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**Title**

Recreational Marijuana Use is Not Associated with Worse Outcomes After Renal Transplantation

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**Abstract**

As marijuana (MJ) legalization is increasing, kidney transplant programs must develop listing criteria for marijuana users. However, no data exist on the effect of MJ on kidney allograft outcomes, and there is no consensus on whether MJ use should be a contraindication to transplantation. We retrospectively reviewed 1,225 kidney recipients from 2008-2013. Marijuana use was defined by positive urine toxicology screen and/or self-reported recent use. The primary outcome was death at one year or graft failure (defined as GFR<20ml/min/1.73m$^2$). The secondary outcome was graft function at one year. Using logistic regression analyses, we compared these outcomes between MJ-users and non-users. Marijuana use was not associated with worse primary outcomes by unadjusted (Odds Ratio 1.07, 95% CI 0.45-2.57, p=0.87) or adjusted (Odds Ratio 0.79, 95% CI 0.28-2.28, p=0.67) analysis. Ninety-two percent of grafts

functioned at one year. Among these, the mean creatinine (1.52, 95% CI 1.39-1.69 versus 1.46, 95% CI 1.42-1.49; p=0.38) and MDRD GFR (50.7, 95% CI 45.6-56.5 versus 49.5, 95% CI 48.3-50.7; p=0.65) were similar between groups. Isolated recreational MJ use is not associated with poorer patient or kidney allograft outcomes at one year. Therefore, recreational MJ use should not necessarily be considered a contraindication to kidney transplantation.

**Key Words**

marijuana, transplantation, graft, use, outcome

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## Introduction

As the campaign to legalize marijuana (MJ) for recreational as well as medical use gains momentum in the United States (1), transplantation guidelines for MJ users deserve examination. Marijuana is the most commonly used "illicit" drug in the world, reportedly used by 12% of Americans aged 12 years or older in 2013 (2). Nine percent of patients with end stage renal disease (ESRD) in the United States report or test positive for illicit drug use. These patients are less likely to be placed on the waiting list for a transplant and less likely to be transplanted once listed (3).

Marijuana is prescribed for many chronic conditions refractory to conventional treatments including pain, nausea, vomiting, cachexia, muscle spasticity, and glaucoma. Benefits notwithstanding, the deleterious effects and associations of MJ are also well documented (4, 5):

development of addiction in 9% of its users (6); impaired cognitive development (7); chronic bronchitis (8); cardiovascular disease (9); mental illness (10, 11); and socioeconomic consequences such as unemployment and criminal behavior (12). Moreover, it is considered a gateway drug and labels the transplant candidate as a substance user, raising concern over the candidate's ability to maintain adherence with immunosuppression regimens and prolonging the candidate's time on a transplant waitlist (3, 13). Indeed, MJ users in a chronic liver disease cohort were more likely to test positive for other illicit drugs such as cocaine and opioids, to have hepatitis C, and to smoke tobacco, and were less likely to receive a liver transplant (14).

Cannabis remains a Schedule I substance under federal law, although four states and the District of Columbia have legalized recreational use as of 2015, and 23 states have legalized medical marijuana (15). Accordingly, it may become increasingly common for selection committees to encounter active MJ use in their assessments of kidney transplant candidacy. While there is no evidence from the literature that recreational MJ use impairs kidney allograft function or threatens kidney transplant survival, many transplant centers consider any MJ use an absolute contraindication to kidney transplantation. These discrepancies between centers came to the authors' attention through one of the online transplant physician discussion forums. Such practices unfairly disadvantage MJ using patients by prolonging the time to listing and by making them seek out (sometimes distant) transplant programs that do accept varying degrees of MJ use for transplantation (anecdotal experiences). The concerns of transplant programs about MJ use include a dread of non-adherence due to potential cognitive effects of MJ, as well as a fear of life-threatening infections from aspergillosis (16,17). At many transplant centers, "substance abuse" remains a poorly defined term without consensus on the acceptable period of abstinence or on the categorization of abused substances. Cocaine and opioid abuse are usually

absolute contraindications (18); tobacco and alcohol use or abuse are often relatively contraindicated. The use of these substances has been linked to graft loss (19, 20), delayed graft function (21), and patient mortality (22, 23, 24). Any MJ use, on the other hand, is frequently banned as an absolute contraindication. Whether active, recreational MJ use alone is associated with inferior outcomes in graft and patient survival after renal transplantation has yet to be determined.

Data on MJ use in the kidney transplant population are not captured in any large national database to our knowledge. Our experience at a high volume academic transplant center has facilitated comparison of patient characteristics and renal graft outcomes between MJ users and non-users in a large, urban, contemporary transplant population. We hypothesized that recreational MJ use is not associated with worse outcomes after renal transplantation and aimed to challenge the current notion that any active marijuana use should contraindicate receiving a kidney allograft.

**Methods**

Data collection and analysis were approved by the University of Maryland Institutional Review Board. Electronic medical records for all adult patients who underwent either live donor or deceased donor renal transplantation at the University of Maryland Medical Center from January 1, 2008 to January 1, 2013 were retrospectively reviewed. This time period was chosen to allow for the evaluation of a contemporary cohort with at least one year of follow-up post-transplantation. Electronic medical records were cross-checked between outpatient and inpatient physician and social work records, along with those of the internal transplant database (Presidio), in order to minimize missing data. Patients were classified as either MJ users or MJ non-users. Marijuana users were defined as those patients who either admitted to current MJ use or tested

positive on urine drug screen for MJ. All others were included in the non-MJ user group, including never-users, past-users, and patients with missing data. Marijuana use history was extracted from urine toxicology screens obtained during pre-transplant evaluation and self-reported histories of active marijuana use. In anuric or severely oliguric patients, when no urine sample could be obtained, no other testing was performed unless the social work evaluation revealed concerns about substance abuse. Patients were questioned about their MJ use by multiple providers, including registered nurses, social workers, and physicians. In order to encourage disclosure, patients were generally told that MJ use was acceptable if it was not abusive. Active alcohol and tobacco history were also noted. At this transplant center, at the time of this study, patients who were diagnosed with addictive behavior with any substance (alcohol, marijuana, or other) were deemed high risk candidates for transplantation, referred to a treatment program, and then re-evaluated for addictive behaviors and other high risk concerns by transplant social workers prior to being listed for transplantation. Addictive behavior was considered to encompass behaviors consistent with substance use disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ edition, along with behaviors aimed at hiding substance use and abuse. Patients with a history of alcohol or marijuana use who did not display addictive behaviors were listed for transplantation. Data on frequency and quantity of MJ use was irregularly collected and generally too vague to analyze, but is presented in Table 5. Recreational MJ was not distinguished from medical MJ use; however, there were no patients who specifically reported medical MJ use.

The primary outcome was graft failure (defined very stringently herein as reaching a Modification of Diet in Renal Disease Glomerular Filtration Rate (MDRD GFR) <20ml/min/1.73m$^2$) or mortality at one year post-transplant. The secondary outcome was renal

function (defined by mean creatinine and MDRD GFR in those patients with a GFR≥20ml//1.73m$^2$) at one year post-transplant.

Patient variables and singular and composite one-year outcomes (death or graft failure at one year) were compared between MJ users and non-MJ users. For the univariate analysis, differences in means were calculated using the unpaired t-test, and differences in proportions were calculated using the two-tailed Fisher's exact test. Logistic regression was performed on unadjusted samples and samples adjusted for Estimated Post-Transplant Survival (EPTS) and living donor status. The EPTS score is a numerical indicator used in the allocation of deceased donor allografts, with a lower EPTS score predicting longer graft function. The EPTS score is based on four factors regarding the candidate time on dialysis (in years), current diagnosis of diabetes, number of prior solid organ transplants, and age in years. The EPTS score was calculated using the formula on the Organ Procurement and Transplantation Network website (25). Statistical significance was defined as $p<0.05$. All statistical analysis was performed on SAS 9.3, SAS/STAT12.1 software (SAS Institute Inc., Cary, NC, USA).

**Results**

Over five years, 1,225 adult patients underwent renal transplantation. A record of self-reported use was available in 1,194 patients and toxicology screens were available in 574 patients. According to records, 1,169 were MJ non-users, and 56 were MJ users (33 of whom admitted to active MJ use, and 23 of whom tested positive on urine toxicology screen) (Figure 1). With these numbers, for a power of 0.8 and an alpha of 0.05, we would be able to detect a >25% difference in combined outcome between MJ non-users and MJ users.

Living donors accounted for 31.7% of transplants. Deceased donor renal transplants included standard criteria donors, donation after cardiac death, and expanded criteria donors. Overall, 59.6% of transplanted patients were male.

Marijuana use was not significantly associated with male gender (p=0.065). The average MJ user was younger than the average non-user (45.8 ± 12.6 versus 53.1 ± 13.7 years, p< 0.0001). Race was not independently associated with MJ use (p=0.69), and the racial composition (White, African American, or Other) was similar across the two groups (Table 1). Marijuana users were less likely than non-users to be married or partnered (40.7% versus 68.7%; p<0.0001), and less likely than non-users to have completed secondary education; 17.3% of MJ users versus 9.1% of non-users had not obtained a high school diploma or GED (p=0.084). Marijuana users were also less likely to hold a college or graduate degree (11.5% versus 32.3%; p=0.003) (Table 1). Presence of non-MJ substances such as opiates, cocaine, and others on urine toxicology screenings was comparable between the two groups (Table 2). However, MJ users were more likely to report ever consuming alcohol (including rare or social use) than those who did not use MJ (65.5% versus 43.4%, p=0.003). MJ users were more likely to report current or prior tobacco use than non-users (78.6% versus 41.3%, p<0.0001). MJ users were also more likely to smoke >10 cigarettes per day (60.7% versus 31.6%, p<0.0001). More patients in the MJ user group were considered moderate or high risk on social worker assessments (61.9% versus 24.6%, p=0.0001); and more patients in the MJ user group had a history of treated substance addiction (17.4% versus 5.6%, p=0.002) (Table 2 and Table 4). Marijuana users had a lower average EPTS score at transplantation compared to non-users (36 ± 27.0 versus 48 ± 31.4, p=0.004) (Table 1), which is likely a result of their younger average age. A slightly higher EPTS

score did ultimately correlate with patient death or graft failure (50.1 versus 45; p=0.046). The self-reported frequency of marijuana use is described in Table 5.

However, despite knowing the lack of power of this study to detect small differences, patient survival at one year post-transplant appears not different between MJ users and non-users (100% versus 97.7%; p=0.622) (Table 3). In addition, the proportion of failed renal allografts (again, defined stringently as MDRD GFR<20ml/min$^2$) at one year post-transplant appears similar between the two groups (19.7% versus 17.4%; p=0.62). Marijuana use did not appear to be associated with the combined outcome of death or graft failure after unadjusted analysis (Odds Ratio 1.07, 95% Confidence Interval (CI) 0.45-2.57, p=0.87) and analysis adjusted for EPTS and living donor status (Odds Ratio 0.79, 95% CI 0.28-2.28, p=0.67). There was no difference in GFR for the remaining functioning grafts in each group (50.7 ml/min$^2$ [95%CI 45.6-56.5] versus 49.5 ml/min$^2$ [95%CI 48.3-50.7], p=0.65), or in the average serum creatinine (1.52 mg/dl [95%CI 1.39-1.69] versus 1.42 mg/dl [95%CI 1.42-1.49], p=0.38). Tobacco use (p=0.594), alcohol use (p=0.403), education (p=0.9), and marital status (p=0.24) were not associated with one-year outcome.

As expected, poor outcomes were more common with deceased donors (9.4% versus 1.3%; P<0.0001). However, after adjustment for EPTS and living donor status, MJ use was still not associated with poorer outcomes (Odds Ratio 0.79, CI 0.28-2.28; p =0.67).

**Discussion**

This study, while underpowered, revealed that isolated recreational MJ use does not appear to be associated with terribly worse renal function or patient and allograft survival at one year. Age, but not race or gender was associated with MJ use. MJ users were more likely to use

tobacco and alcohol, have single marital status, and a lower level of formal education. However, none of these patient factors were associated with one-year allograft outcome.

In 2009, Ranney et al. reported no significant detrimental outcome due to MJ use on overall survival of patients with chronic liver failure awaiting a liver transplant (14). Of MJ users with chronic liver failure, 14.8% were eventually transplanted versus 21.8% of non-users. As in our study, the authors also associated MJ use with younger age, concomitant tobacco use, and (though contrary to our results) male gender. However, unlike our study, their cohort included only pre-liver-transplant patients and thus did not specifically evaluate graft function or patient survival after transplantation. In contrast, our study intentionally limits the analysis to post-kidney transplant patients. It is also the first study to look at the effect of MJ use on patients after renal transplantation.

Perhaps the biggest concern regarding MJ use in transplant recipients is the risk of non-adherence to immunosuppression regimens (26), especially if the patient refuses to commit to a period of abstinence prior to transplant. Forgetfulness and carelessness have been identified as the most significant barriers to medication adherence (27), and MJ use may have a dose-related effect on cognitive distortion and memory impairment (28). However, no study (including this one) has attempted to measure isolated MJ users' compliance with post-transplant medications. A multicenter analysis of non-adherence after renal transplant in France found no association between non-adherence and addiction, antidepressant use, anxiolytic use, education, or employment (27). Single marital status, however, did correlate with non-adherence (27) and may perhaps be a better indicator of patients who will require more aggressive support and follow-up.

Age may play a role in assessing effects of MJ in a potential transplant candidate. Several studies have shown that addiction is more common in those who started smoking MJ as

adolescents, and these early users are more vulnerable to cognitive impairment and forgetfulness (29), using other illicit drugs (30), developing a lower IQ, and dropping out of school (31). Interestingly, some studies suggest that an inverse relationship may exist between education level and medication adherence in transplant patients (32, 33). Moreover, awareness of memory impairment has been shown to improve adherence to post-transplant immunosuppressive regimens (22), suggesting that communication is a key component in preventing errors that stem from cognitive decline. These observations suggest that the consequences of use be discussed with the patient, and that individuals be assessed as to the effect drug use may have on the ability to comply with treatment recommendations (18).

Convincing evidence of direct harm to the allograft by MJ inhalation or ingestion has yet to be established. To our knowledge, two case reports describe exceedingly rare conditions that are attributed to concurrent MJ use: one case of post-transplant invasive pulmonary aspergillosis from inhaling contaminated MJ (34) and one case of de novo allograft membranous glomerulonephritis in a heavy MJ user (35). In a recent case series, synthetic MJ use was associated with acute kidney injury in nine patients, but this was not a transplant population and the mechanism of injury was unclear (36). Indeed, impaired lung defense mechanisms from chronic inhalation of MJ have been linked to infection and cancer (37), risks that would probably increase in the immunosuppressed transplant population. These potential risks should be weighed against the benefits of survival and improved quality of life afforded by receiving a kidney transplant and no longer needing dialysis (38).

This study has several limitations. It is a retrospective and single center study, and thus unable to confirm presence or absence of a causal relationship between MJ use and renal allograft outcome. As a single-center study, is shows data from populations of MJ users and MJ

non-users which may differ from other institutions, limiting generalizability. Our study initially attempted to gather data on the frequency of MJ use. However, these data are entirely self-reported and thus assume the honest disclosure of marijuana use. Furthermore, we assumed that pre-and post-transplant MJ use frequency did not change. We did not attempt to assess the amount of MJ consumed, as MJ comes in different forms and is often used in self-made preparations with no standardized dosing. Most of the transplanted MJ users "used" MJ on a less-than-daily basis (data not shown), which is one of the factors that may be different from MJ users elsewhere.

The small sample size and relatively short follow-up of this study limit statistical power, rendering a type-II error possibility. Furthermore, the study is underpowered to detect a statistically significant difference in combined outcome unless the difference exceeds 25%. However, currently no larger database (such as the United Network for Organ Sharing or the Scientific Registry of Transplant Recipients) captures data regarding MJ use. Hence small studies must be relied upon until MJ use is captured in large transplant databases.

As we chose to study the effects of MJ use on patients who had already undergone renal transplantation, we were not able to assess possible discrimination at our center in access to kidney transplantation based on MJ use, an issue which has previously been addressed (3). Also, because our center does not routinely track data on MJ use after kidney transplantation, we made the assumption that MJ use is a habit that would continue unaltered across the pre-and post-transplant periods. This assumption likely does not hold true for all patients. There may therefore be some contamination of the two groups, with some MJ users possibly quitting this habit and some non-users starting a new habit over time. Indeed, the inclusion of 36 past MJ users in the non-user group suggests that we very likely could have mislabeled some true MJ users as non-

users. This was done intentionally because our alternate hypothesis would have been that MJ use worsens patient and/or graft survival due to an increased risk of life threatening aspergillosis infections or rejection due to non-adherences. Should data from mislabeled MJ users improve outcomes for the non-user group, this would only strengthen our result. On the other hand, it is possible that some MJ users had a false positive test result or lied in saying that they were using MJ, but we think these scenarios are less likely than the converse.

There is the issue of possible confounding, as other variables associated with marijuana use may also affect outcomes, which we tried to adjust for by using a multivariate model. Toxicology screens were incomplete due to inability to obtain urine samples in clinic from patients who were oliguric or anuric; this may have introduced bias in favor of our results by including some MJ users in the non-MJ user group. This study did not specifically examine the effect of MJ use on intervals between ESRD diagnosis, initial evaluation, listing, waiting times, and transplantation. Future studies should examine these additional outcome measures, as well as prospectively assess transplant recipients who are active MJ users, focusing on patterns of non-adherence; potentially confounding concomitant use of other deleterious substances such as cocaine, tobacco, and alcohol; and interactions between MJ and transplant medications.

In conclusion, isolated recreational MJ use does not seem to lead to poorer patient or graft outcomes in a small single center study with limited one-year follow-up . We do not believe that it is justified to view all MJ use as an absolute contraindication to renal transplantation. Instead, recreational MJ use should be systematically evaluated in a larger setting before a decision is made on what, if any, degree of use or abuse should be considered a relative or absolute contraindication, or whether use or abuse should be considered a contraindication. Other key questions to answer relating to MJ use in kidney transplantation include the potential

disadvantages in access to listing and kidney transplantation, the effects of MJ use on outcomes after kidney transplantation, including longer-term patient and graft survivals, as well as infection and rejection rates, and the very difficult question of how to truly assess the amount and frequency of MJ consumption in transplant patients. More work will be required to understand the relationship between MJ use and other factors that affect compliance and outcomes.

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**Table 1: Patient Characteristics**

| | MJ Non-Users (n=1169) | MJ Users (n=56) | P-value |
|---|---|---|---|
| Mean Age (years) | 53.1 ± 13.7 | 45.8 ± 12.6 | <0.0001 |
| % Male | 56.9 | 71.4 | 0.065 |
| Race (%) | | | 0.69 |
| White | 47.3 | 38.1 | |
| African American | 45.6 | 58.7 | |
| Other | 7.1 | 3.2 | |
| % Married or Partnered | 68.7 | 40.7 | <0.0001 |
| % Without High School Diploma or GED | 9.1 | 17.3 | 0.084 |
| % Without College Degree | 11.5 | 32.3 | 0.003 |
| EPTS* score | 48 ± 31.4 | 36 ± 27.0 | 0.0043 |

**EPTS: Estimated Post-Transplant Survival*

| **Table 2: Marijuana Toxicology, Substance Use, and Social Work Risk** | | | |
|---|---|---|---|
| | MJ Non-Users (n=1169) | MJ Users (n=56) | P-value |
| Other Positive Toxicology (%) | | | 0.7555 |
| Narcotics | 3.5 | 2.2 | |
| Cocaine | 0.9 | 2.3 | |
| Other | 0.4 | 0 | |
| Alcohol Use (%) | | | |
| Current or prior | 43.4 | 65.5 | 0.003 |
| Tobacco Use (%) | | | |
| Current or prior | 41.3 | 78.6 | <0.0001 |
| >10 cigarettes/ day | 31.6 | 60.7 | <0.0001 |
| High/Moderate Risk, per Social Work Evaluation (%) | 24.6 | 61.9 | 0.0001 |
| Treated Substance Addiction (%) | 5.6 | 17.4 | 0.002 |

**Table 3: Primary and Secondary Outcomes**

| | MJ Non-Users (n=1169) | MJ Users (n=56) | P-value |
|---|---|---|---|
| Patient Survival (%) | 97.7 | 100 | 0.62 |
| Graft failure* (%) | 17.4 | 19.7 | 0.62 |
| Mean Creatinine of functioning grafts at 1 year, 95% CI | 1.42 mg/dl, 1.42-1.49 | 1.52 mg/dl, 1.39-1.69 | 0.38 |
| Mean GFR of functioning grafts at 1 year, 95% CI | 49.5 ml/min$^2$, 48.3-50.7 | 50.7 ml/min$^2$, 45.6-56.5 | 0.65 |

* Defined as GFR<20 ml/min/1.73m$^2$ at 1 year. Percentages calculated only among those with 1-year follow up data. When those lost to follow up were included in functioning grafts, 1-year graft failure rates are <10% in both groups.

**Table 4. Social Work Risk Assessment of Marijuana Users**

| | | Initial Assessment | Re-evaluation |
|---|---|---|---|
| **Low Risk** | | **23** | **35** |
| | | | |
| **Moderate Risk** | | **14** | **10** |
| | Compliance | 3 | |
| | Psychological Consult | 3 | |
| | Family Teaching | 1 | |
| | Family Support | 3 | |
| | Addiction | 8 | |
| | | | |
| **High Risk** | | **17** | **9** |
| | Compliance | 6 | |
| | Psychological Consult | 3 | |
| | Family Teaching | 3 | |
| | Family Support | 3 | |
| | Health Insurance | 1 | |
| | Addiction | 13 | |

**Table 5. Frequency of Marijuana Use in current MJ users (n=56) and non-MJ users (including 36 past-users).**

| | Marijuana Users (n=56) | Non-Marijuana Users (n=1169)* |
|---|---|---|
| **Never** | 17 | 1034 |
| **Less than 5 times per year** | 1 | 1 |
| **Monthly** | 1 | 0 |
| **Weekly** | 4 | 0 |
| **Daily** | 1 | 1 |
| **Sporadic/Rarely** | 5 | 7 |
| **Frequent** | 10 | 26 |
| **Unknown** | 17 | 67 |
| **Missing Data on Frequency** | 0 | 33 |

*Past marijuana users that denied current MJ use and had a negative or missing toxicology screen were considered non-users, thus frequencies reported related to past marijuana use.

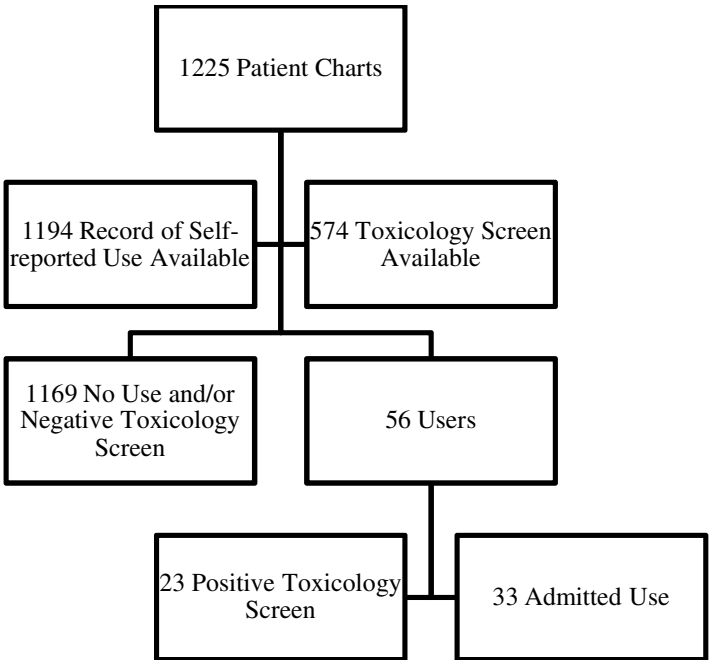


**Figure 1. Study Population. Retrospective review of marijuana toxicology and use in kidney transplant recipients.**