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Liver transplantation for alcoholic liver disease: Lessons learned and unresolved issues

José Ursic-Bedoya, Stéphanie Faure, Hélène Donnadieu-Rigole, Georges-Philippe Pageaux

José Ursic-Bedoya, Stéphanie Faure, Georges-Philippe Pageaux, Liver Transplantation Unit, Digestive Department, Saint Eloi University Hospital, University of Montpellier, 34295 Montpellier Cedex 5, France

Hélène Donnadieu-Rigole, Addictology Department, Saint Eloi University Hospital, University of Montpellier, 34295 Montpellier Cedex 5, France

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Correspondence to: Georges-Philippe Pageaux, MD, PhD, Liver Transplantation Unit, Digestive Department, Saint Eloi University Hospital, University of Montpellier, 34295 Montpellier Cedex 5, France. gp-pageaux@chu-montpellier.fr
Telephone: +33-4-67337077
Fax: +33-4-67337077

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Abstract

The use of liver transplantation (LT) as a treatment for alcoholic liver disease (ALD) has been highly controversial since the beginning. The ever increasing shortage of organs has accentuated the low priority given to patients suffering from ALD, which is considered a "self-inflicted" condition. However, by improving the long-term survival rates, making them similar to those from other indications, and recognizing that alcoholism is a primary disease, ALD has become one of the most common indications for LT in Europe and North America, a situation thought unfathomable thirty years ago. Unfortunately, there are still many issues with the use of this procedure for ALD. There are significant relapse rates, and the consequences of excessive drinking after LT range from asymptomatic biochemical and histological abnormalities to graft failure and death. A minimum three-month period of sobriety is required for an improvement in liver function, thus making LT unnecessary, and to demonstrate the patient's commitment to the project, even though a longer abstinence period does not guarantee lower relapse rates after LT. Recent data have shown that LT is also effective for severe alcoholic hepatitis when the patient is unresponsive to corticosteroids therapy, with low relapse rates in highly selected patients, although these results must be confirmed before LT becomes a standard procedure in this setting. Finally, LT for ALD is accompanied by an increased risk of *de novo* solid organ cancer, skin cancer, and lymphoproliferative disorders, which has a large impact on the survival rates.

Key words: Liver transplantation; Alcoholic liver disease; Cirrhosis; Alcoholic hepatitis; Survival rates; Relapse; Six-month rule; Sobriety; Solid organ cancer

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Core tip: Alcoholic liver disease (ALD) has become one of the leading indications for liver transplantation (LT) over the last twenty years. In the context of scarcity of organs, the excellent survival and compliance rates of LT for ALD make this a favorable procedure. However, there are considerable relapse rates, which can have dire consequences, such as graft loss and death. Other issues have also emerged: increased risk of malignancy, concomitant hepatitis C virus infection, and LT for alcoholic hepatitis. This review will first discuss the highly controversial history of LT for ALD and then focus on the main questions that remain unanswered in 2015.

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INTRODUCTION

Alcohol consumption accounts for 3.8% of global mortality and 4.6% of disability-adjusted life-years (DALYs) lost due to premature death^[1]. Among the various harmful effects of alcohol, alcoholic liver disease (ALD) induces a wide spectrum of liver abnormalities, including simple steatosis, alcoholic hepatitis or steatohepatitis, progressive fibrosis, and ultimately cirrhosis and/or hepatocellular cancer (HCC)^[2]. At least 30% of all steatosis cases can be attributed to alcohol, according to a population-based French study^[3]. The risk of developing ALD increases in a dose-dependent manner, is higher among women, and generally appears after several years of consumption of > 7-13 beverages per week for women and 14-27 beverages per week for men, according to a Danish prospective study including 13285 individuals over a 12-year follow-up period^[4].

The current management of alcoholic cirrhosis comprises abstinence, nutritional therapy rich in calories and proteins^[5], and prophylaxis of any associated complications. Despite this management strategy, hepatic decompensation, disease progression, and life-threatening complications (variceal bleeding, bacterial or fungal infections, hepatic encephalopathy, and HCC) can occur, and liver transplantation (LT) may be needed. ALD, alone or in combination with other liver-related diseases such as hepatitis B or C viruses and NASH, is one of the most common indications for LT in Europe (23% of all LT between 1999-2009 were at least partially attributable to alcohol abuse, according to the European Liver Transplant Registry

ELTR^[6]) and North America (24.1% of all procedures in 2013^[7]). Once decried^[8], LT for ALD has now become an accepted, safe, and common procedure, with excellent survival and reasonable relapse rates^[9]. It is at least partially responsible for the decrease seen in liver-related mortality^[10,11].

BRIEF HISTORY AND CONTROVERSY

Before the advent of cyclosporine, the first report of survival rates from post-LT ALD patients indicated that the short-term prognosis was poor compared to other indications. Of the first ten patients who received a transplant by Starzl *et al.*^[12], nine did not survive the first four months. This was probably due to the selection of critically ill patients who were too sick for improvement even with the intervention. In 1983, the National Institutes of Health predicted that ALD would be a marginal indication for LT. In 1984, Scharschmidt^[13] reported the experience of four transplant centers that had performed 540 transplantations in the United States and Western Europe. The three-year survival rate for the 20 transplant patients after 1980 was 20%; non-alcoholic cirrhosis had an impressive 42% survival rate. The first positive data published about the survival rate of ALD patients after LT, in comparison to other indications, came in 1988. Starzl *et al.*^[14] reported a 73% one-year survival rate among 41 patients when cyclosporine was used as the main immunosuppressive drug. This was confirmed by numerous European and American centers in the early nineties, with one-year survival rates from 66%-96%^[15-22].

Since the beginning, the use of LT to treat alcoholic cirrhosis has been highly controversial. The naysayers believed that alcohol consumption had concomitant multisystem organ consequences that precluded a good result from surgery, relapse induced redevelopment of the liver disease, and patients were unlikely to withstand the psychological issues caused by such a serious operation, resulting in poor compliance^[23,24]. Further taking into account the shortages of available grafts and high cost of LT, many specialists considered it unacceptable to "waste" grafts on alcoholics who were responsible for the harm caused to their liver. This began to change as alcoholism became accepted as a primary chronic disease by the medical community^[25], whereas hitherto it was considered a vice^[26].

TIMING OF REFERRAL FOR TRANSPLANTATION

One of the main issues surrounding LT for ALD is identifying the ideal time to consider the operation. The first parameter to consider is the severity of the disease. The benefit of LT for alcoholic cirrhosis is limited to patients with advanced decompensation

(i.e., a Child-Pugh score of 11-15^[27] or MELD score > 11^[28]). A randomized controlled trial conducted at 13 living donor liver transplantation centers in France that included 120 Child-Pugh stage B patients showed that immediate listing for LT did not improve the five-year survival rates, and it increased the risk of extrahepatic cancer compared to standard care^[29].

There are few therapeutic options for ALD, and the main treatment is complete abstinence^[30]. Therefore, improvement can only be expected in about 66% of Child-Pugh C patients after the first episode of decompensation. This improvement concerns hepatocellular functions and portal hypertension, and these improvements should be visible in the first three months following the discontinuation of alcohol use^[31].

Whether or not the patient remains in end-stage liver disease or has other life-threatening complications, LT should be encouraged as soon as possible. This is the natural course in centers that have a transplantation program, but many reports have indicated insufficient referrals in centers without LT. In 1992, Davies *et al.*^[32] reported that only one out of 42 patients with end-stage alcoholic cirrhosis admitted to a British district general hospital was referred to a transplant center. One of the explanations for this low referral rate was that a vast majority of the alcoholic patients were not abstinent upon admittance, which was considered a mandatory criterion at the time. However, there was also a lack of acknowledgment that LT was a therapeutic option for end-stage liver disease in general, as attested by the under referrals for other etiologies. A more recent study in a large Veterans Affairs medical center in the United States showed similar results. Only 21% of the 199 patients with potential indications for LT (according to the American Association for the Study of Liver Disease guidelines) were referred for a pre-transplant evaluation. The determinants associated with a negative mention of LT were old age, member of a colored population, and ALD^[33].

Most transplantation teams require a 6-mo delay for abstinence. However, the validity of this criterion in predicting post-transplant relapse and prognosis has only been suggested and never convincingly demonstrated^[34-37]. A more pragmatic attitude is to refer the patient regardless of their abstinence and allow the transplant team to judge the need for transplantation.

PRE-LT ASSESSMENT

Like all other LT candidates, patients suffering from ALD must undergo a thorough assessment to detect potential contraindications. Tissues at risk from alcohol damage, such as the heart, kidneys, immune system, and central and peripheral nervous system, must be carefully examined. A retrospective study from the United Kingdom highlights the importance of the pre-LT evaluation. Anand *et al.*^[38] examined data from their selection protocol from 1987-1994, where 180

patients with ALD were referred for LT. Out of the 137 patients with complete information, only 31% received transplants or were awaiting LT; almost 10% died during the evaluation time period, 14% were considered too healthy for transplantation, and 5% refused LT. The remaining 40% of patients were considered too ill, either medically or psychologically unsuitable for the procedure. Although it has been shown that *de novo* cancer mortality increases after LT in alcoholic patients (as discussed below), there is a lack of specific studies examining the approach to improve the detection of patients at risk of malignancies.

MANAGEMENT OF ALCOHOL ADDICTION BEFORE LT

Before LT, alcohol abuse and dependence must be evaluated by an addiction specialist using well-established diagnostic criteria, such as the DSM-IV^[39]. Published data are scarce with regards to addiction management during the waiting-list period. It is common practice to ask patients to sign a contract to remain abstinent and encourage attendance at support groups such as Alcoholic Anonymous. A randomized controlled trial conducted by Weinrieb *et al.*^[40] in two United States centers compared Motivational Enhancement Therapy (MET), a positive reinforcement technique, with referral to local treatment sources ("treatment as usual"). While the study revealed that 25% of the patients drank alcohol before their transplant, MET had little, if any, influence on this event. By contrast, an Italian single-center retrospective report emphasized the importance of having a team of addiction specialists and close follow-up of the patients on the waiting list. After the creation of an Alcohol Addiction Unit within the LT center at the Gemelli Hospital in Rome, post-LT relapse rates decreased significantly. Follow-up of the patients on the LT waiting list or those under consideration for inclusion to the list occurred on a weekly basis during the first month, every other week during the second and third month, and finally every month^[41].

MORTALITY AFTER LT

The graft and patient survival rates of ALD-related LT have consistently improved over time and are now at least as good as other LT indications. The latest reports from large databases such as the ELTR, which includes data from over 89000 LT, has revealed 1-, 5-, and 10-year patient survival rates of 86%, 73%, and 59%, respectively^[6]. These rates are similar to those seen in the United States^[42] and in exclusive living-donor liver transplantation (LDLT) in Japan and South Korea^[43,44]. However, when the primary indication for LT is both ALD and chronic HCV infection, the survival rates decrease significantly^[9,28]. As of now, it is unclear whether the latest and highly active antiviral drugs

Table 1 Summary of the incidence of alcohol relapse after liver transplantation in alcoholic liver disease patients from various studies since 2000

First author (country, yr)	Number of patients	Mean follow-up (mo)	Definition of relapse	Relapse rate	Impact on survival rate
Berlakovich (Austria, 2000 ^[92])	118	53.7 (9-179)	Any consumption	13%	NA
Burra (Italy, 2000 ^[93])	51	40.1 (0-86)	Any consumption	33%	NA
			Occasional drinking	21%	
			Heavy drinking	12%	
Tomé (Spain, 2002 ^[76])	68	38 (12-68)	Any consumption	10%	NA
			> 60 g/d	3%	
Cuadrado (Spain, 2005 ^[69])	54	99.2 (14-155)	Intake > 30 g/d	25.90%	Yes
De Gottardi (Switzerland and France, 2007 ^[37])	387	61.1 ± 47.5	Intake > 40 g/d	11.90%	No
Karim (Canada, 2010 ^[52])	80	NA	Daily intake or associated with medical harm	10%	NA
Dimartini (United States, 2010 ^[66])	265	NA	Any consumption	48%	Yes
			Fluctuating low level	28.60%	
			Early onset rapidly accelerating moderate use	6.40%	
			Steady increase to moderate use after three years post-LT	7.40%	
			Early onset continuously increasing heavy use	5.80%	
Faure (France, 2012 ^[70])	206	81.7 (29-135)	Any consumption	43.70%	Yes
			Slip	7.00%	
			Occasional intake (< 20-30 g/d)	12.40%	
			Excessive intake (> 20-30 g/d)	24.30%	
Egawa (Japan, 2014 ^[44])	140	43.4 (0.1-163)	Any consumption	22.90%	Yes

NA: Not available.

directed against the hepatitis C virus will have any impact on this situation.

The causes of mortality differ between patients who receive a transplant for ALD and patients with other indications. Indeed, cancer (especially of the aerodigestive tract) and cardiovascular-related deaths are over-represented in the ALD group, according to European and United States registries^[9,45]. These data, along with other reports^[45,46], suggest that smoking has a direct influence on the mortality of ALD patients after LT, although this issue has not been extensively studied. DiMartini *et al.*^[47] published a prospective study that included 172 ALD-related LT recipients and focused on the effect of tobacco consumption after the procedure. They found that the smoking prevalence fluctuated from 39%-58% at different time points after the LT, the amount of daily consumption increased over time, and patients quickly become nicotine dependent.

RELAPSE

The first team to report a favorable result for alcoholic patients who underwent an LT was initially optimistic because of their low relapse rates (*i.e.*, only one out of 35 patients who lived for six months or longer relapsed). Starzl *et al.*^[14] referred to LT as "the ultimate sobering experience". While the goal is to have a relapse rate of zero, and reports showing up with up to 46% of patients returning to some kind of alcohol consumption after LT, the transplant community has since been more cautious. Table 1 summarizes the recent data for relapse rates after LT for ALD patients.

Definition

The variability found between reports is, in part, explained by the definition of relapse used. Indeed, it is important to differentiate between those patients who have minor, irregular, and occasional drinks (called "slips"), those who have a regular but moderate alcohol intake, and those who return to major and harmful drinking. In other words, the term relapse, as it relates to drinking, can differ from relapse to alcoholism^[48]. Although minor, "controlled" consumption is unlikely to lead to graft damage, forgoing abstinence, regardless of the frequency or amount of alcohol consumed, is usually considered a relapse. This tenet is supported by a large longitudinal cohort study led by Vaillant who showed that "controlled" drinking cannot be sustained for periods longer than three years before returning to alcohol abuse, which can harm the liver graft^[49].

Pre-transplant risk factors

Numerous reports have tried to predict patients at risk of relapse, using the pre-transplant patient characteristics and addiction, psychiatric, medical, personal, and family history. While some of the data are contradictory, the following factors have been identified in patients who relapsed after their LT: < six months of sobriety pre-LT^[34,37]; family history of alcoholism^[50]; psychiatric comorbidities, including other substance abuse^[37,50,51]; diagnosis of alcohol dependence^[51]; prior alcohol rehabilitation^[51]; and female gender^[52].

The high risk alcoholism relapse (HRAR) scale is a clinical score developed to predict the risk of relapse

among veterans^[53] according to their daily alcohol consumption, length of their drinking history, and previous treatment history. While this scale showed that the six-month abstinence criterion alone would penalize a significant number of candidates who had a low relapse risk based on their HRAR score^[54], it proved inefficient, when used by itself, to distinguish between those who relapsed and those who did not in a United States transplant population^[55]. In a Franco-Swiss cohort of 387 patients who underwent LT for alcoholic cirrhosis, a HRAR score > 3 was one of the three factors associated with a relapse to harmful drinking (defined by a declared alcoholic consumption level > 40 g/d and the presence of alcohol-related damage), along with < six months of abstinence and presence of psychiatric comorbidities. The absence of all of these factors resulted in a 5% relapse rate, which increased to 18%, 64%, and 100% when one, two, or three factors were identified, respectively. It is noteworthy to point out that the vast majority (94%) of the cohort had less than two risk factors^[37].

Detection

A patient's reliability regarding their alcohol history can be problematic, especially before transplantation, because candor can have negative consequences on their disease management (*e.g.*, waiting-list withdrawal, no re-transplantation). Yates *et al.*^[56] interviewed 50 patients with alcoholic cirrhosis and compared their results with those from an interview with an unbiased source who was unaware of the patient's alcoholism history. They found a good correlation between the two versions, concluding that patients suffering from ALD were reliable. By contrast, random blood alcohol level tests performed on patients who were on the waiting-list revealed hidden consumption in two studies^[57,58]. After transplantation, several methods have been tested to identify relapsing patients, including histological findings^[16,59], patient and entourage interviews^[17,60], and blood and/or urine analyses^[61,62]. Our transplant center^[63], like others^[64], uses a multi-detection method, combining clinical, biochemical, urinary and blood alcohol levels, and histological findings. This seems to be the most relevant method to detect alcohol relapse after LT^[65].

Consequences of relapse

DiMartini *et al.*^[66] prospectively followed 208 patients who received a LT for ALD and characterized five different trajectories of behavior towards alcohol after the surgery. Over half of the patients (54%) did not consume any alcohol (group 1). Non-abstainers were divided into four categories: fluctuating low level of use (group 2, 26%), early moderate use that diminished over time (group 3, 6%), late moderate use that increased over time (group 4, 7%), and early heavy use that increased over time (group 5,

6%). Five deaths occurred in the study, which were all attributed to recurrent ALD. Interestingly, these patients were only from the early relapse groups (groups 3 and 5). These patients had more biopsy-diagnosed steatohepatitis and acute rejection than the other patients and were more prone to graft failure. In another study, Rice *et al.*^[67] showed that continuous heavy drinking is a risk factor of graft loss.

A relapse to harmful drinking seems to have an impact on the survival rates when it is assessed ten years after the LT^[68,69]. Interestingly, Faure *et al.*^[70] revealed the negative impact of excessive alcohol consumption on survival after an LT irrespective of the primary indication. This emphasizes the importance of detecting this behavior in every LT recipient.

ALCOHOLIC HEPATITIS

Among all of the complications associated with ALD, acute alcoholic hepatitis is one of the deadliest. The standard of care includes 28-d oral steroid therapy for the severe forms of the disease, which are defined by a Maddrey's discriminant function > 32^[71]. Response to this therapy is defined by a seven-day Lille score < 0.45. The six-month mortality is approximately 15% for patients who respond to therapy; it raises to over 75% for non-respondents^[72]. These patients were initially excluded from transplantation programs because their condition implies a lack of abstinence. Based on pathological analyses of the excised liver, some reports have suggested a good outcome after LT; however, these studies did not include pre-LT histological proof of alcoholic hepatitis, and the patients were not prioritized according to the severity of their disease^[73-75], except in one study^[76].

In 2011, a French and Belgian group, led by Mathurin^[77], conducted a trial that included 26 highly select patients suffering from biopsy-proven severe acute alcoholic hepatitis without response to corticosteroids who were listed shortly after the assessment of non-response. After receiving an early LT, the patients' six-month survival increased dramatically to 77%; the control group had a six-month survival of 30%. Only three of the patients resumed drinking, and none experienced graft dysfunction. The inclusion criteria for the early LT were: severe alcoholic hepatitis as the first liver-decompensating event, presence of close supportive family members, absence of severe coexisting or psychiatric disorders, and patient agreement to adhere to lifelong total alcohol abstinence. These stringent selection criteria resulted in less than 2% inclusion of patients in the study. Despite the new wave of controversy caused by this study^[78], many transplant programs decided to accept patients for LT under these conditions^[79]. A clinical trial is currently being conducted to confirm the low relapse rates observed^[80].

OTHER PARTICULAR FEATURES OF ALD PATIENTS AFTER LT

Malignancy risk

It is well established that patients who receive a liver transplant have a 2-3-fold increased risk of developing solid organ cancer; this climbs to 10-30-fold for developing post-transplant lymphoproliferative disorders (PTLD) and skin cancers, when compared to general population^[81-84]. Since the 1990's, several reports have determined that the risk of malignancy for PTLD and solid organ cancer was higher among patients who received a transplant for ALD^[45,46,85,86]. The survival rates are heavily impacted by the occurrence of a non-skin malignancy^[45]. Upper aerodigestive squamous and lung carcinomas are overrepresented in the ALD population after LT, suggesting there is an influence of tobacco consumption. It is unclear whether a relapse in harmful drinking also increases the malignancy risk.

Compliance and rejection rates

Thirty years ago, it was commonly believed that ALD patients would have difficulties following the stringent restrictions required by the immunosuppressive drugs, which would cause low compliance and high rejection rates; however, the situation is more nuanced than this. Indeed, patient compliance is high overall, similar to that found for other indications^[9,59]. Furthermore, data from the 1990's, when tacrolimus was not as widely used as it is now, suggest that ALD patients present lower rates of acute cellular rejection^[21,87]. A relapse to drinking can have two types of consequences for liver rejection. If the relapse is accompanied by a significant reduction in the intake of immunosuppressive drugs, there is an increase in the acute and chronic rejection rates^[63]. By contrast, a return to drinking without discontinuation of medication can lead to lower rejection rates^[88], probably from the effects of alcohol-related immunosuppression.

Neurological complications and depression

The neurological system can be damaged by excessive alcohol consumption, which can manifest in both the central and peripheral nervous systems. Buis *et al*^[89] compared the resulting neurological complications following LT between patients transplanted for ALD or HCV as the primary indication. They found that the ALD patients experienced acute confusion for three or more days more often than the HCV patients (48% vs 6%, respectively, $P < 0.0001$). A shorter duration of sobriety before the LT was a risk factor, and the acute confusion experienced by the ALD patients caused a longer hospital stay. Additionally, ALD increases the risk of posterior reversible encephalopathy syndrome, although this remains an uncommon event^[90].

Finally, in 2011, DiMartini *et al*^[91] reported a prospective study that examined depressive symptoms in ALD patients after LT. They found three different

trajectories of depressive symptoms that evolved within the first year after LT: consistently low depression levels (group 1), initial low depression levels that rose over time (group 2), and high depression levels at all time points (group 3). Interestingly, the ten-year survival rates differed significantly between group 1 (66%) and the other two groups (46% and 43% for groups 2 and 3, respectively). It is still unknown whether the type of depression management employed has an impact because the study was not designed to address this particular matter.

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