REVIEW ARTICLE

Medical adherence and liver transplantation: a brief review

Carl Hammond MBChB, MRCP[1], Trana Hussaini PharmD[2], Eric M Yoshida MD, FRCPC[3]

ABSTRACT

Liver transplantation remains the only feasible long-term treatment option for patients with end-stage liver disease. Despite significant medical and surgical advances over the decades, liver transplantation remains a complex undertaking with the need for indefinite immunosuppression and avoidance of patient behaviours that may jeopardize the allograft. Adherence (formerly called "compliance") to medical recommendations in terms of anti-rejection medications and—in the case of alcoholic liver disease, abstinence—is considered a key cornerstone to long-term allograft and patient survival. Not surprisingly, a history of habitual non-adherence is considered a contraindication to liver transplantation, especially re-transplantation. It is often assumed that non-adherence policies are "self-evidential" based on "common sense" and "expert opinion." In fact, non-adherence and its negative effects have been well studied in medicine, including in solid organ transplantation. In this review, we present the evidence that non-adherence to medical advice is clearly associated with worse medical outcomes, supporting the concept that efforts to support patient adherence post-transplant need to be optimized at all times.

KEYWORDS: abstinence; adherence; alcohol; antirejection; compliance; liver; medications; transplantation

Author Affiliation

[1]*Department of Gastroenterology, University Hospital Coventry & Warwickshire, United Kingdom;* [2]*Department of Pharmacy, Vancouver General Hospital, Vancouver, British Columbia, Canada;* [3]*Division of Gastroenterology, the University of British Columbia, Vancouver, British Columbia, Canada*

Correspondence: Eric Yoshida, Division of Gastroenterology, Vancouver General Hospital, Diamond Health Care Centre, 5153-2775 Laurel Street, Vancouver, British Columbia V5Z 1M9 Canada. Telephone: 604-875-5371. Fax: 604-875-5447. E-mail: eric.yoshida@vch.ca

Liver transplantation is an established part of the modern hepatologist's armoury, with 470 adult transplants undertaken Canada-wide in 2018. Nevertheless, demand continues to outstrip supply, with 190 patients dying on the waiting list in the same year. The effective utilization of each available organ is of paramount importance. Despite this, it is difficult to identify which patients will adhere to the more rigid aspects of post liver transplant care such as lifelong immunosuppressive medication adherence and a commitment to lifelong abstinence from alcohol, in cases where this is the precipitant for liver disease. Progress has been slow in identifying robust pre-transplant factors that will translate into post-transplant success.

Among the challenges, both clinically and academically, with liver transplant patients is that this is an intrinsically heterogeneous group. Liver transplantation can be indicated in a previously healthy patient with fulminant liver failure from a spontaneous acetaminophen overdose. It could just as likely be offered for the inexorable progress of an autoimmune disease over years or even decades. The mindset of these differing individuals going into a transplant cannot necessarily be reconciled by a "one size fits all" predictive model.

What is not often appreciated by clinicians is that medication adherence in general is poor across all patient groups, regardless of specialty, and this has been demonstrated widely. As an example, adherence rates of 30%–50% for antihypertensive medications have been reported in the literature (1–5). One might expect better rates among solid organ transplant recipients given the potentially catastrophic effects of rejection, but this unfortunately does not seem to be the case. Various studies over the last 20 years have reported non-adherence rates of 20%–50% to immunosuppressive medication in this group (2). In kidney transplant patients, global non-compliance rates have been reported as high as 22.3% (3) and 47% (4). Among liver transplant recipients, the numbers are similar (15%–40%), which is closely mirrored by rates of non-attendance at clinic appointments (3%–47%) (5).

The pattern of non-compliance is often difficult to grasp, and may be unpredictable in many cases. Nevertheless, some patterns have emerged. Perhaps unsurprisingly, a close relationship between attendance at clinic appointments and adherence to medications has been shown in the past (2). A Scottish population study (6) from 2006 looked at 304 current liver transplant patients and 44 who had subsequently died, all at least 1 year after their transplant operation (6). They used audit of missed appointments at transplant review clinics as a behavioural measure of compliance. Trough immunosuppressant drug levels, and episodes of cellular rejection at least 6 months post-transplant, were biochemical markers, while an anonymized self-reported questionnaire formed the psychological assessment of adherence. In their analysis, the authors remarked that it was "notable that approximately 1 in 5 (of those still living) either missed or cancelled more than 25% of the appointments made available to them, compared to about 1 in 3 patients who had since died" ($p = .144$). Additionally, in analyzing the percentage of patients who had at least one episode of late acute cellular rejection *6 months or more after* transplantation, a distinct between-group difference emerged. Of those patients who were still alive ($n = 308$), approximately 1 in 9 had at least one documented episode of cellular rejection. This is in stark comparison to approximately 1 in 4 for those patients who had subsequently died ($n = 75$). As well, poor pre-operative adherence (e.g., to outpatient clinics) is a behaviour that seems to persist post-transplant as a major determinant of long-term non-compliance (7,8).

Socio-demographic factors may also help to predict non-compliance post-transplant. The extremes of age (children, adolescents, and those >70 years) tend to be most at risk of non-compliance (7), but is of more relevance to the pediatric transplant population, in which non-adherence rates are nearly 4-fold higher (5). Unemployment at time of listing for liver transplant was a significant predictor of subsequent non-adherence in one study. Patients who were unemployed at the time of transplant and had a history of pre-transplant non-adherence, had a higher standard deviation in tacrolimus trough levels indicating higher variability in tacrolimus exposure likely due to non-adherence. (9) Another study covering 236 liver transplant patients across two large centres in the United States (US) demonstrated increased odds ratios (ORs) for non-compliance among males (OR 2.46, $p = .01$) and those with a pre-transplant diagnosis of mood disorder (OR 2.52, $p = .01$) (10). Indeed those patients with at least one self-reported 24-hour immunosuppression "holiday" in the past 6 months were more likely to have a pre-transplant mood disorder (65% versus 44%; $p = .004$), a limited social support system (48% versus 28%; $p = .004$), and an unstable support system (34% versus 20%; $p = .02$). The same study also categorized patients according to the presence or absence of six psychosocial variables existing pre-transplant. These included

1. DSM-IV compliant diagnosis of mood or anxiety disorder within the 24 months prior to transplant;
2. passive versus active coping styles in the face of emotional stressors;
3. presence or absence of documented medication adherence issues prior to transplant;
4. presence or absence of DSM-IV diagnostic criteria for substance abuse/dependence prior to transplant;
5. presence or absence of a primary caregiver as social support for the transplant recipient; and

6. the presence or absence of documented concerns regarding the stability of that social support system.

Patients were then classified depending on how many of the six psychosocial risk factors they possessed. Analysis confirmed that those deemed high-risk (4–6 risk factors present) demonstrated a significantly higher percentage (60%) of medication and treatment non-adherence post-transplant, when compared to moderate-risk patients (2–3 risk factors present; 32% non-compliance) and low-risk patients (0–1 risk factors present; 18% non-compliance) (10). Social support is undoubtedly of importance, with a host of other studies alluding to its influence. Lack of a stable relationship was a predictor of graft loss in one particular study (OR = 4.9) (5). Others have demonstrated higher rates of missed medication doses in divorced patients (8). These findings have not always been reproducible however, and gender, race, occupation, and educational attainment have proved less relevant across a number of other studies (11–14).

Psychological factors, perceptions of illness, quality of life, and medication beliefs are all postulated to impact on an individual patient's compliance. In the previously mentioned study of Scottish liver transplant recipients, the greater the self-rated consequences of the transplant on the patient's life, the poorer their adherence (6). This finding is reproducible across various studies in both transplant and non-transplant populations (6). Perhaps unsurprisingly, transplant patients as a cohort appear to have a higher perceived need for their medications than those studied on long-term treatment for asthma, chronic kidney disease, psychiatric diagnoses, and cardiac issues. This may well reflect the more immediate adverse consequences of non-compliance in rejection and graft loss than for a patient who discontinues their anti-hypertensives, for example. Nevertheless, among transplant patients, Kung et al showed that non-adherent patients had lower perceptions about the necessity of medication, weaker beliefs that immunosuppressants could prevent rejection, and higher concerns about its harms than non-adherers (15). They were also more likely to believe that medications were over-prescribed by doctors (15). Non-adherers in the same study perceived that their transplant and associated medication regime caused more symptoms, and they were more distressed by those symptoms than adherent patients (15). The authors postulate that such illness perceptions may be modifiable by behavioural interventions, with consequential improvement in adherence and long-term graft outcome. The perceived risk of non-compliance appears to decline over time, so targeting patients who have had their transplant for a longer period, with timely pharmacist-led education sessions, may be one avenue to target for long-term graft survival.

A relapse to alcohol after transplant is itself a serious manifestation of medical non-adherence as all patients selected for liver transplantation pledge to abstain from alcohol. The assessment of patients referred with alcohol-related liver disease, however, has seen significant evolution in recent years. The traditional 6-month abstinence rule has recently been challenged amid conflicting evidence of its use in predicting both post-transplant recidivism and long-term outcomes (16–21). For example, Perney et al (19) studied 61 patients in a large French centre, all more than 6 months post liver transplantation for alcohol-associated liver disease. Relapse was defined as any alcohol relapse post-transplant, with severe relapse greater than 21 units/week for males, and 14 units/week for females. The impact of relapse on liver biochemistry and graft function disproportionately affected the severe relapse group (n = 8), with biopsy findings of steatosis, alcoholic hepatitis, and in one case, cirrhosis. By contrast, those transplant patients who engaged in occasional "slips" but did not progress to harmful relapse appeared to have similar outcomes to fully abstinent patients. Subgroup analysis revealed a mean length of abstinence pre-transplant among severe relapsers of 6 months, compared to a much longer abstinence period of 22 months for those without severe recidivism (n = 53). Thus, compliance with the established 6-month period would not have identified these higher-risk patients. Further complicating the picture is the condition of severe alcoholic hepatitis, in which expected mortality does not allow for a 6-month wait time, and where Mathurin et al have demonstrated clear benefits of transplantation over standard of care (77% survival at 6 months versus 23% for those not transplanted) (22). These results have been reproduced in a large North American series. The ACCELERATE-AH trial (23) spanned 12 transplant centres and 147 patients who received liver transplantation for severe alcoholic hepatitis. All participants were deemed to have strong social support from family and friends as determined by a transplantation social worker assessment (all 12

centres) and a separate addiction specialist assessment (11 out of 12 centres). There was no mandated alcohol-free period, and the median duration of abstinence prior to transplant was 55 days (IQR 36–91days). Cumulative post-transplant survival at 1 year and 3 years was 94% and 84%, respectively, which compared favourably with transplant outcomes for non-alcohol indications. Moreover, rates of sustained or harmful drinking post-transplant were 11%, similar to or even better than reported rates in patients subject to the traditional 6-month abstinence criteria. Of interest, consumption of >10 alcoholic drinks per day was a predictor of death post-transplant in this study. Moreover, in multivariable analysis only younger age was significantly associated with relapse to alcohol following transplant (p = .01). In conjunction with evidence for the value of robust social supports, it is clear that risk assessment of this patient group is more nuanced than simply the length of time since their last drink. Understandably, transplant programs are being forced to think again, and many currently find their selection criteria in a state of flux as new evidenced-based criteria will need to be established.

Nevertheless, regardless of the criteria for transplant listing in alcohol-related disease, recidivism remains a real risk. The exact proportion of alcohol-related liver disease (ArLD) patients who drink after liver transplant is unclear, but best estimates in the literature suggest 12%–33% will relapse to abusive or harmful amounts of drinking (16,24–26). It is tempting to ask the relevance of this, given that overall survival for patients transplanted for ArLD is comparable or even higher than for non-ArLD indications (27–30). However, as alluded to by Perney et al, separate studies have identified excessive and harmful drinking to be associated with increased rates of graft rejection and failure, presumably because of non-adherence to immunosuppressive medications (17,29,31–33). For example, Pfitzmann et al investigated the relevance of sobriety for outcomes after orthotopic liver transplantation (17). A retrospective analysis of 300 patients transplanted for ArLD at a single US centre between 1989 and 2002 identified some degree of relapse to drinking in 19% of the cohort. Of these, 30% slipped but did not then return to their pre-transplant behaviour of harmful drinking. Forty-one percent suffered a recurrence of abusive dependence. In the remainder (29%), the severity of alcohol consumption was unknown. Recurrent alcohol consumption was observed more frequently in those transplanted under the age of 40 years than over 40 years (32.6% versus 17.0%; $p < .03$). Those divorced or separated were statistically more likely to recede to drinking than those married or living with a companion (45% versus 17.6%; p = .02). Those with underage children were also significantly more at risk than those with adult children (31.3% versus 13.2%; p = .01). Numerous other studies echo these findings: marriage has been found to have a protective role against binge drinking (25,30), while pre-transplant psychiatric comorbidities (16,34), and cigarette smoking are positive correlates of alcohol relapse. In the Pfitzmann study, the outcome of this behaviour appears clear: the 5- and 10-year survival rates for those abstinent (including those with only temporary slips to drinking) was 90.3% and 81.5%, respectively. In sharp contrast, the same figures for those returning to harmful and abusive drinking were 69.5% and 20.1%, respectively (17). Among the 16 deaths reported in this latter group, 14/16 (87.5%) were attributable to recurrent ArLD. The remaining two deaths were from esophageal cancer, a condition with clear aetiological links to excessive alcohol consumption (17).

Given the available evidence, what—if anything—can be done to improve patients' adherence post-transplant? Medication education sessions outlining the importance of immunosuppression and the pitfalls of non-adherence are vital, and the presence of a dedicated transplant pharmacist is vital in this respect. Nevertheless, such interventions alone may not completely overcome some patients' inherent perceptions as to the efficacy and harms of their prescription medications. From a practical perspective, another avenue is to simplify drug regimens where safe and feasible. A number of studies have persistently shown higher-intensity treatment plans (i.e., twice-daily versus once-daily dosing) to be considered higher risk for non-adherence (35). These include the French PREDICT trial from 2012, which enrolled 370 patients who were screened by 71 physicians from 33 centres (21 kidney transplant, 12 liver transplant) across the country (36); 235 patients had a renal graft, and 146 had a liver graft. All immunosuppressants are state-funded in France, which would appear to remove cost barriers as an impact on medication compliance. The median number of months post-procedure was 39 months and 49 months in the kidney and liver groups, respectively. Patients were assessed by anonymized

completion of a compliance evaluation test (CET), a six-item Yes/No questionnaire. Adherence was defined by a score of 0 (i.e., "No" responses to all questions, indicating complete engagement with medication regimens). Physicians simultaneously scored their patients' perceived compliance on a visual analogue scale of 0–10. Analysis revealed an adherence rate of 32% across the whole cohort. Among the kidney group, this figure dropped to 27%, while it was 40% in the liver group, a finding perhaps correlating with the more intensive immunosuppressive regimens seen among the kidney transplant recipients in this study. The data also demonstrated falling adherence rates with the *number* of immunosuppressants prescribed (44.6% for 1 drug versus 32.2% for 2 drugs and 24.3% for 3 drugs; $p = .02$) (36). Use of once-daily tacrolimus preparations could therefore be considered in those *suspected* of non-compliance. As a final note of caution, the authors also point out that physicians' evaluations of patient adherence were significantly higher than that actually reported by the patients themselves (47% for physician assessment versus 32% for patients' self-report), suggesting non-adherence is underestimated in transplant programs.

In terms of ArLD patients and adherence to abstinence, attempts at a scoring system to predict alcohol relapse post-transplant have so far proved to be elusive. Several exist, including the Alcohol Relapse Risk Assessment (ARRA) scale (37) and the High-Risk Alcoholism Relapse (HRAR) scale. Unfortunately, the former is yet to be externally validated while the latter has not been shown in two subsequent studies to correlate with post-transplant recidivism (38,39). Indeed, DiMartini et al investigated the HRAR scale in their transplant population in the hope that it would help identify those most at risk of post-operative recidivism (39). The HRAR scale was initially developed outside of a transplant population, from a cohort of male veterans undergoing alcohol rehabilitation. In this setting, it has predictive validity for early relapse within 6 months, with a sensitivity of 69% and specificity of 65% (39). It has since been incorporated into the transplant workup for several US centres. Severity is graded 0–6 across a sum of three items (scored 0–2 each), covering the duration of heavy drinking, the quantity of daily consumption, and the history of previous engagement with alcohol rehabilitation programs. High-risk is defined as a grade ≥4. Looking at 207 candidates with ArLD presenting for transplant candidacy, the authors noted that HRAR scores did not appear to distinguish those eventually listed from those declined, nor to differentiate those who drank post-transplant from those who maintained sobriety (39).

Clearly, risk scores alone do not solve the problem. If applied too stringently, they risk excluding from transplant consideration large numbers of patients who otherwise might do well; if too lenient, outcomes will suffer, with the potential for premature graft loss; in an era of discrepancy between organ donor need and availability, many would consider that unacceptable. Instead, they should be able to identify those whose risk is present, but nevertheless manageable with appropriate support. In this respect, there is favourable evidence for using active addiction treatment to moderate the recidivism rates of ArLD patients. Bjornsson et al report on their experience in a Swedish transplant centre, with particular relevance to the recidivism rates before and after introduction of a specialized alcohol and substance use assessment service in 1998 (40). They report a risk-reduction of >50% post-intervention: 19/40 (48%) of patients transplanted before 1998 relapsed to alcohol post-transplant. After 1998, this was just 13/58 patients (22%) (40). In addition to this, Rodrigue et al (41) have demonstrated the benefit of continuing substance abuse treatment *after* transplant. Among 118 patients undergoing liver transplantation at a single US centre between 2002 and 2011, 61 (52%) received treatment for their alcohol dependence pre-operatively. These "treated" patients did not differ significantly in rates of recidivism from those who received none (30% versus 39%; $p = .2$). Moreover, there was no significant difference in relapse risk based on whether patients received low-, medium- or high-intensity substance abuse (SA) treatment before their operation ($p = .33$). Strikingly though, when assessing those patients who received further addictions treatment *post*-transplant, a marked difference in outcomes was observed. With all three subgroups—that is, no SA treatment ($n = 54$) versus SA treatment pre-transplant only ($n = 29$) versus SA treatment both pre- and post-transplant ($n = 32$)— matched for sex, age, race, marital status, abstinence duration pre-transplant, and ARRA score, those receiving treatment both pre- *and* post-transplant had significantly lower rates of relapse (16%) than those with pre-transplant only (45%) or no treatment at all (41%) (41). Furthermore, Addolorato et al (18)

found that post-transplant addictions counselling administered by a specialist embedded within the transplant unit achieved better results than in those patients followed by an addictions specialist unaffiliated with the transplant program. In following 92 patients transplanted at a single Italian centre over a 15-year period, alcohol relapse rates were found to be significantly lower among patients treated by the "in-house" alcohol addictions unit (AAU) (n = 55) than in those monitored by an external agency (alcohol relapse rate 16.45% versus 35.1%; p = .038)) (18). Emphasizing the value of these interventions, the mortality rates were also significantly lower in this group (14.5% versus 37.8%; p = .01).

In conclusion, while no socio-demographic factor has been consistently shown as independently predictive of poor adherence after transplant, it seems logical that multiple risk factors in one patient (e.g., poor social support, pre-existing psychiatric comorbid state, lack of effective coping strategies) would constitute an additive risk. These factors in isolation should not necessarily exclude a patient from transplant listing, particularly if the medical indication is particularly strong, but rather serve to flag these patients as in particular need of extra help in the peri- and post-transplant phases. Allied health professions, in particular social workers, psychologists, and addictions counsellors are of utmost importance, but all too often their role is limited to the truncated pre-operative assessment, with patients and clinicians left to fend for themselves in the post-transplant phase. As transplant programs come under increasing scrutiny to use their limited organ pool effectively and for maximal benefit, this must change. They in turn must be bestowed with sufficient resources and funding to enable these challenges to be met effectively.

CONTRIBUTIONS: Conceptualization, CH, TH, EMY; Writing – Original Draft, CH, TH, Writing – Review and Editing, CH, TH, EMY.
ETHICS APPROVAL: N/A
INFORMED CONSENT: N/A
REGISTRY AND REGISTRATION NO. OF THE STUDY/TRIAL: N/A
FUNDING: No funding was received for this work.
DISCLOSURES: The authors have nothing to disclose.
PEER REVIEW: This article has been peer reviewed.

REFERENCES

1. Stephenson J. Noncompliance may cause half of antihypertensive drug "failures". JAMA 1999;282(4):313–4. https://doi.org/10.1001/jama.282.4.313. Medline:10432015
2. Laederach-Hofmann K, Bunzel B. Noncompliance in organ transplant recipients: a literature review. Gen Hosp Psychiatry. 2000;22(6):412–24. https://doi.org/10.1016/S0163-8343(00)00098-0.
3. De Geest S, Borgermans L, Gemoets H, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation. 1995; 59(3):340–7. Medline:7871562
4. Paris W, Muchmore J, Pribil A, Zuhdi N, Cooper DK. Study of the relative incidences of psychosocial factors before and after heart transplantation and the influence of posttransplantation psychosocial factors on heart transplantation outcome. J Heart Lung Transplant. 1994;13(3):424–30. Medline:8061018
5. Burra P, Germani G, Gnoato F, et al. Adherence in liver transplant recipients. Liver Transpl. 2011;17(7):760–70. https://doi.org/10.1002/lt.22294. Medline:21384527
6. O'Carroll RE, McGregor LM, Swanson V, et al. Adherence to medication after liver transplantation in Scotland: a pilot study. Liver Transpl. 2006;12(12):1862–8. https://doi.org/10.1002/lt.20828. Medline:16773637
7. Bunzel B, Laederach-Hofmann K. Solid organ transplantation: are there predictors for posttransplant noncompliance? A literature overview. Transplantation. 2006;70(5):711–6. https://doi.org/10.1097/00007890-200009150-00001. Medline:11003346
8. Lamba S, Nagurka R, Desai KK, et al. Self-reported non-adherence to immunesuppressant therapy in liver transplant recipients: demographic, interpersonal, and intrapersonal factors. Clin Transplant. 2012; 26(2):328–35. https://doi.org/10.1111/j.1399-0012.2011.01489.x. Medline:21955028
9. Lieber S, Volk M. Non-adherence and graft failure in adult liver transplant recipients. Digest Dis Sci. 2013;58(3):824–34. https://

doi.org/10.1007/s10620-012-2412-0. Medline:23053889

10. Rodrigue JR, Nelson DR, Hanto DW, et al. Patient-reported immunosuppression nonadherence 6 to 24 months after liver transplant: association with pretransplant psychosocial factors and perceptions of health. Prog Transplant. 2013;23(4):319–28. https://doi.org/10.7182/pit2013501. Medline:24311395
11. Dew MA, Roth LH, Thompson ME, Kormos RL, Griffith BP. Medical compliance and its predictors in the first year after heart transplantation. J Heart Lung Transplant. 1996;15(6):631–45. Medline:8794030
12. Siegal BR, Greenstein SM. Postrenal transplant compliance from the perspective of African-Americans, Hispanic-Americans, and Anglo-Americans. Adv Ren Replace Ther. 1997;4(1):46–54. https://doi.org/10.1016/S1073-4449(97)70016-5. Medline:8996620
13. Hilbrands LB, Hoitsma AJ, Koene RA. Medication compliance after renal transplantation. Transplantation. 1995;60(9):914–20. Medline:7491693
14. Grady KL, Russell KM, Srinivasan S, Costanzo MR, Pifarre R. Patient compliance with annual diagnostic testing after heart transplantation. Transplant Proc. 1993;25(5):2978–80. Medline:8212300
15. Kung M, Koschwanez HE, Painter L, et al. Immunosuppressant nonadherence in heart, liver, and lung transplant patients: associations with medication beliefs and illness perceptions. Transplantation. 2012;93(9):958–63. https://doi.org/10.1097/TP.0b013e31824b822d. Medline:22343337
16. De Gottardi A, Spahr L, Gelez P, et al. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med. 2007;167(11):1183–8. https://doi.org/10.1001/archinte.167.11.1183. Medline:17563028
17. Pfitzmann R, Schwenzer J, Rayes N, et al. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl. 2007;13(2):197–205. https://doi.org/10.1002/lt.20934. Medline:17205563
18. Addolorato G, Mirijello A, Leggio L, et al. Liver transplantation in alcoholic patients: impact of an alcohol addiction unit within a liver transplant center. Alcohol Clin Exp Res. 2013;37(9):1601–8. https://doi.org/10.1111/acer.12117. Medline:23578009
19. Perney P, Bismuth M, Sigaud H, et al. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease? Transpl Int. 2005;18(11):1292–7. https://doi.org/10.1111/j.1432-2277.2005.00208.x. Medline:16221161
20. Jauhar S, Talwalkar JA, Schneekloth T, et al. Analysis of factors that predict alcohol relapse following liver transplantation. Liver Transpl. 2004;10(3):408–11. https://doi.org/10.1002/lt.20086. Medline:15004769
21. Osorio RW, Ascher NL, Avery M, et al. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. Hepatology. 1994;20(1 Pt 1):105–10. https://doi.org/10.1002/hep.1840200117. Medline:8020879
22. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790–800. https://doi.org/10.1056/NEJMoa1105703. Medline:22070476
23. Lee BP, Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. Gastroenterology. 2018;155(2):422–30.e1. https://doi.org/10.1053/j.gastro.2018.07.004. Medline:29655837
24. Lucey MR. Liver transplantation in patients with alcoholic liver disease. Liver Transpl. 2011;17(7):751–9. https://doi.org/10.1002/lt.22330. Medline:21567894
25. DiMartini A, Day N, Dew MA, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. Liver Transpl. 2006;12(5):813–20. https://doi.org/10.1002/lt.20688. Medline:16528710
26. Rice JP, Eichoff J, Agni R, et al. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. Liver Transpl. 2013;19(12):1377–86. https://doi.org/10.1002/lt.23762. Medline:24115392

27. Burra P, Zenzolo M, Adam R et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant. 2010;10(1):138–48. https://doi.org/10.1111/j.1600-6143.2009.02869.x. Medline:19951276

28. United Network for Organ Sharing (UNOS) [homepage on the Internet]. Richmond, VA: UNOS; c2019 [cited 2020 Jul 20]. Available from: https://www.unos.org/.

29. Faure S, Herrero A, Jung B, et al. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. J Hepatol. 2012;57(2):306–12. https://doi.org/10.1016/j.jhep.2012.03.014. Medline:22521352

30. Lucey MR, Schaubel DE, Guidinger MK, et al. Effect of alcoholic liver disease and hepatitis C infection on waiting list and posttransplant mortality and transplant survival benefit. Hepatology. 2009;50(2):400–6. https://doi.org/10.1002/hep.23007. Medline:19472315

31. Pageaux GP, Bismuth M, Perney P, et al. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? J Hepatol. 2003;38(5):629–34. https://doi.org/10.1016/S0168-8278(03)00088-6. Medline:12713874

32. Addolorato G, Bataller R, Burra P, et al. Liver transplantation for alcoholic liver eisease. Transplantation. 2016;100(5):981–7. https://doi.org/10.1097/TP.0000000000001156. Medline:26985744

33. Rustad JK, Stern TA, Prabhaker M, Musselmann D. Risk factors for alcohol relapse following orthotopic liver transplantation: a systematic review. Psychosomatics. 2015;56(1):21–35. https://doi.org/10.1016/j.psym.2014.09.006. Medline:25619671

34. Kelly M, Chick J, Gribble R, et al. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol Alcohol. 2006;41(3):278–83. https://doi.org/10.1093/alcalc/agh257. Medline:16476764

35. Morales JM, Varo E, Lázaro P. Immunosuppressant treatment adherence, barriers to adherence and quality of life in renal and liver transplant recipients in Spain. Clin Transplant. 2012;26(2):369–76. https://doi.org/10.1111/j.1399-0012.2011.01544.x. Medline:22035067

36. Dharancy S, Giral M, Tetaz R, et al. Adherence with immunosuppressant treatment after transplantation: results from the French trial PREDICT. Clin Transplant. 2012;26(3):E293–9. https://doi.org/10.1111/j.1399-0012.2012.01652.x. Medline:22686953

37. Rodrigue JR, Hanto DW, Curry MP, et al. The Alcohol Relapse Risk Assessment: a scoring system to predict the risk of relapse to any alcohol use after liver transplant. Prog Transplant. 2013;23(4):310–8. https://doi.org/10.7182/pit2013604. Medline:24311394

38. Egawa H, Nishimura K, Teramukai S, et al. Risk factors for alcohol relapse after liver transplantation for alcoholic cirrhosis in Japan. Liver Transpl. 2014;20(3):298–310. https://doi.org/10.1002/lt.23797. Medline:24470014

39. DiMartini A, Magill J, Fitzgerald MG, et al. Use of a high-risk alcohol relapse scale in evaluating liver transplant candidates. Alcohol Clin Exp Res. 2000;24(8):1198–201. https://doi.org/10.1111/j.1530-0277.2000.tb02083.x. Medline:10968657

40. Björnsson E, Olsson J, Rydell A, et al. Long-term follow-up of patients with alcoholic liver disease after liver transplantation in Sweden: impact of structured management on recidivism. Scand J Gastroenterol. 2005;40(2):206–16. https://doi.org/10.1080/00365520410009591. Medline:15764153

41. Rodrigue JR, Hanto DW, Curry MP, et al. Substance abuse treatment and its association with relapse to alcohol use after liver transplantation. Liver Transpl. 2013;19(12):1387–95. https://doi.org/10.1002/lt.23747. Medline:24123780