The Alcohol Relapse Risk Assessment: a scoring system to predict the risk of relapse to any alcohol use after liver transplant

Context—Alcohol relapse after liver transplant heightens concern about recurrent disease, nonadherence to the immunosuppression regimen, and death.

Objectives—To develop a scoring system to stratify risk of alcohol relapse after liver transplant.

Design—Retrospective medical record review.

Setting and Participants—All adult liver transplants performed from May 2002 to February 2011 at a single center in the United States.

Main Outcome Measure—The incidence of return to any alcohol consumption after liver transplant.

Results—Thirty-four percent (40/118) of patients with a history of alcohol abuse/dependency relapsed to use of any alcohol after liver transplant. Nine of 25 hypothesized risk factors were predictive of alcohol relapse after liver transplant: absence of hepatocellular carcinoma, tobacco dependence, continued alcohol use after liver disease diagnosis, low motivation for alcohol treatment, poor stress management skills, no rehabilitation relationship, limited social support, lack of nonmedical behavioral consequences, and continued engagement in social activities with alcohol present. Each independent predictor was assigned an Alcohol Relapse Risk Assessment (ARRA) risk value of 1 point, and patients were classified into 1 of 4 groups by ARRA score: ARRA I = 0, ARRA II = 1 to 3, ARRA III = 4 to 6, and ARRA IV = 7 to 9. Patients in the 2 higher ARRA classifications had significantly higher rates of alcohol relapse and were more likely to return to pretransplant levels of drinking.

Conclusion—Alcohol relapse rates are moderately high after liver transplant. The ARRA is a valid and practical tool for identifying pretransplant patients with alcohol abuse or dependency at elevated risk of any alcohol use after liver transplant.


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Approximately half of all patients presenting for liver transplant are estimated to have a history of alcohol abuse or dependency, whether or not alcohol is the primary cause of their liver disease. Favorable liver transplant outcomes have been reported for patients with alcohol-related liver disease who maintain alcohol abstinence after transplant. These outcomes may be attributable, in part, to the careful selection of patients thought to be at low risk of alcohol relapse, minimum abstinence duration requirements, provision of substance abuse treatment, and/or regular monitoring via toxicology testing. Despite such policies and practices, however, relapse to alcohol use after liver transplant occurs in one-third to one-half of recipients and heightens concern about recurrent disease, nonadherence to the immunosuppression regimen, and death.

Since the early years of liver transplant, the identification of patients at high risk of relapse to alcohol use after liver transplant has been of clinical importance. Numerous sociodemographic, psychiatric, and social variables have been examined, but few reliable predictors have been identified across studies. This lack of reliable predictors makes it difficult to identify high-risk candidates for whom preventive and therapeutic interventions may be useful. Duration of abstinence before transplant was thought to be an important predictor as well, which led to the widespread adoption of the so-called “6-month rule.” However, short-term abstinence duration has not proven to be a reliable predictor of postransplant relapse and the 6-month rule has come under considerable scrutiny and criticism.
A clinical tool to guide the alcohol relapse risk assessment during the pretransplant period would help to identify patients at heightened risk of posttransplant relapse and guide the development of program policy and clinical interventions. Several researchers have advanced the concept of a scoring algorithm for predicting alcohol relapse in the context of liver transplant, but these methods have not been widely evaluated or clinically adopted by most transplant programs. Therefore, the primary objective of this study was to conduct a more comprehensive evaluation of pretransplant predictors and to develop a scoring system to stratify relapse risk to any alcohol use after liver transplant.

Methods

Data Collection

Using a prospectively collected transplant database (ie, Organ Transplant Tracking Record, OTTR), we conducted a retrospective review of all adult primary liver or liver-kidney transplants at Beth Israel Deaconess Medical Center in Boston, Massachusetts, from May 1, 2002 to February 28, 2011. A trained clinician who was blinded to the patient’s outcome after liver transplant reviewed the pretransplant evaluation records and recorded the presence or absence of each risk factor (see below) for all patients with any documented history of alcohol abuse or dependency. To assess interrater reliability, the clinician ratings for a subset (30/118, 25%) of the patients were compared with the ratings of another clinician unaffiliated with the liver transplant service. The Committee on Clinical Investigation at Beth Israel Deaconess Medical Center approved the study protocol.

Outcome Variable

The primary outcome variable was the incidence of return to any alcohol consumption after liver transplant. Much of the prior research on alcohol relapse after transplant has focused on “harmful” drinking, which has been inconsistently defined and poorly operationalized. For instance, Kelly et al defined harmful drinking as consuming more than 140 g of ethanol a week or drinking with noted medical or social harm. Perney et al reported harmful use as more than 21 units per week for males and 14 units per week for females, and Mackie et al described heavy use as more than 50 units per week. Clinically, however, our program uses a lifetime abstinence model of care, in which patients are educated, counseled, and expected to refrain from any alcohol consumption after transplant. For our study, any documented report or evidence of alcohol consumption after liver transplant was recorded. We reviewed all outpatient and inpatient clinic notes, our clinical database (ie, the OTTR), toxicology results, and our transplant center’s health assessment questionnaire that is completed annually by liver transplant recipients.

Predictor Variables

Based on a review of the liver transplant and general addictions literatures, consultation with substance abuse researchers and treatment specialists, and our own clinical experiences, we developed a list of 25 dichotomized variables hypothesized to be associated with risk of alcohol relapse after liver transplant (Table 1). We chose to assess 3 different durations of alcohol abstinence, based on our program policy (3 months), the commonly cited 6-month rule, and the longer abstinence period (12 months) required by some programs. Alcohol abuse/dependence, polysubstance abuse/dependence, and psychiatric comorbid conditions were determined on the basis of the diagnosis given by the evaluating mental health clinician, using established criteria in the Diagnostic and Statistical Manual of Mental Disorders-IV. Nonadherence was defined as persistent failure to follow the prescribed medication regimen, no-show or cancellation (not due to hospitalization) of at least 20% of scheduled outpatient clinic appointments, and/or failure to make other prescribed lifestyle modifications (eg, fluid or sodium restrictions) as determined by patient self-report or documentation in the medical record. Patients for whom employment consequences, income or housing loss, loss of marital or committed relationship, or legal problems (eg, violation of probation) could reasonably be expected with resumption of regular alcohol use were considered to have potentially serious behavioral consequences with relapse.

Other Variables

The following characteristics were recorded from the patient’s medical record: age at time of evaluation for liver transplant, sex, race, cause of primary liver disease, presence of hepatocellular carcinoma, time (days) to alcohol relapse after liver transplant, and survival status (alive, dead) and duration (days) at time of study initiation. Additionally, for alcohol relapers, we coded the intensity of the relapse as follows: low (≥1 slip to alcohol use that was isolated and followed by an extended period of abstinence), moderate (return to daily or near daily alcohol use, but at amounts less than levels before liver transplant), and high (return to close contact at frequency or amounts at or higher than levels before liver transplant). This information was ascertained from clinic notes written by members of the transplant team, reports by caregivers to transplant providers who then documented this information in our clinical database (ie, the OTTR), or patients’ disclosure on our annual transplant recipient health assessment in which patients are asked to describe the amount and frequency of alcohol use.
Continuous variables are presented as means and standard deviations, and \( t \) tests were used to examine differences between relapers and nonrelapers. Either \( \chi^2 \) or Fisher exact tests were used to identify differences between these 2 groups of patients on categorical variables. Variables with \( P \) less than .05 in the univariate analysis were included in a stepwise logistic regression analysis to identify predictors of relapse to any alcohol use after liver transplant. Only those variables with an adjusted \( P \) less than .05 were included in the final model. Cohen kappa was used to assess interrater agreement on coding of both predictor and outcome variables.

A clinical score (ie, Alcohol Relapse Risk Assessment, or ARRA, score) was constructed on the basis of the total score. Relapse-free survival curves by ARRA risk category were computed by using Kaplan-Meier methods and were compared by using log rank tests. Finally, a receiver operating characteristic curve and the area under the curve were calculated to assess the discriminative ability of the ARRA score. The area under the curve is interpreted as the probability that a randomly selected patient who relapsed to alcohol use after liver transplant will have a higher ARRA score than a randomly chosen patient who did not relapse. Generally, values of 0.7 and higher for area under the curve are considered clinically meaningful. PASW 17.0 (IBM Corporation) was used for all statistical analyses.

**Results**

**Recipient Characteristics**

Two hundred forty-three primary transplants (223 liver, 20 liver-kidney) were performed during the study period. On the basis of the total score, relapse-free survival curves by ARRA risk category were computed by using Kaplan-Meier methods and were compared by using log rank tests. Finally, a receiver operating characteristic curve and the area under the curve were calculated to assess the discriminative ability of the ARRA score. The area under the curve is interpreted as the probability that a randomly selected patient who relapsed to alcohol use after liver transplant will have a higher ARRA score than a randomly chosen patient who did not relapse. Generally, values of 0.7 and higher for area under the curve are considered clinically meaningful. PASW 17.0 (IBM Corporation) was used for all statistical analyses.
observation period (Figure 1). One hundred thirty-eight patients (57%) had a history of alcohol abuse or dependence, although 20 patients were excluded from analysis because they died less than 6 months after transplant or never left the rehabilitation center or hospital before dying. Of the remaining 118 patients, 101 (86%) were male, 99 (84%) were white, and mean age was 54.7 (SD, 8) years. One hundred six (90%) received a liver transplant only, 69 (58%) had hepatitis C virus infection, 45 (38%) had alcohol as the primary cause of liver disease, and 48 (41%) had hepatocellular carcinoma. Mean laboratory Model for End-Stage Liver Disease (MELD) score at the time of liver transplant was 22.0 (SD, 11; range, 7-48) and mean MELD score with exception points at time of liver transplant was 28.2 (SD, 7; range, 9-40). Mean duration of follow-up after liver transplant was 55 months.

Interrater Agreement
Examination of interrater agreement yielded a Cohen kappa of 0.80 (95% CI, 0.72-0.97) across the categorical coding of predictor and outcome variables, which suggests substantial agreement.

Relapse to Alcohol After Liver Transplant
Forty patients (34%) relapsed to any alcohol use (Figure 2). The time from liver transplant surgery to alcohol relapse ranged from 60 days to 7 years (median, 625 days). Relapsers did not differ significantly ($P > .05$) from nonrelapsers with respect to sex, race, age, MELD score at the time of liver transplant, or survival status. However, compared with nonrelapsers, relapsers had significantly shorter duration of abstinence before listing for liver transplant (mean [SD], 102.5 [118.0] months vs 27.7 [55.3] months, $P < .001$), were more likely to have alcohol as their primary cause of disease (28% vs 58%, $P = .003$), and were less likely to have hepatocellular carcinoma (54% vs 15%, $P < .001$). Of the 40 relapsers, 9 (22%) had a low-intensity relapse, 19 (48%) had a moderate-intensity relapse, and 12 (30%) had high-intensity relapses (Figure 2).
Univariate and Multivariate Analyses

In univariate analysis, 16 variables met the inclusion criteria and were associated with a higher incidence of alcohol relapse after liver transplant (Table 2). In the subsequent multivariate prediction model, 9 variables were statistically significant (Table 3), explaining 73% of the variance in the outcome ($P < .001$) and correctly classifying the outcome of 91% of patients. The model had a positive predictive value of 87%, correctly classifying 34 of 39 patients it predicted would relapse to any alcohol use after liver transplant. The negative predictive value was 92%, where the model correctly classified 73 out of 79 patients it predicted would have no relapse to alcohol use.

ARRA Prediction Score

An ARRA prediction score was calculated by adding points assigned to each of 9 statistically significant predictor variables in the final regression model. For the purpose of simplicity, and pending validation of these study findings, we assigned 1 point to each variable despite the difference in regression coefficients. The resulting ARRA score ranged from 0 to 9. Four groups of patients were defined on the basis of the ARRA score: score of 0 for ARRA I (8%), 1 to 3 for ARRA II (43%), 4 to 6 for ARRA III (36%), and 7 to 9 for ARRA IV (14%). The ARRA score was predictive of relapse to any alcohol use after liver transplant (log rank $\chi^2 = 57.9, P < .001$). The alcohol relapse rates were 0% for the ARRA I, 8% for the ARRA II, 57% for the ARRA III, and 75% for the ARRA IV group ($P < .001$). Also, ARRA classification was associated with relapse intensity for those who returned to alcohol use ($\chi^2 = 15.7, P = .003$). Low- and moderate-intensity relapsers were more likely to be in ARRA III classification, whereas high-intensity relapsers were more likely to be in the ARRA IV group (Figure 3). The area under the receiver operating characteristic curve was 0.892 (95% CI, 0.833-0.950) for the simplified ARRA total score.

Discussion

In this study, we present a new scoring system (ARRA) based on 9 pretransplant clinical parameters, which may help to identify before liver transplant those patients who are at high risk of relapsing to alcohol use after transplant. The ARRA score allowed patients to be classified into 4 groups with minimal (0/9, 0%), low (4/51, 8%), moderate (24/42, 57%), and high (12/16, 75%) risk of relapse to any alcohol use after
liver transplant. Supporting the clinical utility of the ARRA score is an area under the curve of 0.892, which suggests that if a relapser and nonrelapser were both drawn at random, the probability that the patient who relapsed to alcohol use would have a higher ARRA score is 89.2%.

The ARRA score is based on 9 parameters, including some that have previously been identified as correlates or predictors of alcohol relapse after transplant. Importantly, these predictors seem logical and clinically meaningful. All but 2 of the predictors (presence/absence of hepatocellular carcinoma, continued alcohol use after liver disease diagnosis) are modifiable, which suggests that risk factors can be attenuated or reduced with appropriate intervention before liver transplant. Many active alcohol relapse prevention programs (eg, Motivational Enhancement Therapy)\(^\text{34}\) target greater insight into one’s substance abuse patterns, the acquisition of more effective coping and stress management skill, the identification of high-risk social situations (eg, social activities involving alcohol), and strategies to avoid or manage such situations effectively. Additionally, treatment efforts focused on identifying the relative benefits and rewards of continued alcohol abstinence after liver transplant may improve the patient’s motivation for sustained lifestyle change after transplant. Of particular note, cigarette smoking commonly co-occurs with alcohol abuse or dependence,\(^\text{35}\) and smokers appear to be at higher risk of relapse after treatment for alcohol dependence.\(^\text{36,37}\) For exsmokers, the development of effective coping skills to prevent relapse and the positive reinforcement associated with smoking cessation may be beneficial in facilitating longer-term abstinence from alcohol. In contrast, continued smoking may, over time, contribute to cue-induced craving for alcohol,

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Regression coefficient</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of hepatocellular carcinoma</td>
<td>-1.89</td>
<td>0.15 (0.06, 0.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tobacco dependence</td>
<td>2.24</td>
<td>2.46 (1.18, 10.65)</td>
<td>.01</td>
</tr>
<tr>
<td>Continued alcohol use after liver disease diagnosis</td>
<td>1.80</td>
<td>1.79 (1.13, 3.27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low motivation for relapse prevention treatment</td>
<td>1.62</td>
<td>1.59 (1.06, 2.41)</td>
<td>.02</td>
</tr>
<tr>
<td>Poor stress management skills</td>
<td>1.31</td>
<td>3.61 (1.09, 14.12)</td>
<td>.049</td>
</tr>
<tr>
<td>Lack of a rehabilitation relationship</td>
<td>1.67</td>
<td>2.09 (1.13, 4.65)</td>
<td>.04</td>
</tr>
<tr>
<td>Limited social supports</td>
<td>1.59</td>
<td>3.02 (1.72, 10.19)</td>
<td>.03</td>
</tr>
<tr>
<td>Lacks nonmedical behavioral consequences</td>
<td>1.89</td>
<td>6.15 (1.23, 18.42)</td>
<td>.01</td>
</tr>
<tr>
<td>Continued engagement in social activities with alcohol present</td>
<td>2.31</td>
<td>8.77 (2.01, 42.17)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Figure 3 The association between Alcohol Relapse Risk Assessment (ARRA) classification and alcohol relapse intensity. None of the patients in the ARRA I classification had an alcohol relapse. ARRA II = 1-3 points, ARRA III = 4-6 points, ARRA IV = 7-9 points.
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especially in the context of psychological distress. Many liver transplant programs strongly advise or require patients to quit smoking before transplant surgery to decrease the risk of adverse health risks.\textsuperscript{36-40} Our data suggest that patients with an alcohol history should be offered interventions to facilitate smoking cessation (eg, online programs, self-help groups, behavioral and pharmacological interventions), as this may also attenuate the risk of alcohol relapse after liver transplant.

One interesting finding is that having hepatocellular carcinoma was associated with a lower likelihood of relapse. Research has shown that adults who believe an unhealthy lifestyle contributed to a cancer diagnosis are more likely to make and maintain lifestyle changes.\textsuperscript{41-44} It is possible that the heightened sense of urgency, higher risk of mortality, and added uncertainty of cancer progression and possible removal from the transplant list before liver transplant contribute to a greater commitment to maintaining an alcohol-free lifestyle after transplant. Based on their understanding or representation of hepatocellular carcinoma, some liver transplant recipients may maintain alcohol abstinence because they believe doing so will prevent cancer recurrence. Further study of cancer-specific beliefs and their association with other lifestyle changes, in addition to alcohol abstinence, is warranted.

Several variables were associated with alcohol relapse in the univariate analysis but were not significant predictors in the multivariate analysis, including cause of primary disease, abstinence duration before transplant listing, prior unsuccessful alcohol treatment, poor insight, and nonadherence with other aspects of liver disease management. Many other studies have focused exclusively on evaluating relapse rates in patients with alcoholic liver disease as the primary indication for liver transplant. Indeed, we found that those with alcoholic liver disease had a higher rate of alcohol relapse and a shorter duration of pretransplant abstinence compared with those with other primary indicators for transplant. However, patients with any diagnosis may have a history of alcohol abuse or dependency, and decisions about substance abuse policy or practices should not be made on the basis of disease etiology alone. Indeed, those for whom alcohol was not the primary indicator for liver transplant consumed as much alcohol per day (224 g vs 205 g, \(P = .56\)) as those with alcoholic liver disease. In our own program, we require a minimum of 3 months of out-of-hospital abstinence before a patient, including those without alcoholic liver disease, with any history of substance abuse can be listed for transplant. Most patients (89\%) in our study met this criterion; however, 13 patients (46\%) were abstinent for less than 3 months and 6 patients (46\%) relapsed to alcohol use after transplant. Regardless, it appears that abstinence duration is a less salient indicator of relapse after liver transplant than other variables, a finding consistent with several other studies.\textsuperscript{8,10,12,14,22,45-46} The recent study by Mathurin et al\textsuperscript{47} showing that early liver transplant for those with acute alcoholic hepatitis yields favorable outcomes and low short-term relapse rates further calls into the question the need for a specified abstinence period before transplant.

Findings should be evaluated within the context of several important study limitations. First, this is a single-center study, and findings cannot be generalized beyond the characteristics of our particular sample (eg, predominantly male, white, and having infection with hepatitis C virus as the primary diagnosis). The ARRA scoring system requires external validation by researchers in other transplant programs and with different populations of patients. Such validation is especially important given the inherent selection bias in a study of this nature, where it is possible that our program’s selection criteria for liver transplant most likely excluded patients who were thought to be at the highest risk of alcohol relapse after liver transplant. Second, it is possible that our alcohol relapse rates are higher than reported in this study, because our data collection processes may not have detected some patients who returned to drinking. Similarly, the length of time from liver transplant to return to drinking may have been shorter than described because some patients may have successfully concealed their drinking from members of the transplant team, other health providers, and family members. Third, the number of predictor variables is large and the number of events (ie, relapse) is small, possibly resulting in overfitting of the model. Also, we may have overlooked other variables that may be important to consider in assessing risk to alcohol relapse after transplant, including genetic markers.\textsuperscript{48}

The aforementioned limitations notwithstanding, this study has several notable strengths. For instance, it includes all patients with a history of alcohol abuse or dependence, not only those with alcoholic liver disease. This factor is clinically important because all patients, regardless of the cause of their liver disease, are advised to adopt a lifetime abstinence model to reduce the risk of liver graft injury, to ensure adherence to the immunosuppression regimen, and to optimize the patient’s overall health and well-being. Moreover, including patients with all indications for liver transplant broadens the potential utility of the ARRA scoring system. Another relative strength is that our primary outcome was any alcohol use after liver transplant, regardless of amount or level of harm potential as has been previously reported.\textsuperscript{4} The ARRA classification could be used to distinguish those patients with high-intensity relapses from those who had an isolated slip, thus suggesting that the scoring system may have some utility in...
identifying patients at risk of more harmful levels of drinking. This finding warrants replication in a larger cohort of patients because of the small cell sizes in the present study. Finally, we used multiple strategies to identify patients who had returned to any alcohol use, including self-reports, caregiver reports, confirmed clinical suspicion, medical records and hospital notes, and toxicology results.

Clinically, we recommend a strategy for risk stratification of patients with a history of alcohol abuse or dependence being evaluated for liver transplant and a tailoring of alcohol treatment on the basis of risk level. Our relapse rate of 34%, while consistent with the rates reported in other studies, is higher than what we expected. Historically in our program, all patients with a substance abuse history have been referred for relapse prevention treatment, but we have not closely monitored the frequency and intensity of treatment and have not distinguished between those at low versus high risk of relapse. The ARRA risk stratification offers the possibility of stratifying patients on the basis of risk level for relapse and prescribing relapse prevention treatment on the basis of such risk. Additionally, because two-thirds of alcohol relapses occurred more than 1 year after liver transplant, programs should consider recommending booster sessions for those who are no longer in treatment after transplant.

Predicting relapse to alcohol use after liver transplant is clinically important and represents a ripe area for scientific inquiry. Future studies should validate the predictive utility of the ARRA model with other patient populations at other transplant centers. Other recommended areas of study include assessing interrater agreement among liver transplant team members in classifying patients based on ARRA risk score, assessing the utility of the ARRA score in predicting relapse to other substances of abuse, and determining whether specific interventions can mitigate the risk level of patients and reduce the incidence of alcohol relapse after transplant.

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