Liver Transplantation for Alcohol-Related Liver Disease

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Alcoholic liver disease (ALD) is a common indication for liver transplantation. It is a much debated indication for deceased donor liver transplantation due to organ shortage and potential of alcohol relapse after liver transplantation. A six-month abstinence before liver transplantation is required at most centers to decrease chances of alcohol relapse after liver transplantation. However, this rule is not relevant for patients with severe alcoholic hepatitis or severely decompensated patients who are unlikely to survive till 6 months. Long-term care of these patients after liver transplantation includes assessment of relapse, smoking, and surveillance of de novo malignancies. Current review discusses role of abstinence, factors affecting alcohol relapse, liver transplantation for alcoholic hepatitis, role of living donor liver transplantation, and long-term care of ALD patients who undergo liver transplantation.
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Alcoholic liver disease (ALD) is common indication for liver transplantation worldwide,[1,2] and is a common cause of decompensated cirrhosis and acute-on-chronic liver failure in India as well.[3,4] ALD has good outcome after liver transplantation that is comparable or better than other etiologies of liver transplantation. Recent European liver transplant registry data showed 73% 5-year and a 59% 10-year survival rate for ALD.[2] However, survival is lower in recipients who relapse to harmful pattern of drinking as noted in a systemic review of 13 studies by Rustad et al.[5] Liver transplantation for ALD leads to improvement in quality of life and employment rates.[6,7] During selection of these patients for liver transplantation, it is important to identify other alcohol-related problems like cardiomyopathy, chronic pancreatitis, skeletal muscle wasting, and neurotoxicities that may preclude or impair outcome of liver transplantation.[8] Patients who have lack of social support, are active smokers, and have psychiatric disorders or alcohol dependence should be listed only with reservations.[9] Smoking worsens the outcome of alcohol-related liver disease[10] and active smoking at the time of liver transplantation has been shown to be associated with post-transplant recidivism also.[11]

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Abbreviations: ALD: alcoholic liver disease; CDT: carbohydrate-deficient transferring; GGT: gamma-glutamyltranspeptidase; HRAR: High Risk Alcoholism Relapse score; LDLT: living donor liver transplantation; MELD: Model for End-Stage Liver Disease score
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PREDICTORS OF RELAPSE

While liver transplantation improves functions of liver and cures complications of portal hypertension, it does not affect alcoholism and recipients may relapse again, sometimes to harmful levels of drinking, and pretransplant sobriety does not confirm sobriety after liver transplant.[12–14] Relapse may be in the form of occasional slips or harmful drinking pattern for a prolonged period; the later affects graft and patient survival.[5,11] Initially, 6-month abstinence was considered as a requirement before allocating organ to patients with ALD; however, it was based on poor quality small data.[15] The 6-month rule serves 2 purposes; it provides patient time to demonstrate a certain period of abstinence and patient may recover on medical management, and thus preemptive liver transplantation may be avoided.[16] However, patients who are very sick may not survive for a period of 6 months. The authors of Lille model (6 variables: age, renal impairment, albumin, prothrombin time, bilirubin at baseline, and at day 7 of treatment with steroids) showed that survival was only 25% in nonresponder to steroid group.[17] Mathurin et al. showed a cumulative 6-month survival rate of $77 \pm 8\%$ in patients with severe nonresponding alcoholic hepatitis who had early liver transplant versus $23 \pm 8\%$ for controls, $P < 0.001$.[18] Prevalence of alcohol relapse after liver transplantation varies widely.[19–21] This wide range of relapse after liver transplantation reflects several methodological differences among studies, variable follow-up, and difference in definition of relapse (any alcohol intake versus harmful drinking).[21] Mackie et al.[22] compared alcohol intake in alcoholics with other etiologies of liver transplantation and found similar rates. Several larger studies evaluating rate of relapse and factors predicting relapse after liver transplantation are shown in Table 1, the relapse rate varies from 16% to 42% and harmful relapse rate varies from 10% to 18%.[11,23–33] Various factors found to predictive of post-transplant alcohol relapse are shown in

Table 1 Rate of Alcohol Relapse in Various Studies.

Author, year	*N*	Follow-up	Relapse rate %
Björnsson,[23] 2005	103	31 months (median)	33%, 18% heavy drinking
DiMartini,[24] 2006	167	5 years (mean)	42%
Pfitzmann,[25] 2007	300	89 months (median)	19%
De Gottardi,[26] 2007	387	61.2 months (mean)	11.9% harmful alcohol consumption
Gedaly,[27] 2008	142	41.2 months (median)	19%
Tandon,[28] 2009	171	64.8 months (mean)	24%, 13% problem drinking
Karim,[29] 2010	80	Not mentioned	10% harmful relapse
Hartl,[30] 2011	120	31 months (mean)	16%
Rodrigue,[31] 2013	118	55 months (mean)	33.8%
Deruytter,[32] 2013	108	55 months (mean)	29%, 16% problem drinking
Egawa,[33] 2014	140	1319 days (median)	22.9%, living donor liver transplantation
Satapathy,[11] 2015	128	1354 days (mean)	16 (10.8%) harmful alcohol consumption

Table 2. Following variables have been shown to be associated with risk of post-transplant alcohol relapse: absence of structured management program pretransplant, length of pretransplant sobriety, alcohol or other substance dependence, prior alcohol rehabilitation, poor social support/lack of partner, poor psychosomatic prognosis or psychiatric comorbidity, female sex, patients' nonacceptance of having an alcohol problem before LT, continued alcohol use after liver disease diagnosis, low motivation for alcohol treatment, and presence of a first-degree relative with alcohol abuse in family.[11,23–33] Pretransplant sobriety predicting absence of alcohol relapse after liver transplant is not a universal finding.[11,15,23–33] Scoring systems also have been proposed to predict post-transplant alcohol relapse. In a study of 118 patients by Rodrigue et al.,[31] the authors advised a scoring system (Alcohol Relapse Risk Assessment) to predict risk of relapse. They studied 25 hypothesized risk factors and found 9 as significantly predictive of relapse after transplant. These factors were absence of hepatocellular carcinoma, dependence on tobacco, ongoing alcohol use after diagnosis of liver disease, poor skills of stress management, absence of rehabilitation relationship, low motivation for alcohol treatment, limited social support, lack of nonmedical behavioral consequences, and continued engagement in social activities with presence of alcohol. Each predictor was given a score of 1 and patients were classified into 1 of 4 groups by ARRA score. Patients in groups ARRA III (score 4–6) and ARRA IV (score 7–9) had significantly higher rates of alcohol relapse and were more likely to return to pretransplant levels of drinking. Another score found to be useful to predict post-transplant alcohol relapse is High Risk Alcoholism Relapse (HRAR) score;[26] it consists of the following three variables: duration of heavy drinking, number of daily drinks, and number of prior alcoholism inpatient treatment experiences. Each item is scored as 0–2 and total possible score ranges from 0 to 6. The authors have shown a HRAR score higher than 3 as associated with high risk of alcohol relapse after liver transplantation.[26]

Dew et al.[13] found alcohol relapse rate of 5.6 cases (any alcohol use) and 2.5 cases (heavy alcohol use) per 100 liver transplant recipients per year in a meta-analysis including 50 liver transplantation studies conducted between 1986 and 2005 in North America or Europe. These studies were mainly cross-sectional or retrospective (n = 44) and included a total of 3551 recipients with median follow-up of 3.4 (range 0.9–12.3 years). The authors studied 12 psychosocial variables and found small (effect size 0.17–0.21) but significant association of post-transplant relapse with poorer social support, pretransplant sobriety <6 months, and alcohol abuse/dependence history in family, thus having some predictability but not high degree of accuracy to predict post-transplant relapse. The factors not found to be significant were male sex, higher age, higher education, unmarried status, unemployment, poorer social support, presence of psychiatric history before transplant, use of illicit drugs, history of alcohol abuse or dependence on family, and no alcohol rehabilitation before liver transplantation.[13]

In a systemic review of 13 studies published since 2004, Rustad et al. found shorter sobriety before transplantation as a significant predictor of time to first and binge alcohol use. Other factors predicting alcohol relapse included presence of alcohol dependence/psychiatric comorbidity and higher score on High-risk Alcoholism Relapse scale. Recipients with early-onset accelerating moderate/increasing heavy use had more than twice prevalence of steatohepatitis or rejection and graft failure/mortality than late-onset (peak of drinking at 6 years after transplantation) alcohol users.[5]

Active involvement of a psychiatrist may decrease relapse after liver transplant.[23,34] In a study of structured management program including a psychiatrist, Björnsson et al. demonstrated relapse rate of 48% (19/40) compared

Table 2 Predictors of Alcohol Relapse After Liver Transplantations in Different Studies.

Author, year	*N*	Pretransplant factors	Demographic factors	Psychosocial factors	Post-transplant
Björnsson,[23] 2005	103	Structured management program decreased relapse	[a]	[a]	Structured management program decreased relapse
DiMartini,[24] 2006	167	Length of sobriety	[a]	Alcohol dependence, other substance use, and prior alcohol rehabilitation	[a]
Pfitzmann,[25] 2007	300	Abstinence <6 months		Absence of companion in life, presence of young children, and poor psychosomatic prognosis	
De Gottardi,[26] 2007	387	Abstinence <6 months	[a]	High-risk alcoholism relapse high score (4–6), and presence of psychiatric comorbidity	[a]
Gedaly,[27] 2008		Abstinence <12 months	[a]	[a]	
Tandon,[28] 2009		Shorter pretransplant abstinence[b]			
Karim,[29] 2010	80	Abstinence <6 months	Female sex, age < 50 year	Psychiatric comorbidity	
Hartl,[30] 2011	120	Abstinence of <3 months	[a]	Nonacceptance of having an alcohol problem	[a]
Rodrigue,[31] 2013	118	Absence of hepatocellular carcinoma Tobacco dependence Continued alcohol use after liver disease diagnosis	[a]	Low motivation for alcohol treatment, Poor stress management skills, no rehabilitation relationship, limited social support, lack of nonmedical negative behavioral consequences, and continued engagement in social activities with alcohol	[a]
Deruytter,[32] 2013	108	A shorter pretransplant abstinence (in univariate)	Presence of a first-degree relative with alcohol abuse	[a]	[a]
Egawa,[33] 2014	140	Preoperative alcohol consumption was not a risk factor for relapse	[a]	History of treatment for psychiatric diseases other than alcoholism	[a]
Satapathy,[11] 2015	128	Abstinence <6 months (in univariate) Active smoking	Younger age No support of immediate family member	Nonalcohol-related criminal history	[a]

[a]Not mentioned/not studied/not found important.
[b]For every 1-month increment in pretransplant abstinence, authors found a 5% decrease in the adjusted relapse rate.

to 22% (13/58) before and after start of program, $P = 0.002$. In another study of 92 cirrhotic alcoholic recipients, relapse was lower (16.45%) in recipients managed by Alcohol Addiction Unit within transplant center as compared to 35.1% in patients managed by psychiatrist not affiliated to liver transplant unit. Also, in patients managed by within transplant center program, there was no significant difference in relapse rate between ≥6 and <6 months of alcohol abstinence pretransplant.[34] DiMartini et al.[35] reported lower 10 years post-transplant survival rate (46% and 43%) for the increasing depression and high depression groups as compared to low depression group (66%). Whether treatment of depression may lead to improvement of survival rates is not clear at present.

Living Donor Liver Transplantation and Alcoholic Liver Disease

While most of the data regarding relapse after liver transplantation is from deceased donor liver transplantation, there is limited literature from living donor liver transplantation (LDLT). The deceased organs are public resource and allocation of organs to ALD patients generates controversy because of sharing scarce resources in the

presence of increasing organ shortage to patients who developed disease due to their alcoholism and have potential to return to alcoholism after liver transplantation. However, with the emergence of LDLT, this does not hold true, as some family member may donate organ to the patient. LDLT offers several advantages over DDLT; these include immediate availability of organ to sick patients or patients with hepatocellular carcinoma (thus decreasing wait list mortality) and option of patient optimization as surgery can be timed accordingly. Also, the relapse rates may be different in LDLT as patients are being watched by donor/relatives and in many cases donor may be living with recipient in same household.

Two LDLT studies have shown results of relapse in ALD patients. In one multicentre study from Japan involving 38 centers, the authors found a relapse rate of 22%. The survival rate was worse for recipients who had relapsed as compared to recipients who had not relapsed 18 months after transplantation (21.9% and 73.8% patients, respectively). The authors found lower relapse rates in patients whose parents or siblings were donors.[33] Kawaguchi et al. published a small single-center study of 13 patients of whom 1 had relapse to alcohol. This study followed a 6-month abstinence rule and participation in a rehabilitation program, psychiatric consultation, and written agreement declaring an intention of lifetime abstinence.[36] We found relapse rate of 10.7% in 270 LDLT patients (published in abstract form).[37] The lower relapse rate in our series could be secondary to LDLT, active psychiatrist involvement, close follow-up of patients after liver transplantation, and role of strong Indian family support. However, determination of exact impact of each of these factors is not possible due to their subjective nature.

Liver Transplant for Alcoholic Hepatitis

Alcoholic hepatitis is a clinical syndrome, which occurs in persons drinking excessively, usually for many years. It presents as new-onset jaundice, which is accompanied by ascites, cachexia, and hepatomegaly. It has characteristic pathologic findings, which include Mallory bodies, ballooned hepatocytes, steatosis, and pericellular fibrosis. Abstinence from alcohol is the key to recovery from alcoholic hepatitis. However, alcoholic hepatitis represents a spectrum of clinical severity, and the outcome for patients who manifest the most severe liver function derangement is poor and mortality remains high even in those patients who abstain from alcohol. Severe alcoholic hepatitis can be defined by prognostic scores based on clinical data, such as the Maddrey discriminant function, the Model For End-Stage Liver Disease (MELD) score, and the Glasgow alcoholic hepatitis score.[38] Patients with alcoholic hepatitis historically have been excluded from access to the transplant on account of an insufficient period of abstinence. In 2005, therapeutic trials of liver transplantation in patients with severe acute alcoholic hepatitis who have failed to respond to medical treatment were advocated by a French Consensus Conference, regardless of the period of their abstinence.[39] Mathurin et al.[18] conducted a case–control study of early transplantation in a highly selective group of patients with severe alcoholic hepatitis who had failed to respond to medical therapy. Selected patients also had supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. The selected group constituted <2% of total severe alcoholic hepatitis patients and only 2.9% of available grafts were used for this indication. The cumulative 6-month survival rate (±SE) was higher among patients who received early transplantation than among those who did not (77 ± 8% vs. 23 ± 8%, $P < 0.001$). This benefit of early transplantation was shown to be maintained through 2 years of follow-up. Three patients resumed drinking alcohol (at 720, 740, and 1140 days) after transplantation.[18] Singal et al. reviewed the United Network for Organ Sharing database from 2004 to 2010 and found 130 patients who had alcoholic hepatitis and had been "listed" for transplantation, of whom 59 received a transplant,[40] 11 had histologic appearances of alcoholic hepatitis on explant pathology, 33 had cirrhosis, and the remainder had other diagnoses. The graft and patient survivals were similar in the alcoholic hepatitis cohort compared to a control cohort of nonalcoholic recipients, which was selected by sequential matching according to gender, ethnicity, year of transplant, age (±5 years), donor risk index, and MELD score (±5 points).[40] Wells et al.[41] retrospectively reviewed the explanted livers of 148 patients transplanted for ALD alone, drawn from a single-center cohort of 1097 patients transplanted over a period of 18 years. The histological features of alcoholic hepatitis were found in 32 (22%) patients. In this series, the recorded duration of pretransplant abstinence did not correlate with the explant histology. Furthermore, patient and graft survivals were similar in patients with bland alcoholic cirrhosis or cirrhosis plus alcoholic hepatitis, and among 125 matched non-ALD recipients.[41] At our center, out of the 270 patients,[37] explants data were seen in those with clinical acute alcoholic hepatitis/acute-on-chronic liver failure ($n = 23$). Among these, 18 had features of alcoholic hepatitis. Survival of these 18 recipients was not statistically different from other alcoholic cirrhosis/other etiologies of cirrhosis.

HOW TO ASSESS RELAPSE AFTER LIVER TRANSPLANT

As described earlier, patients with harmful pattern of drinking have lower survival rates than patients with occasional drinking; hence, it is important to know about relapse/recidivism. The diagnosis of recidivism is made based on information obtained from the patient and or family member/partner (spouse predominantly). Self-reported alcohol use after liver transplant may underreport

the problem. It is important to get information from partner or spouse, as the patient may not be forthcoming with the same at initial visit.

While measuring occasional small amount of alcohol in the past is often not possible, moderate/heavy alcohol intake can be measured by biomarkers. Blood or breath tests only allow very recent (few hours back) alcohol intake only. There are several studies on carbohydrate-deficient transferring (CDT) and urinary ethyl glucuronide.[42–45]

Carbohydrate-deficient transferrin can be used for initial screening or to measure relapse.[39] Transferrin (glycoprotein) is secreted by liver. Fifty to eighty grams daily alcohol intake for several days decreases the carbohydrate content of transferrin (hence, carbohydrate-deficient transferrin). After cessation of alcohol intake, serum CDT level decreases to normal values in approximately 2 weeks. CDT levels are influenced by smoking, weight, liver diseases, and female sex.[42,46,47] In a large study by Anton et al.,[48] 444 recently inpatient alcoholics were compared to 204 matched social drinker controls. The authors found that CDT had similar sensitivity to gamma-glutamyltranspeptidase (GGT) as a marker of alcohol intake and combination of both was better. Increase in CDT values from baseline also helps to identify relapse. CDT is more specific than GGT.[48–50]

Ethyl glucuronide is a direct metabolite of alcohol and it can be measured in tissues, blood, hair, and urine.[42] Urinary ethyl glucuronide offers several advantages over other biomarkers of alcohol relapse. It is detectable up to 80 h after ethanol elimination from the body and it is positive even after small amount of alcohol consumption (<5 g). It offers better sensitivity and specificity than CDT.[51,52] Staufer et al. measured urinary ethyl glucuronide, ethanol, methanol, alanine transaminase, aspartate transaminase, GGT, mean corpuscular volume, and CDT along with other biomarkers in 141 liver transplant candidates and recipients (308 outpatient visits) and compared these markers to self-reported alcohol intake. The authors found better sensitivity and specificity of urinary ethyl glucuronide (89.3% and 98.9%) than of CDT (25% and 98.6%). They found urinary EtG as best independent predictor of alcohol consumption in multivariate analysis with a positive predictive value of 89.3% and negative predictive value of 98.9%.[45]

RISK OF MALIGNANCY AFTER LIVER TRANSPLANT

Several studies have shown that liver transplant recipients are at higher risk of development of malignancies. In a systemic review of de novo malignancy development after liver transplantation, Chak et al. identified immunosuppression, hepatitis C virus infection, smoking, alcoholic cirrhosis, and sun exposure as significant factors.[53,54] Studies addressing different etiologic profiles have shown that ALD patients are at higher risk of de novo malignancy development after liver transplant and the risk is more for oropharyngeal malignancies.[55–57] In a long-term follow-up of 171 adult transplants, Watt et al. found higher risk of nonskin malignancies in primary sclerosing cholangitis (22% at 10 years) and ALD (18% at 10 years) compared to other etiologies (10% at 10 years). Multivariate analysis indicated that increasing age by decade (hazard ratio 1.33), smoking (hazard ratio 1.6), primary sclerosing cholangitis (hazard ratio 2.5), and ALD (hazard ratio 2.1) were significantly associated de novo solid malignancies after liver transplantation.[58]

Smoking is common in ALD and patients tend to smoke after transplant also.[59–61] DiMartini et al. showed that 40% of ALD recipients resume smoking, generally in early post-transplantation period and they tend to have tendency to increase consumption over time and to become tobacco dependent. Active smoking after transplantation in ALD has been shown to be an independent predictor of long-term morbidity and mortality, either from cardiovascular complications or from de novo neoplasms.[61] Herrero et al.[62] showed that withdrawal smoking was associated with lower risk of de novo malignancies after liver transplantation. Also, smoking is a major risk for cardiovascular disease, and thus contributes to late mortality after transplantation, independent of malignancy development.[63]

CONCLUSION

ALD patients have good outcome after liver transplantation. Recent data also point toward a good outcome of liver transplantation in highly selected patients with alcoholic hepatitis. Pretransplant evaluation should screen for comorbidities associated with alcohol intake. Patients with harmful alcohol intake after liver transplant have inferior outcomes as compared to those who remain sober. Recent emerging experience suggests potential role of LDLT in selected group of ALD patients. Active involvement of psychiatrist may decrease relapse rates. Besides routine care, long-term management of these patients should include assessment of smoking and de novo malignancies.

CONFLICTS OF INTEREST

The authors have none to declare.

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