public-stop-using-tetrahydrocannabinol-thc-containing-vaping. Accessed December 5, 2019.
34. Lieber SR, Volk ML. Non-adherence and graft failure in adult liver transplant recipients. *Dig Dis Sci*. 2013;58(3):824-834.
35. Shakowski C, Freedman S, Schwarz K, Page RL II. Effect of marijuana exposure on calcineurin inhibitor dose to trough ratios in heart transplant recipients. *J Heart Lung Transplant*. 2018;37(4S):207 (Abstract).
36. Shover CL, Davis CS, Gordon SC, Humphreys K. Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci USA*. 2019;116(26):12624-12626.
37. Serrano Rodriguez P, Strassle PD, Barritt AS IV, et al. Marijuana consumption in liver transplant recipients. *Liver Transpl*. 2019;25(5):734-740.
38. Staufer K, Andresen H, Vettorazzi E, Tobias N, Nashan B, Sterneck M. Urinary ethyl glucuronide as a novel screening tool in patients pre-and post–liver transplantation improves detection of alcohol consumption. *Hepatology*. 2011;54(5):1640-1649.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Likhitsup A, Saeed N, Winder GS, Hassan A, Sonnenday CJ, Fontana RJ. Marijuana use among adult liver transplant candidates and recipients. *Clin Transplant*. 2021;35:e14312. https://doi.org/10.1111/ctr.14312