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REVIEW

# Liver transplantation in alcoholic patients

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## Summary

Alcoholic liver disease is one of the most common causes of cirrhosis and indications for orthotopic liver transplantation in Europe and North America. The reluctance to transplant alcoholics stems in part from the view that alcoholics bear responsibility for their illness. There is also the perception that the alcoholic person is likely to relapse into alcohol use after transplantation and thereby damage the allograft.

In this review, we considered the evaluation for and outcome of liver transplantation in alcoholics with special attention to the specific risks of alcohol relapse, to show that alcoholism should be considered like other co-morbid states rather than as a moral flaw.

## Introduction

Alcoholic liver disease is one of the most common causes of cirrhosis and indications for orthotopic liver transplantation in Europe and North America [1,2]. It is a paradox, therefore, that the general public, and even medical professionals, continue to question the propriety of providing liver transplantation to alcoholic patients. The reluctance to transplant alcoholics stems in part from the view that alcoholics bear responsibility for their illness [3]. For example, an opinion poll in Great Britain showed that family physicians believed that, given the scarcity of donor organs, alcoholic patients should take lower priority than other candidates, even when the latter had less chance of a successful outcome from transplantation [4]. The conviction that alcoholism is self-inflicted must be reconciled with the strong evidence supporting genetic and environmental influences on alcohol dependence [5]. Alcohol abuse and dependence are diagnoses for which there are established diagnostic criteria such as the DSM-IV diagnostic system [6].

A second source of concern regarding liver transplantation in alcoholics is the perception that the alcoholic person is likely to relapse into alcohol use after transplantation and thereby damage the allograft. Alcohol abuse and dependence may be associated with personality disorders, depression, anxiety, polysubstance abuse and other psychiatric disorders, which may further promote the risk of alcohol relapse [7].

In this review, we will consider the evaluation for and outcome of liver transplantation in alcoholic persons. We will pay special attention to the specific risks of alcohol relapse. In this way, we aim to show that alcoholism should be considered like other co-morbid states such as diabetes mellitus or hypertension rather than as a moral flaw.

## Alcoholic liver disease as an indication for liver transplantation

Alcoholic liver disease ranges from steatosis or steatofibrosis to liver cirrhosis; acute alcoholic hepatitis is a syndrome presenting as acute liver damage following

recent excessive drinking and is associated with a poor prognosis.

### Acute alcoholic hepatitis

A review of the management of acute and chronic alcoholic liver disease is beyond the scope of this paper [8]. Sufficed to say, that many patients with severe alcoholic hepatitis, whether occurring in the previously healthy liver or in patients with established cirrhosis, fail to recover despite abstinence and maximal medical therapy. The severity of acute alcoholic hepatitis is assessed using the Maddrey discriminant function based on prothrombin time and serum bilirubin concentration measured in units of mg/dl [4.6 × (prothrombin time − control prothrombin time) + serum bilirubin]. Values of 32 or greater indicate a high risk of early mortality [9]. The development of acute renal failure in the acute alcoholic hepatitis indicates an especially bad prognosis. Intensive medical management including dialysis, of 15 patients with severe alcoholic hepatitis complicated by renal failure admitted consecutively to a specialist liver unit in Birmingham (UK), was followed by death in 12 of 15 patients, despite renal function recovering in three patients [10]. Most transplant programs in the US and Europe require a minimal interval of abstinence of 6 months before transplanting patients with decompensated liver disease. Conversely, Veldt *et al.* [11] asserted that if there is no substantial improvement by 3 months of medical management including abstaining from alcohol, the chances of spontaneous recovery by patients with acute alcoholic hepatitis and cirrhosis are poor. There is only limited experience of transplantation in patients with acute alcoholic hepatitis and minimal abstinence and the current consensus in most European and North American transplant centers is that patients with acute alcoholic hepatitis should not undergo liver transplantation.

### Alcoholic cirrhosis

Liver transplantation in patients with alcoholic cirrhosis was first acknowledged by the statement of the National Institutes of Health Consensus Conference on Liver Transplantation in 1983: 'patients with alcoholic liver disease who are judged likely to abstain from alcohol and have established clinical indicators of fatal outcome may be candidates for liver transplantation.' [12]. In 1997, a conference on liver transplantation in alcoholic liver disease patients under the auspices of the National Institutes of Health confirmed that the outcome of liver transplantation is positive for most patients with alcoholic cirrhosis and strongly supported efforts to understand the mechanisms leading some patients to relapse and adapting patient management to restrict the risks of relapse and graft loss [13]. The efficacy of liver transplantation for alcoholic cirrhosis was best demonstrated by Poynard who used modeling techniques to show that there was a survival benefit when patients with advanced decompensation (i.e. 11–15 points on the Child-Turcotte-Pugh scoring system) underwent transplantation [14]. There was no survival benefit when alcoholic patients with better compensated liver function were transplanted.

### Alcoholic cirrhosis and hepatitis C virus (HCV)

Chronic HCV infection often co-exists with alcoholic liver disease and the combination may act synergistically to cause liver disease. Patients positive for anti-HCV who drink more than 50 g of alcohol a day develop cirrhosis more rapidly than anti-HCV+ patients with lower alcohol consumption [15]. Consequently, combined alcoholism and HCV infection are common among patients under evaluation for liver transplantation. Indeed, it is incumbent on the transplant center to evaluate for alcoholism in patients wherein HCV is the considered diagnosis, and vice versa. Histological changes of HCV infection are common in the explants and post-transplant biopsies from anti-HCV+ alcoholics who undergo liver transplantation [16].

### Alcoholic cirrhosis and hepatocellular carcinoma

Primary hepatocellular carcinoma may complicate alcoholic cirrhosis and the risk is greater when there is a concomitant chronic viral infection, especially in males [17]. The candidate's management is based on the assessment of the accepted criteria for liver transplantation in the presence of hepatocellular carcinoma [18].

## Assessing the severity of liver disease and timing for liver transplantation

Reference has already been made to the Maddrey Discriminant Function (DF) to stratify patients with acute alcoholic hepatitis according to risk of dying [9]. Assessment of the risk of dying among patients with alcoholic cirrhosis depended, in the past, on the Child-Turcotte-Pugh (CTP) classification. Although the CTP class is a useful method to stratify groups of patients, its utility in assessing individual patients is flawed by subjectivity in assessing ascites or encephalopathy, lack of distinction between patients in that not all CTP class C patients are at equal risk, and the so-called ceiling effect whereby all levels of abnormality above a threshold get the same score. Finally, the CTP class did not recognize the prognostic significance of renal failure in cirrhotics.

In more recent years, a new prognostic system has been developed, called Model for End-Stage Liver Disease (MELD). MELD predicts liver disease severity on the basis of serum creatinine, serum total bilirubin and INR. The MELD system has been adopted by UNOS (the United Network for Organ Allocation) to determine the urgency of patients awaiting liver transplantation in the US. The ability of the MELD score to correctly rank potential liver recipients according to the severity of their liver disease and mortality risk on the waiting list was prospectively applied to estimate 3-month mortality in 3437 adult liver transplant candidates with chronic liver disease on the waiting list between November 1999 and December 2001. Waiting list mortality increased in direct proportion to the MELD score, with a 12% mortality during the 3-month follow-up period. Patients with a MELD score <9 experienced a 1.9% mortality, whereas patients with a MELD score ≥40 had a mortality rate of 71.3%. In this series, alcohol was the cause of liver disease in 27.6% of cases [19]. For any given MELD score, the magnitude and direction of change in the MELD score during the previous 30 days (deltaMELD) was also a significant independent mortality predictor, reflecting liver disease progression and providing additional prognostic information to consider in the further evaluation of liver allocation policy [20]. MELD scores may be calculated using a hand held calculator or by accessing the UNOS website: http://www.unos.org. We would suggest that any cirrhotic patient with a MELD score of 12 or greater should be considered for transplantation.

Previous studies have failed to demonstrate that other clinical manifestations of liver decompensation such as variceal hemorrhage, hepatic encephalopathy, new onset ascites or spontaneous bacterial peritonitis, were independent predictors of survival over and above the MELD score [21]. Nonetheless, the onset of any of these features in an abstinent alcoholic should prompt the managing physician to consider referral to a transplant center.

Two prognostic models have been developed for patients with alcoholic liver disease, the first developed by Poynard, the proportional hazards prognostic model (the Beclere model), using only variables that are readily available to the clinician (serum bilirubin, albumin, age in years and encephalopathy) [22], and the second, the Birmingham model, based on a similar methodology (serum bilirubin, blood urea, serum albumin, ascites, bacterial peritonitis) [23]. Prognostic models are useful in identifying variables associated with a given outcome but must be used with caution in individual patients, as confidence intervals are wide and application of models derived from one population may not be necessarily valid in another group [3].

## Medical assessment of the alcoholic candidate

In addition to evaluating the severity of the liver disease and its complications, the pre-transplant investigation is based on assessing the patient's general health, focusing on conditions and co-morbidities that might limit the potential for successful operation – such as pancreatitis, central and peripheral neuropathy, heart disease, myopathy, renal insufficiency or poor nutritional status [24]. Chronic alcohol consumption is associated with impaired lymphocyte recruitment which may explain the increased morbidity and mortality of pulmonary infections in alcoholic subjects [25]. Tuberculosis might be a risk for alcoholic patients [26] and all candidates evaluated for liver transplantation should have a skin test for reactivity to the purified protein derivative. It is also crucial to rule out any neoplastic disease or pre-neoplastic conditions, since such patients appear to have a higher incidence of certain malignancies after liver transplantation, especially of the upper airways and upper gastrointestinal tract [27].

When hepatocellular carcinoma is suspected, the evaluation is based on several methods, e.g. abdominal ultrasound, CT scan, angiogram, MRI, angio-MRI, alpha-fetoprotein levels. Local ablative treatments such as ethanol injection, radiofrequency ablation, transarterial embolisation with or without chemotherapy may be applicable in selected patients while waiting liver transplantation [28,29] (Table 1).

## Psychological evaluation of the alcoholic candidate

A psycho-social assessment to establish the likelihood of long-term abstinence after liver transplantation should be performed in patients with alcoholic liver disease. It is common practise to evaluate alcohol abuse and dependence according to the well established diagnostic criteria such as the DSM-IV diagnostic system [6]. Since alcohol abuse and dependence may be associated with personality disorders, depression, anxiety, polysubstance abuse and other psychiatric disorders, a psychiatric evaluation may be necessary [7]. The role of the length of pre-transplantation abstinence, the so-called '6-month rule', as predictor of post-transplantation abstinence is still questionable [23,24,30,31]. There is however a subset of patients with end-stage liver disease and alcohol dependence who might be identified before liver transplantation as likely to remain abstinent after liver transplantation. A multidisciplinary approach that evaluate not only medical, but also psychological suitability for liver transplantation is then mandatory.

**Table 1.** Medical assessment of the alcoholic candidate in addition to evaluating the severity of the liver disease and its complications.

| Disease | Assessment |
|---|---|
| Cardiovascular disease | Electrocardiogram, chest X-ray, echocardiography, Holter test, myocardioscintigraphy, dobutamine echocardiography*, cardiac catheterization* |
| Acute and chronic pancreatitis | Abdominal ultrasound, CT scan, pancreatic amylase |
| Central nervous system abnormalities | Electroencephalography<br>Brain imaging (CT scan, MRI)<br>SPECT, PET, BAERS only in selected patients |
| Malnutrition | BMI |
| Upper and lower gastrointestinal neoplasms | Esophagogastroduodenoscopy, colonoscopy |
| Respiratory tract neoplasms | Laryngoscopy, chest X-ray, lung CT scan, bronchoscopy |
| Tuberculosis | Skin test for reactivity to purified protein derivative, chest X-ray, bronchoscopy** |

CT scan, computerized tomography scan; MRI, magnetic resonance imaging; SPECT, single positron emission tomography; PET, positron emission tomography; BAERS, brainstem auditory evoked responses; BMI, body mass index.
*Advisable in suspected miocardial disease or coronary artery disease.
**If tuberculosis is suspected.

## Survival

Several studies have demonstrated that the survival of patients transplanted for alcoholic cirrhosis is comparable with the situation in patients transplanted for nonalcoholic cirrhosis [32]. The experience at Padua is typical in that the cumulative survival rates at 3 and 5 years after transplantation for alcoholic liver disease were identical to those observed in patients transplanted for nonalcoholic liver disease. When the group of alcoholic cirrhosis patients was divided according to anti-HCV positive or negative status prior to transplantation, the cumulative survival was not statistically different [16]. Even the presence of the histological markers for acute alcoholic hepatitis in the explant was not associated with reduced survival after transplantation surgery [33].

## Retransplantation

Retransplantation for alcoholic cirrhosis due to relapsing alcohol consumption after the first transplant is usually not indicated in the majority of centers [34]. One case of retransplantation followed by a good outcome and compliance has been reported, however [35].

## Alcohol use after transplantation

In this review, we will use the term 'relapse' rather than the more pejorative 'recidivism' [36,37]. In studies of alcohol use after liver transplantation, 'relapse' is generally defined as *any* alcohol intake. This is in contrast to studies from the literature on addiction medicine in which success is often defined in terms of relative reduction of drinking and relapse as a resumption of heavy alcohol intake. This semantic distinction signifies a fundamental difference of perspective between liver transplant physicians and surgeons on the one hand, and 'addictionologists' on the other. The latter regard alcoholism as a disorder in which relapse and remission are inevitable, and consequently that complete and absolute abstinence from alcohol an unattainable goal for many patients. Such experts consider significant reductions in alcohol use to be meaningful, whereas the 'transplanters' would still classify such results as failure. This dichotomy of opinion regarding the definition and significance of relapse is well summed up by Fuller who used the analogy of diabetes control when he said that 'in alcoholism, as in diabetes a substantial partial response is better than no response' [38].

Studies which have evaluated relapse into alcohol consumption after liver transplantation for alcoholic cirrhosis have reported a wide range of frequencies ranging from 10% to 50% in up to 5 years follow up [31,39].

There are many flaws in these data. First as mentioned is the reliance on 'any use' to define relapse. Another caveat about these estimates relates to the difficulty of getting accurate data on drinking behavior. Most studies document alcohol consumption after transplantation by retrospective analysis of routine screening tests, questionnaires or interviews with patients and/or family during routine follow up. There is a substantial risk that these methods may underestimate the patient's real drinking habits, partly due to retrospection, but also due to the pressures on patients to deny drinking.

In 51 patients with alcoholic liver disease who underwent strictly medical and psychological evaluation before and after liver transplantation, alcohol abuse was recorder in 60% and alcohol dependence in 40% of them before transplantation. Alcohol relapse was observed in 33% of transplanted patients, 64% of whom were occasional and 36% were heavy drinkers. The admission of alcoholism by the patient and his/her family prior to transplantation significantly predicted abstinence after transplantation [40].

Relapse is considered a shameful behavior, and may lead the transplant program to deny some elements of care to the patient. Indeed it has been argued that the inhibition on candor may be harmful to the well-being of alcoholic transplant recipients [31,41].

Despite these caveats, it makes sense to combine results from many studies and postulate that a third to half the alcoholic transplant recipients start drinking again after transplantation; that about 10% resume drinking in an abusive or dependent fashion and that resumption of alcohol often begins within the first year after surgery [41].

### Histological assessment of alcohol-related liver injury

The prevalence and severity of alcohol-related liver injury after liver transplantation for alcoholic liver disease is not well known and has been reported in only a few studies with serial liver biopsies, the clinical utility of which remains to be seen [42]. In the Padua series, histological liver damage was not as impressive after relapse as in some reports since no cases of cirrhosis were seen [16]. Nevertheless, our data were consistent with others describing fatty liver or steatohepatitis as the main histological features of alcohol relapse, albeit without a discernable influence on clinical outcome [43]. Fatty changes and pericellular fibrosis were significantly more severe in patients who were heavy drinkers than in occasional drinkers and abstainers, but it generally seems that liver damage is slow to develop after alcohol relapse [16]. Since concomitant infection with HCV and/or HBV is common, it should also be said that such histopathological changes are often difficult to interpret in patients transplanted for alcoholic liver disease with concomitant chronic viral disease who resume alcohol consumption [44].

## Treatment of alcoholism

Few studies have attempted to treat alcoholism within the context of liver transplantation. Weinrieb *et al.* found that alcoholic liver transplant recipients usually refused standard treatments for alcoholism [45]. Among the reasons that alcoholic patients gave for refusing treatment were preoccupation with the demands of the transplant, and the conviction by the patient that alcoholism was no longer a problem. We investigated these surprising results further in a case controlled study which demonstrated that alcoholic patients awaiting liver transplantation have less craving for alcohol and less motivation for treatment than typical alcoholics in treatment studies, despite similar lifetime drinking histories [46]. These data explain one of the paradoxes of liver transplantation: namely that the rate of abusive drinking in the first few years is low compared to studies of alcoholism treatment in general. The data suggest that the selection process identifies a cohort of alcoholic patients with favorable prognosis for sobriety. However, the data also point out an inherent difficulty in preventing relapse in this cohort, given their self-belief that their alcoholism is a 'thing in the past'. Future treatment interventions should be directed to sustaining sobriety through medical recovery, and assisting early intervention to ameliorate initial relapses (so-called 'slips').

## Acute and chronic rejection

Alcoholic patients experience fewer episodes of acute cellular rejection after liver transplantation than patients transplanted for other reasons [47,48]. Histologically proven acute cellular rejection was reported in 14% of patients 23–180 days after liver transplantation for alcoholic cirrhosis [16].

Chronic ductopenic rejection is also very uncommon in alcoholics receiving liver transplants. In Padua, since November 1990, 415 patients have undergone 480 liver transplantations. Eighty of whom were transplanted for alcoholic liver disease either alone or in combination with viral hepatitis or hepatocellular cancer. Among 312 long-term survivors, chronic rejection was seen in 6 (5%).

## Medical complications following liver transplantation

Infections are common after liver transplantation for alcoholic liver disease. Bacterial infections seem to be more frequent than in patients transplanted for other causes. The incidence of cytomegalovirus infection was reportedly 14.3% in patients transplanted for alcoholic cirrhosis, which is no different from the 25% incidence observed in patients transplanted for other causes. The incidence of new-onset insulin-dependent diabetes is reportedly less than 10%, while for hypertension it is around 33%, again much the same as in patients transplanted for nonalcoholic liver disease [49].

Many functional alterations in brain physiology in alcoholic cirrhotic patients are reversed after successful liver transplantation, but a reduction in the frontal cerebral blood flow may persist for up to 12 months after surgery [50].

## *De novo* neoplasms

An increased risk of *de novo* malignancies after liver transplantation has been reported to rise from 6% to 55% at 15 years after liver transplantation and to account for a significant risk of late death [51]. An overall incidence of oropharyngeal squamous cell carcinoma of 17% in alcohol-induced cirrhosis transplant patients was reported [52]. In another series of patients who underwent liver transplantation for alcoholic liver disease, an incidence of 4.2% of oropharyngeal and esophageal

malignancies were seen between 8 and 40 months after surgery [27].

## Quality of life and compliance

Whatever the reason for liver transplantation, quality of life improves after surgery in most domains [53]. Overall quality of life and employment levels appear similar between patients transplanted for alcoholic and nonalcoholic liver disease [54] or even better, broadly similar to the levels expected in the normal population [32,55,56]. The relative prognostic importance of minimum abstinence periods, social support, or the psychological profile of alcoholic patients on a return to problematic drinking post-transplantation affecting the quality of life remain unresolved however [55].

Compliance of patients suffering from alcoholic cirrhosis is still under discussion. After liver transplantation no difference between patients with or without alcohol relapse concerning compliance with medication, incidence of rejection or adherence to check-ups were reported [57]. They appear to return to society to lead active and productive lives, despite they seem less likely to be involved in structured social activities than patients transplanted for nonalcoholic liver disease [58].

## Conclusion

In conclusion, alcoholic cirrhosis is a widely accepted indication for liver transplantation, whereas there is only limited experience of transplantation in patients with acute alcoholic hepatitis and minimal abstinence. Consequently, the current consensus is that patients with acute alcoholic hepatitis should not undergo liver transplantation. The outcome of liver transplantation is positive for most patients with alcoholic cirrhosis and a survival benefit is seen when patients undergo liver transplantation with advanced decompensation. The assessment of the risk of dying among patients with alcoholic cirrhosis was based, in the past, on the Child-Turcotte-Pugh classification whereas in more recent years, a new prognostic system has been developed, called Model for End-Stage Liver Disease (MELD) which predicts liver disease severity on the basis of serum creatinine, serum total bilirubin and INR.

Combined alcoholism and HCV infection are common among patients under evaluation for liver transplantation and histological changes of HCV infection are also common in post-transplant biopsies from these patients. In addition, the hepatocellular carcinoma may develop on top of cirrhosis, and in this case the candidate's management is based on the accepted criteria for liver transplantation in the presence of hepatocellular carcinoma. Co-morbidities that might limit the potential for successful operation – such as pancreatitis, central and peripheral neuropathy, heart disease, myopathy, renal insufficiency or poor nutritional status should be assessed during the candidate's management.

A psycho-social assessment to establish the likelihood of long-term abstinence after liver transplantation and a psychiatric evaluation should be performed in all patients with alcoholic liver disease. It is common practice to evaluate alcohol abuse and dependence according to the well established diagnostic criteria such as the DSM-IV diagnostic. The role of the length of pre-transplantation abstinence, the so-called '6-month rule', as predictor of post-transplantation abstinence is still questionable.

The rate of relapse into alcohol consumption after liver transplantation ranges from 10% to 50% in up to 5 years follow up. Survival of patients transplanted for alcoholic cirrhosis is comparable to patients transplanted for nonalcoholic cirrhosis. Although only about 10% of alcoholic liver allograft recipients resume drinking in an abusive or dependent fashion, efforts to restrict the risks of relapse and graft loss are mandatory. Histological changes are usual mild and liver damage is slow to develop after alcohol relapse but fatty changes and fibrosis are more severe in patients who are heavy drinkers than in occasional drinkers and abstainers.

Alcoholic patients experience fewer episodes of acute cellular rejection after liver transplantation than patients transplanted for other reasons and chronic ductopenic rejection is also very uncommon. Conversely, infections are common after liver transplantation for alcoholic liver disease as well as the development of *de novo* malignancies.

Finally, the quality of life and employment levels appear similar or even better between patients transplanted for alcoholic and nonalcoholic liver disease, whereas the compliance of such patients is still under discussion despite no difference between patients with or without alcohol relapse concerning compliance with medication, incidence of rejection or adherence to check-ups have been reported.

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