

## WJG 20<sup>th</sup> Anniversary Special Issues (10): Alcoholic liver disease

# Challenges in transplantation for alcoholic liver disease

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alcohol relapse at an early stage, thus permitting the initiation of adequate treatment. Patients with alcoholic cirrhosis are at high risk of developing head and neck, esophageal, or lung cancer. The higher risk of malignancies should be considered in the routine assessment of patients suffering from alcoholic cirrhosis. Tumor surveillance protocols for liver transplant recipients, currently being developed, should become a part of standard care; these will improve survival by permitting diagnosis at an early stage. In conclusion, the key factor determining the outcome of transplantation for alcoholic cirrhosis is intensive lifelong medical and psychological care. Post-transplant surveillance might be much more important than pre-transplant selection.

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**Key words:** Alcoholic liver disease; Liver transplantation

## Abstract

Transplantation for the treatment of alcoholic cirrhosis is more controversially discussed than it is for any other indication. The crucial aspect in this setting is abstinence before and after liver transplantation. We established pre-transplant selection criteria for potential transplant candidates. Provided that the underlying disease can be treated, there is no reason to withhold liver transplantation in a patient suffering from alcoholic cirrhosis. Evaluation of the patient by a multidisciplinary team, including an addiction specialist, is considered to be the gold standard. However, several centers demand a specified period of abstinence - usually 6 mo- irrespective of the specialist's assessment. The 6-mo rule is viewed critically because liver transplantation was found to clearly benefit selected patients with acute alcoholic hepatitis; the benefit was similar to that achieved for other acute indications. However, the discussion may well be an academic one because the waiting time for liver transplantation exceeds six months at the majority of centers. The actual challenge in liver transplantation for alcoholic cirrhosis may well be the need for lifelong post-transplant follow-up rather than the patient's pre-transplant evaluation. A small number of recipients experience a relapse of alcoholism; these patients are at risk for organ damage and graft-related death. Post-transplant surveillance protocols should demonstrate

**Core tip:** Transplantation for the treatment of alcoholic cirrhosis is more controversially discussed than it is for any other indication. The greatest concern in this setting is abstinence before and after liver transplantation. The outcome of liver transplantation for alcoholic cirrhosis appears to be determined by the risk of malignancy and cardiovascular disease rather than the relapse of alcoholism after transplantation. A review of the most recent literature on this subject disclosed problems associated with alcoholic liver disease as an indication for transplantation.

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## INTRODUCTION

Alcoholic cirrhosis is a leading cause of end-stage liver disease and the second most common indication for liver

transplantation in the Western world<sup>[1,2]</sup>. Liver transplantation is a standard treatment and, in fact, the only option for saving the lives of patients with end-stage liver disease. With the exception of the brain, the liver is the only vital organ for which no artificial substitute is available. Although liver transplantation is a life-saving treatment for many indications, the fact of organ shortage makes it accessible to no more than a selected group of patients. Widely accepted disease-specific selection criteria exist for the majority of indications, but the selection of alcoholic candidates remains controversial. These patients constitute a challenge because of several pre-, intra- and post-transplant issues, many of which are induced by their alcohol abuse<sup>[3]</sup>.

## SELECTION OF POTENTIAL CANDIDATES FOR TRANSPLANTATION - ASSESSMENT OF ADDICTION

Alcoholism is a lifelong disease, frequently marked by episodes of relapse and a poor likelihood of sustained sobriety<sup>[4]</sup>. One problem is inconsistency in the definition and interpretation of alcoholism, which ranges from “any consumption of alcohol” to “only harmful drinking”<sup>[5]</sup>. Based on the widely used definition, published rates of alcohol relapse are subject to over-estimation as well as under-estimation. Besides, a follow-up period exceeding 5 years has been reported in no more than a handful of studies.

Alcoholism is the underlying disease in patients suffering from alcoholic cirrhosis. In fact, cirrhosis in this setting is a secondary complication. Provided that the underlying disease can be treated, there is no reason to withhold liver transplantation in a patient with alcoholic cirrhosis. The debate derives from the widespread opinion that alcoholism is not a disease but a fault. This opinion prevails in the public as well as among medical professionals<sup>[6]</sup>. Our knowledge of alcoholism has been greatly enhanced in the last few decades by informative campaigns and education.

The alcohol dose required for liver injury may differ from person to person<sup>[7]</sup>. The inability to keep alcohol consumption within safe limits is partly determined by genetic factors<sup>[8]</sup>. Progression to alcoholic cirrhosis is also influenced by genetic polymorphism, related to alcohol-mediated initiation of inflammation and fibrogenesis<sup>[9]</sup>.

The controversy about alcoholic cirrhosis as an indication for liver transplantation is fostered by the shortage of donor livers. Given the discrepancy between available organs and potential recipients, selection criteria need to be established for all indications and potential candidates. Unequivocal selection criteria will permit a clear distinction between the usefulness and futility of the procedure, as well as provide favorable long-term outcomes after transplantation.

Uniform disease-specific selection criteria do not exist for patients with alcoholic cirrhosis. Evaluation by a

multidisciplinary team including an addiction specialist is the gold standard, but several centers demand a specified period of abstinence (usually 6 mo) irrespective of the specialist's assessment<sup>[7,10]</sup>.

An interval of sobriety prior to transplantation is very desirable from the medical point of view. Abstinence may improve liver function most markedly. However, with regard to alcoholism, a mandatory period of abstinence as such is a poor predictor of the risk of relapse<sup>[11,12]</sup>. Pre-transplant abstinence does not reliably predict post-transplant abstinence or compliance. Besides, we have no published national or international guidelines concerning the duration of abstinence for liver transplantation<sup>[13]</sup>. The most commonly used cut-off period of 6 mo is arbitrary and by no means based on evidence. According to publications on alcohol dependence outside the setting of liver transplantation, sobriety becomes robust only after 5 years of sustained abstinence<sup>[4]</sup>.

The term *addiction* is not easily defined. It does not merely refer to the violation of a specified period of abstinence from substance abuse. Assessment by a substance abuse professional will identify protective and/or negative prognostic factors. Patients living in social isolation, with a family history of alcoholism, repeated attempts at rehabilitation, uncontrolled polysubstance abuse, and unstable character disorders are clearly associated with a poor prognosis<sup>[14,15]</sup>. On the other hand, a potential candidate with social support, sources of improved self-esteem and a future-oriented approach may well experience a successful outcome after liver transplantation<sup>[4,16]</sup>.

In a multivariate analysis, Pfitzmann *et al*<sup>[17]</sup> established similar risk factors for recurrent alcohol consumption (divorce, a poor psychosomatic prognosis), but this is one of the few publications in which a sobriety period < 6 mo prior to transplantation was identified as a risk factor. However, this may have been due to observational bias or the retrospective design of the study. Living in a household with underage children was another surprising risk factor reported in this publication.

Patients with alcoholic cirrhosis should be assessed by a multidisciplinary approach, including an evaluation by a medical specialist as well as an addiction specialist in order to identify those at high risk of relapse<sup>[11,18]</sup>.

## ALCOHOL-BASED COMORBIDITIES

Chronic consumption of alcohol damages liver parenchyma and also exerts adverse effects on other organ systems. Any evaluation of a patient for liver transplantation should include screening for comorbidities and extra-hepatic alcoholic organ damage<sup>[10]</sup>.

### *Alcoholic cirrhosis and the heart*

Excessive use of alcohol may affect the heart as well<sup>[19]</sup>. Patients with no signs or symptoms of heart disease may have demonstrable evidence of asymptomatic myocardial disease<sup>[20]</sup>. The identification and treatment of alcohol-

associated cardiac issues is critical in the pre-, intra- and perioperative phase of transplantation<sup>[3]</sup>. Subclinical cardiac disease influences the risk of surgery and long-term outcome.

Preoperative evaluation of cardiac function is facilitated by characteristic hemodynamic changes associated with portal hypertension<sup>[21]</sup>, increased cardiac output, systolic and diastolic dysfunction, and electrophysiological abnormalities<sup>[22]</sup>. Patients with Child-Pugh C have the greatest hemodynamic derangements and are most difficult in terms of intraoperative management.

Patients with alcoholic liver disease were considered to be relatively well protected from coronary artery disease. However, the protective effect of moderate drinking is not only dose dependent, but is also significantly modified by gender<sup>[23]</sup>. A large number of recipients who are heavy drinkers are also erstwhile heavy smokers. Both conditions jointly signify an additional risk factor for coronary artery disease.

According to the American Association for the Study of Liver Diseases practice guidelines for the evaluation of patients for liver transplantation, a person with any one of the following characteristics is considered to be at high risk for coronary artery disease: smoker, age > 50 years, diabetes mellitus, history of coronary artery disease, or a positive family history. Candidates with a high-risk profile should undergo screening including a dobutamine stress echocardiogram. If the latter is positive, a coronary angiography should be performed<sup>[24]</sup>.

Cardiovascular complications are a leading cause of non-graft-related death in the post-transplant period<sup>[19,25]</sup>. The risk of cardiovascular disease increases in direct proportion to the improvement of long-term survival among liver transplant recipients. This is mainly due to the adverse effects of prolonged immunosuppressive treatment, which include hypertension, diabetes, dyslipidemia, and obesity. All of these conditions constitute risk factors for cardiovascular events. Patients undergoing transplantation for alcoholic cirrhosis are at significantly higher risk of cardiovascular mortality<sup>[26]</sup>.

### **Alcoholic cirrhosis and the brain**

Chronic alcohol consumption and liver disease are independent factors associated with impaired neuropsychological function, which is manifested by deficits in attention and concentration, memory and learning, mental efficiency, abstract reasoning, and motor skills<sup>[27]</sup>. These deficits are associated with the quantity and duration of alcoholism; cognitive deficits resolve after cessation of alcohol use<sup>[28]</sup>. Neuropsychological impairment may be a confounding factor when it occurs in the presence of an alcohol-related disorder and end-stage liver disease; in this setting it is mainly triggered by the severity of liver disease<sup>[29]</sup>.

Patients with alcoholic liver disease experience improvement of many neuropsychological symptoms after liver transplantation, but the outcome might be poorer than it is after liver transplantation for other indications<sup>[27]</sup>.

Peripheral neuropathy is not uncommon in patients with end-stage liver disease, irrespective of the etiology. It does not seem to be associated with an adverse outcome and is known to improve after liver transplantation<sup>[11]</sup>.

### **Alcoholic cirrhosis and malignancies**

Liver cirrhosis of any etiology is a major risk for hepatocellular carcinoma (HCC). The mechanisms that contribute to HCC in patients with cirrhosis are complex, including telomere shortening, loss of cell cycle functions, and the activation of oncogenic pathways<sup>[30]</sup>. Certain unique mechanisms contribute to the development of HCC in alcoholic cirrhosis<sup>[31,32]</sup>, including the formation of acetaldehyde, a carcinogen with mutagenic properties, and the immunosuppressive effect of alcohol.

*De novo* head and neck malignancies - including esophageal cancer - occur at a higher rate after transplantation in patients with alcoholic liver disease<sup>[3,33,34]</sup>. Previous alcohol abuse was shown to be associated with a three-fold higher risk of *de novo* tumor after liver transplantation<sup>[33,34]</sup>. The mean period of time until diagnosis has been reported to range between three and five years after liver transplantation<sup>[34-36]</sup>.

Apart from the universally accepted detrimental effect of smoking on cardiovascular mortality, its role in malignancy after liver transplantation - especially lung cancer - is becoming increasingly evident<sup>[37]</sup>. According to van der Heide *et al*<sup>[38]</sup>, at 10 years smoking significantly increases the risk of non-skin malignancies to 13%, compared to 2% in non-smoking recipients. The mean period of time until the identification of lung cancer in liver transplant recipients ranged from 3.5 to 4 years. Lung cancer was usually diagnosed in an advanced stage and has been associated with a poor prognosis<sup>[35,39]</sup>. It is difficult to distinguish between the effects of alcohol abuse and those of smoking because patients with alcoholic cirrhosis tend to be heavy smokers as well<sup>[40]</sup>. A significantly higher incidence of lung and oropharyngeal cancer has been registered in (previous) smokers undergoing transplantation for alcoholic cirrhosis than in the general population<sup>[34,37,40]</sup>.

The high risk of malignancies should be considered in the routine assessment of patients suffering from alcoholic cirrhosis. Tumor surveillance protocols are currently being developed for liver transplant recipients. These should become a part of standard care<sup>[40-42]</sup>. Tumor surveillance protocols will improve survival by permitting detection of the disease at an early stage.

## **INCIDENCE AND IMPACT OF ALCOHOL RELAPSE**

Relapse of alcoholism among patients undergoing liver transplantation for alcoholic cirrhosis is reported to occur at diverse rates of 10%-50%<sup>[12,14,15,17,43,44]</sup>. Tome and Lucey presented an excellent summary of salient publications on alcohol relapse after liver transplantation<sup>[45]</sup>. With regard to alcohol relapse and the duration of follow-up, relapse rates were consistently about 30% in studies com-

prising more than 5 years of follow-up, whereas relapse rates were below 20% in studies with a shorter follow-up period. However, it should be noted that the above mentioned analysis was published 10-20 years ago; a multidisciplinary transplant team including an addiction specialist was not available in all centers at the time.

In 1994 we reported a relapse rate of 32%<sup>[46]</sup>. A few years later, after a specialist psychologist became a permanent member of our transplant team and was involved in pre-transplant evaluation as well as post-transplant care, the relapse rate dropped to 13%<sup>[47]</sup>. Careful patient selection as well as pre- and post-transplant counseling may minimize the relapse of alcoholism after liver transplantation<sup>[3,47]</sup>. Early identification and monitoring of alcohol relapse are essential determinants of the long-term outcome of transplantation. Biochemical tests are considered less sensitive than questionnaires in screening for alcohol abuse, but may be useful in identifying relapse<sup>[48-50]</sup>.

Close monitoring of patients transplanted for alcoholic cirrhosis by addiction specialists might not be feasible. Carbohydrate-deficient transferrin (CDT) was identified as a useful monitoring marker for alcohol relapse in patients after liver transplantation because it permits selection of those patients who need special attention from the psychologist<sup>[49]</sup>. CDT, a biological marker for alcohol abuse, was found to be independent of the severity of liver disease. In the psychiatric literature, CDT is reportedly not influenced by clinical events<sup>[51]</sup>. However, the severity of liver disease might differ significantly in patients referred for liver transplantation compared to patients undergoing long-term treatment by an addiction specialist. The loss of functioning hepatocytes in cirrhosis is associated with impaired cellular activity, potentially affecting one or more steps of CDT metabolism. Thus, CDT is of limited use as a pre-transplant screening marker for the selection of potential transplant candidates suffering from alcoholic cirrhosis<sup>[52]</sup>.

A large body of evidence has shown that non-compliance with immunosuppressive drugs is associated with a high risk of late acute rejection. Drug non-compliance in conjunction with alcohol relapse is controversially discussed, as is the impact and degree of injury to liver parenchyma due to alcohol relapse<sup>[47,53-55]</sup>. Published data concerning the impact of alcohol relapse on patient survival are inconsistent. In most studies, patient survival was not influenced by recurrent alcohol abuse, regardless of whether liver injury - including fibrosis - was detected on histological investigation. A handful of single-center studies reported reduced patient survival in patients suffering relapses of alcoholism<sup>[17,43,44]</sup>. The cause of death in these patients was predominantly related to the liver, whereas the causes of death in abstinent patients were mainly cardiovascular disease or malignancy.

Irregular follow-up and non-compliance with therapy are observed in a minority of patients. Graft rejection rates are similar or even less in patients transplanted for alcoholic cirrhosis compared to those transplanted for

other indications<sup>[47,56,57]</sup>.

## OUTCOME AFTER LT FOR ALCOHOLIC CIRRHOSIS COMPARED TO OTHER INDICATIONS

Five- and 10-year patient survival rates after liver transplantation for alcoholic cirrhosis in Europe are 73% and 58%, respectively<sup>[2]</sup>.

Overall survival rates in patients undergoing liver transplantation for alcoholic cirrhosis did not differ from those in patients transplanted for most other indications, and were better than those for patients with HCV<sup>[1]</sup>. The reasons for death after transplantation differ in recipients with alcoholic cirrhosis. In a retrospective analysis of the European Liver Transplant Registry, cardiovascular causes and *de novo* malignancies were significantly overrepresented in these patients<sup>[2]</sup>. Similar results were registered in a large single-center series: 1-, 5-, and 10-year survival rates were 96%, 88% and 76%, respectively, in patients transplanted for alcoholic cirrhosis; and 97%, 80%, and 72%, respectively, for other patients<sup>[17]</sup>. Recurrent alcoholic liver disease was the cause of death in 87.5% (14 of 16) of patients who returned to heavy drinking. Patients with non-abusive drinking behavior or abstinent patients died mainly due to infection, malignant tumor, or cardiovascular disease<sup>[17]</sup>.

Dumortier *et al*<sup>[58]</sup> reported a similar patient survival rate of > 70% at 10 years after liver transplantation. The male gender, a history of smoking, and *de novo* malignancies were identified as significant prognostic factors for survival, but were not modified by alcohol relapse after transplantation.

In contrast, Cuadrado *et al*<sup>[44]</sup> registered a significantly lower 10-year survival rate in patients suffering an alcohol relapse (45% *vs* 85.5%). No significant association was observed between recurrent alcoholism and graft rejection, infection, liver transplant-associated comorbidities, or compliance. The lower survival rate was attributed to more numerous deaths due to cancer and cardiovascular disease.

## ALCOHOLIC HEPATITIS

Historically, patients suffering from acute alcoholic hepatitis have been rejected as candidates for liver transplantation because they do not fulfill disease-specific selection criteria. First, a severely ill patient cannot undergo a psychological evaluation. Second, the patient's addiction cannot be treated. Third, the potential recovery of the liver cannot be monitored<sup>[59,60]</sup>. Six-month mortality rates exceed 70% in patients with severe alcoholic hepatitis and failed medical therapy<sup>[61]</sup>. In fact, the use of liver transplantation in this setting is under discussion and revision<sup>[62]</sup>. According to the EASL therapeutic algorithm, liver transplantation is a treatment option in selected patients with alcoholic hepatitis<sup>[7]</sup>. In retrospective stud-



ies, small cohorts of patients transplanted for alcoholic cirrhosis had similar patient and graft survival rates as did those in a matched control population<sup>[63,64]</sup>.

The retrospective diagnosis of alcoholic hepatitis in explant histology is clearly different from the patient presenting with acute clinical symptoms of alcoholic hepatitis. Mathurin *et al*<sup>[65]</sup> recently published a prospective pilot study of liver transplantation as rescue treatment for severe alcoholic hepatitis resistant to steroid therapy. All potential candidates had a normal psychosocial profile. Selection required the consensus of a multidisciplinary team, the patient, and his/her family. The 6-mo survival rate after transplantation was 78%, compared to 24% in historical controls undergoing standard treatment. The clear benefit of liver transplantation in acute alcoholic hepatitis is comparable to the results of liver transplantation for other acute indications. This subgroup constituted less than 3% of all liver transplants during the study period. Prospective studies will be needed to explore the impact of waiting lists, post-transplant outcomes, and ethical issues by extending the indications for liver transplantation to include alcoholic hepatitis.

## CONCLUSION

Transplantation for the treatment of alcoholic cirrhosis has caused greater debate and controversy than transplantation for any other indication<sup>[66]</sup>. The greatest concerns in this setting are related to abstinence before and after liver transplantation. Patients may resume alcohol abuse after transplantation, resulting in non-compliance with immunosuppressive treatment, direct hepatotoxic effects, graft loss, or death. However, no evidence has been obtained yet for any of these conditions.

Furthermore, no clear rationale has been established yet for a specified period of abstinence before LT. As the 6-month period is not based on prospective data but on custom and practice, its validity has been questioned. However, a period of abstinence may be necessary to permit spontaneous recovery. It will also give professionals sufficient time to work with patients and assess the likelihood of compliance with post-transplant requirements. This period is currently ensured by the waiting time, which exceeds 6 mo at the majority of centers. As there is widespread agreement on the need for pre-transplant assessment by a multi-disciplinary team including an addiction specialist, the discussion concerning a fixed period of abstinence before transplantation may well be irrelevant in clinical practice. The 6-mo rule certainly cannot be used for patients suffering from acute alcoholic hepatitis. The clear benefit of liver transplantation in this setting was demonstrated in selected patients to a similar degree as it was for other acute indications. Thus, alcoholic hepatitis appears to be of increasing clinical relevance.

Screening for malignancies before listing for transplantation is a standard procedure. Established guidelines exist for this purpose and are followed at the majority of

centers.

The real challenges in liver transplantation for alcoholic cirrhosis pertain to long-term post-transplant follow-up. Despite routine follow-up, special surveillance protocols have to be established for these recipients, especially with reference to screening for oropharyngeal and pulmonary malignancies. The greatest challenge is the implementation of a psychological surveillance protocol for sobriety in order to detect and treat alcohol relapse at a very early stage and thus prevent organ damage. Long-term psychological surveillance after transplantation is offered at a very small number of centers. This is mainly due to restricted resources and because the patient may not be followed at the transplant center. The key determinant of excellent outcomes in transplantation for alcoholic cirrhosis is intensive lifelong medical and psychological care. Post-transplant surveillance might be much more important than pre-transplant selection.

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