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TOPIC HIGHLIGHT

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Liver transplantation for alcoholic liver disease

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Abstract

Alcoholic liver disease (ALD) is the second commonest indication for liver transplantation after viral hepatitis in the United States and Europe. Controversies surround the indications and allocation of scarce and expensive resource for this so called self inflicted disease. Controversies stem from the apprehension that alcoholic recipients are likely to relapse and cause damage to the graft. There is a need to select those candidates with lower risk for relapse with the available predictive factors and scores. Substance abuse specialist and psychiatrists are mandatory in the pre-transplant evaluation and in the post-transplant follow-up. There is conflicting evidence to support a fixed period of pretransplant abstinence, although most units do follow this. Alcoholic hepatitis (AH) continues to be a contraindication for transplantation, however there is a need for further research in this field as a subset of patients with AH who do not respond to medical treatment, have high early mortality and could benefit from transplantation. One year, 3-year, and 5-year survival post-transplant is similar for both ALD and non-ALD recipients. The incidence of post-transplant rejection and retransplantation is also similar to other recipients. ALD with viral hepatitis especially hepatitis C virus leads to a more aggressive liver disease with early presentation for transplantation. ALD patients are more prone to develop *de-novo* malignancy; this is attributed to the long term effect of alcohol, tobacco combined with immunosuppression. Post-transplant surveillance is important to detect early relapse to alcoholism, presence of *de-novo* malignancy and treat the same adequately.

Key words: Alcoholic liver disease; Orthotopic liver transplantation; Pre-transplant abstinence; Acute alcoholic hepatitis; *De-novo* malignancy; Predictors of relapse; Alcoholic liver disease; Hepatitis C virus

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INTRODUCTION

Alcoholic liver disease (ALD) is one of the leading causes of chronic liver disease and accounts for 50% of deaths from end stage liver disease (ESLD) in western countries[1]. It is the main indication for orthotopic liver transplantation (OLT) in males and after viral hepatitis, is the second commonest indication overall in the United States and Europe[2] (Figures 1-4). ALD accounts for approximately 17%-25% of all transplants performed in the United States and Europe[3,4]. Without transplant 5-year survival in patients with ALD is as low as 23% which improves to 88% with OLT[1,5].

OLT for ALD continues to be controversial because of the ever increasing demand for donor organs and the inadequate rate of organ donation, combined with the

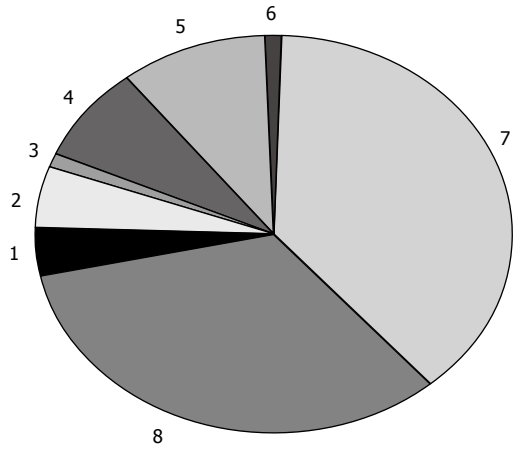
concern that alcoholic patients might relapse to drinking, thereby damaging the transplanted liver. There was an apprehension that the outcome of transplantation in these patients may not be as expected in other indications for OLT. In the initial reports, post-transplantation survival in ALD was poor (20% at 3 years), which was attributed to excessive alcohol consumption causing significant extra-hepatic organ damage, such as pancreatitis, cardiomyopathy, and cerebral dysfunction. Poor nutritional state along with the above co-morbidities was thought to impair the chances for post-transplantation survival[6]. However, there is increasing evidence that most ALD patients selected for transplantation have similar, if not better survival than those who undergo transplantation for other indications (1 year survival of 86% and 5 years survival of 74%)[7].

Patient selection for liver transplantation has always been a demanding responsibility for the transplantation professional. Less than 4% of patients with cirrhosis due to alcohol were listed in the United States in 2007. This pattern of referral may lead to as many as 12000 deaths per year[8,9]. Reasons for poor referral of these patients are multi-factorial and occur at all levels. Poor patient self identification, referring clinician misinformation, delayed intervention in alcohol cessation and counselling, premature and absolute attribution of liver disease to another aetiology (hepatitis C/B) are just some of the factors limiting effective management of alcohol related cirrhosis[4,10,11].

HISTORICAL PERSPECTIVE

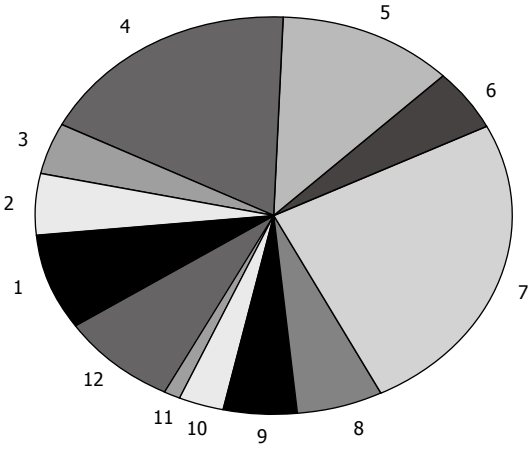
The National Institute of Health (NIH) Consensus Conference on Liver Transplantation in 1983 concluded that ALD is an appropriate indication for OLT, provided the patient is judged likely to abstain from alcohol after transplantation[12]. Following this, there was an increase in the number of transplants being performed for ALD. Starzl *et al*[13] reported that 73% of ALD patients who received a liver transplant were surviving 1 year following the procedure and that only 3% of those patients had relapsed to alcoholism. This was a convincing argument in favour of OLT for ALD patients. The Health Care Financing Administration in 1991 identified ALD as one of the seven conditions for which it approved payment for OLT, but it recommended a "significant" period of abstinence for alcoholics before undergoing the procedure as well as the availability of a reasonable social support system. Beresford *et al*[14] proposed a selection method to identify alcoholic patients suitable for OLT. Lucey *et al*[15] reported on a multidisciplinary collaboration of transplant hepatologists, surgeons and psychiatrists that identified psychosocial predictors of long term sobriety and compliance after OLT in alcoholics.

The NIH workshop in 1996 on OLT for patients of ALD concluded that liver transplantation provides a good outcome in alcoholic patients and that relapse rates after OLT were lower if the patient had successfully completed conventional alcohol rehabilitation program prior to OLT[2].



1 Viral + alcoholic 1759 (4%)
2 Autoimmune 1786 (5%)
3 Secondary biliary 495 (1%)
4 Unknown causes 3274 (8%)
5 Primary biliary 4277 (10%)
6 Others 531 (1%)
7 Virus related 15936 (38%)
8 Alcoholic 13638 (33%)

Figure 1 Indications for orthotopic liver transplantation according to the European Liver Transplant Registry (2008). Alcoholic liver disease (ALD) was an indication in 33%, 4% had combined aetiology of ALD and hepatitis C/B.



1 Cryptogenic 8140 (8%)
2 Cong cholestasis 5261 (5%)
3 Metabolic dis 3967 (4%)
4 Others 17384 (18%)
5 Alcoholic 11641 (12%)
6 Alcoholic + HCV 4946 (5%)
7 Viral 24762 (25%)
8 PSC 5918 (6%)
9 PBC 4932 (5%)
10 Autoimmune 3314 (3%)
11 Sec biliary 586 (1%)
12 Malignancy 8360 (8%)

Figure 2 Indications for orthotopic liver transplantation according to the United Network for Organ Sharing (2009) data. ALD was an indication in 17% of recipients, 5% had combined indication of ALD and viral cirrhosis. HCV: Hepatitis C virus; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis.

ABSTINENCE BEFORE TRANSPLANTATION

Since Starzl *et al*[13] first reported on transplantation for ALD, the evidence has continued to strengthen the merit in selecting appropriate ALD candidates for transplantation[16]. Nevertheless the issue of which candidates are considered "appropriate" remains a topic of debate[17]. Without known exception, what has been accepted as standard across trans-

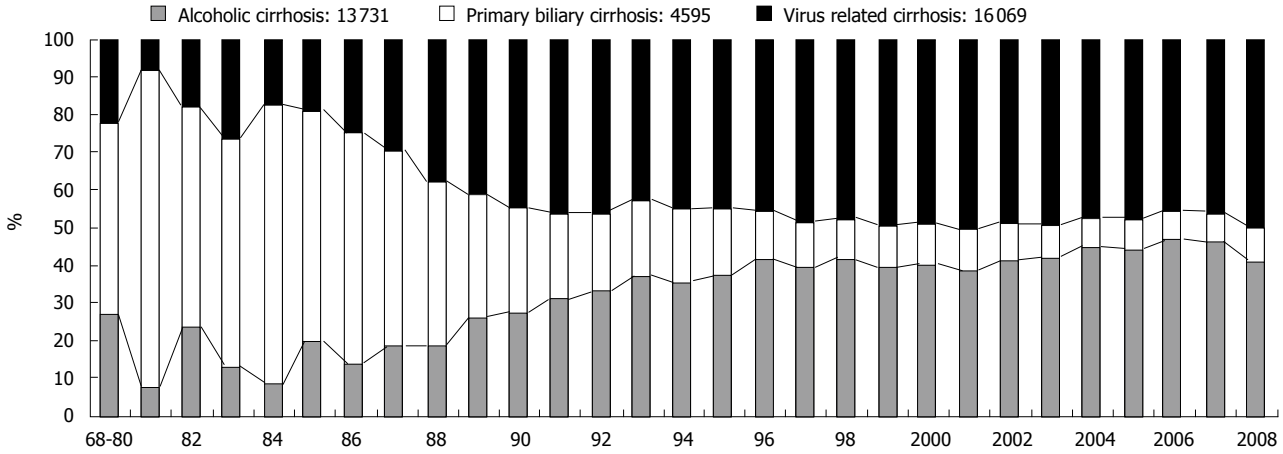


Figure 3 Evolution in the indication for orthotopic liver transplantation in European Liver Transplant Registry (2008), alcoholic liver disease is the second common indication after viral cirrhosis.

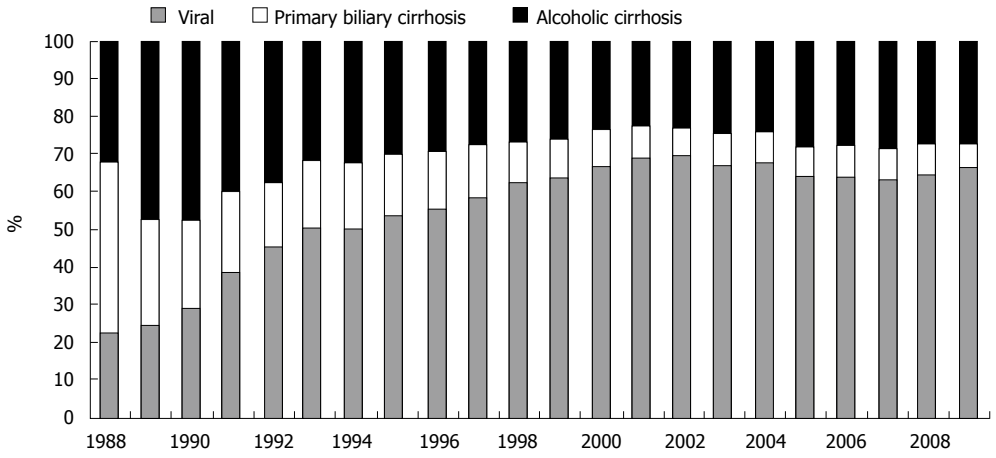


Figure 4 Evolution in the indications for orthotopic liver transplantation in the United Network for Organ Sharing (2009) data, viral cirrhosis and alcoholic liver disease are the main indications.

plant centres has been the insistence on abstinence from alcohol at the point of listing[18,19], however, the debate on the required length of pretransplant abstinence continues.

Pretransplant abstinence broadly achieves two goals; it allows a window of opportunity for the liver to stabilize, and it allows opportunity to examine the patient's commitment. This period of abstinence is important as it not only gives time for the addiction team to assess the patient and organise any support measures, it also improves the patient's condition in so much so that a few of them may no longer require transplantation. Many transplant programs (85%) in the United States require 6 mo of abstinence before transplantation[20]. About 75% of centres would expect the patients to sign a formal contract, in addition, for alcohol rehabilitation. This has however changed after 2005, following UNOS and French Consensus Conference on LT, in view of absence of enough evidence to support the 6 mo sobriety[21]. It is unclear whether this is an effective predictor for post transplant abstinence or simply a method of consistent selection - popular with insurance companies. Pfitzmann *et al*[5] in their study identified less than 6 mo period of abstinence prior to LT as a significant factor associated with relapse to harmful drinking, which was an important factor associated with reduced long term survival. Six months abstinence is mandatory in their centre before listing for LT. Gedaly *et al*[22] in a large retrospective study identified a significant association between post-transplant relapse and less than 12 mo of sobriety before transplantation. Many liver transplant programs in Europe also require pre-transplant abstinence of 6 mo to a year.

Even where there is evidence that shorter prelisting abstinence correlates to shorter time to first drink post transplant, an optimal period of pretransplant abstinence remains unclear[20,22-24]. According to the Liver Advisory Group in the United Kingdom, a fixed period of abstinence allows the addiction team to assess the patient and also provides an opportunity for improvement in these patients with ALD. UK guidelines propose that both length and context of abstinence are among factors to be considered in the wider psychosocial assessment and literature appears to support this approach[19,20,22-26] (Appendix-1[23]).

There is controversial evidence to suggest that patients with family history of alcoholism have an increased rate of relapse[8,25,27]. However, there is no strong evidence to suggest that patients of ALD with no family history of

alcoholism should be listed notwithstanding the period of abstinence.

INDICATIONS FOR OLT

Indications for OLT in patients with ALD are not different from any other cause of end stage liver disease. Minimal listing criteria include a Child-Turcotte-Pugh score greater than or equal to 7, an estimated 1 year survival without transplantation to be less than 90%, single episode of spontaneous bacterial peritonitis or the presence of stage Ⅱ hepatic encephalopathy in the presence liver failure. Allocation of organs is according to the Model for End-Stage Liver Disease regression equation which takes into account serum bilirubin, serum creatinine, and international normalized ratio and calculates a score which predicts 3 mo survival[28]. The UK Liver Transplant Units have developed a new scoring system to predict the waiting list mortality, the UKELD score (United Kingdom Model for end-stage liver disease) which is calculated from the patient's serum bilirubin, INR, creatinine and sodium. A UKELD score more than 49 is a predictor of greater than 9% 1-year mortality and is the minimum criteria for entry to the waiting list under this category. This scoring system is being followed for listing patients for OLT throughout UK liver Transplant Units[26,29,30].

The contraindications to listing were those factors which would result in poor outcome for the graft. (1) Alcoholic hepatitis (AH) which is a clinical syndrome of jaundice and coagulopathy in the presence of active alcohol intake and not a histological diagnosis is a contraindication for listing; (2) Repetitive episodes (more than 2) of noncompliance with medical care where there was no satisfactory explanation. This should not be confined to management of their liver disease; (3) Return to drinking following full professional assessment and advice (this includes permanent removal from the list if found drinking while listed); and (4) Concurrent or consecutive illicit drug use.

Once the multi-disciplinary team (MDT) opines that the patient is to be listed, then the patient is asked to sign an agreement that they will continue to abstain from alcohol in the post transplant period and will comply with follow-up. Signing of agreement is not being followed universally in all the transplant centres.

Immediate vs delayed listing

It is universally recognised that liver transplantation improves survival in patients with end stage liver disease due to alcoholic aetiology. However, for those patients whose liver function would spontaneously improve with alcohol withdrawal and conservative treatment there are no studies to compare the outcome of liver transplantation *vs* conservative treatment, especially so for patients with Child-Pugh stage B cirrhosis. It is important in an era of organ shortage to recognise which group of patients could be offered standard treatment and which group of patients should be immediately listed. The present system of organ allocation in the United States and Europe gives highest priority to the sickest patients. There have been proposals that outcome in these patients would be better if they were transplanted in the earlier stage of the disease and that this might reduce the mortality of patients on the waiting list. We have the results of a recently conducted multi centre randomized controlled trial which compared immediate listing for liver transplantation *vs* standard care for patients with Child-Pugh Stage B alcoholic cirrhosis. Patients on standard care were listed for transplantation once they progressed to Child-Pugh stage C cirrhosis[31].

This study provides four relevant results: (1) Immediate listing for liver transplantation was not associated with improved survival in patients with Child-Pugh stage B alcoholic cirrhosis. Available medical therapies are effective in preventing death not only in patients with Child-Pugh stage C disease but in those at earlier stages as well. Immediate listing for liver transplantation was in itself ineffective in preventing liver-related mortality; (2) Patients who received liver transplantation had an unexpectedly high rate of *de-novo* extrahepatic cancer, which included many upper aerodigestive tract neoplasias. These are known to be associated with alcohol intake and smoking. The occurrence of these tumors was associated with high risk of mortality. This was a deleterious effect of transplantation and immunosuppressive agents; (3) Patients with continued alcohol consumption had poor outcome regardless of the treatment received; and (4) Child-Pugh score greater than 7 was the cut-off value for predicting poor survival whereas recovery from Child-Pugh stage C was associated with a better survival. The study concludes that patients with Child-Pugh stage B alcoholic cirrhosis should not be listed for liver transplantation, especially when alcohol withdrawal is associated with recovery of liver function or when the Child-Pugh score is less than 8. The best strategy would be to consider liver transplantation on the basis of patient outcome and to actively screen these patients for extrahepatic cancer before and after liver transplantation. The results of this study support the current policy of giving priority for organ allocation to the sickest patient. There are other studies in the past which have stated that Child-Pugh stage C patients following transplantation had a higher 1- and 5-year survival than their matched controls, whereas among those with Child-Pugh stage A or B, there was no statistically significant survival difference between transplanted and their matched and simulated controls[31,32].

PRE-TRANSPLANT EVALUATION

Amidst all controversies, where there does appear to be agreement is in the timeliness of referrals to transplant centres[33,34]. Assessment from both a medical and psychosocial perspective takes time. Later referrals leave little scope to explore further medical management options or allow time to work with the substance misuse or psychiatric team. Family support may be more difficult to engage, monitoring of treatment concordance or substance misuse treatment engagement is less likely and medical conditions such as advanced hepatic encephalopathy rule out any reasonable psychotherapeutic treatment opportunities. It is a common practice - and indeed encouraged by guidelines - for units to employ the services of psychiatrists, psychologists, mental health nurses and social

Table 1 Michigan alcoholism prognosis scale

Criterion	Points
Acceptance of alcoholism	
Patient and family	4
Patient only	3
Family only	2
Neither	1
Prognostic indices	
Substitute activities	Yes 3, No 1
Behavioral consequences	Yes 3, No 1
Hope/self-esteem	Yes 3, No 1
Social relationship	Yes 3, No 1
Social stability	
Steady job	1
Stable residence	1
Does not live alone	1
Stable marriage	1
Rating	/20[1]

[1]Maximum score.

Table 2 High-risk alcoholism relapse scale

Item	Score
Duration of heavy drinking (yr)	
≤ 11	0
11-25	1
≥ 25	2
Daily drinks[1] (*n*)	
≤ 9	0
9-17	1
≥ 17	2
Prior alcoholism inpatient treatments (*n*)	
0	0
1	1
≥ 1	2

[1]One drink = 12 g of ethanol.

workers in the pretransplant assessment and evaluation of candidates with ALD[19,21,23,30].

UK Liver Transplant Group Recommendations for ALD, states that all these patients should be assessed by a specialist in substance misuse, who should have dedicated time for this purpose.

Formal pretransplant substance misuse evaluations require a broad psychosocial and substance misuse assessment which will commonly examine the nature and pattern of previous alcohol use, diagnose an alcohol use disorder, length of abstinence and factors which are likely to indicate risk of future alcohol consumption[22,35]. A number of predictive tools have been considered as part of the assessment. The University of Michigan Alcoholism Prognosis Scale examines a number of psychosocial domains with a higher score suggesting an increased stability linked to improved prognosis (Table 1), and Lucey *et al*[36] have recommended such a broad based tool as a useful alternative to a pre-transplant fixed abstinence period. Other tools include the alcohol abstinence self-Efficacy Scale which rates an individual's ability to self-determine in the context of relapse precipitants[37]. Though it shows good reliability and validity in alcohol treatment settings, it has yet to be proven in the liver transplant setting. A recent French study proposes the high-risk alcoholism relapse scale as a simple and useful predictor to be incorporated into assessment screening[38] (Table 2). The use of agreed clinical guidelines and candidate selection criteria offer the assessment team a framework upon which to base complex decisions and an opportunity to explain the assessment and decision making process. Transplant centres have a responsibility to audit their selections and outcomes against accepted listing criteria and the bodies approving the criteria have a subsequent duty to review guidance within an acceptable timeframe.

Psychiatric evaluation

Liver transplantation is a demanding procedure both in the acute stage and in the long-term. Early factors are considered to be the stress of waiting for a liver transplant - with its uncertainty in terms of both timing and outcome - as well as the physical and psychological demands of the procedure in the pre- and post-transplant period. Long term demands are linked to general quality of life (QOL) and treatment adherence. Much has been written of the need for psychological support in transplantation, though whether the ALD patient requires more input than a young person with acute liver failure or a fulminant patient secondary to a paracetamol overdose is open to debate. Dobbels *et al*[35] argue that pretransplant psychosocial screening in all transplant candidates highlights predictors and risks associated with post transplant adherence and clinical outcome, though do not single out the ALD cohort specifically. Psychiatric assessment of the ALD transplant candidate has been both undertaken and recommended for many years and the role of the psychiatrist and psychiatric team has developed and evolved, with a focus on assessment, objectivity and support - to both transplant team and patient - but at the same time caution against acting as the ethicist for the transplant team[39-42]. People judged suitable for OLT included patients with severe ESLD who showed a clear understanding of the risks and benefits of the procedure, had a favourable psychiatric assessment including acceptance of alcoholism, and had favourable prognostic factors for the future sobriety.

Results vary on the psychosocial outcomes of the transplant recipient. A single centre study of 30 UK transplant recipients reported improved QOL post transplant but not at levels consistent with the general population[43]. This is at odds with a contemporary study from another centre in the same city of a cohort of 20 subjects which found that ALD graft recipients do not have higher levels of psychiatric morbidity than other graft recipients and also found that psychiatric symptoms abated in their cohort over time[44]. A larger and more recent UK study prospectively assessed psychiatric "caseness" in 155 transplant assessment candidates. Higher rates of psychological distress were associated with greater severity of liver disease, unemployment and tobacco smoking. A DSM-IV diagnosis of alcohol abuse or dependence was not a significant predictor of psychiatric morbidity[45].

Table 3 Comorbidities associated with alcohol related liver disease

Cardiovascular	Alcoholic cardiomyopathy
	Cirrhotic cardiomyopathy
	Coronary artery disease
Musculoskeletal	Myopathy
	Osteopenia
Neurologic	Wernicke-Korsakoff psychosis
	Alcoholic dementia
	Alcoholic cerebellar degeneration
	Peripheral neuropathy
Malnutrition	
Chronic pancreatitis	
Hepatocellular carcinoma	
Hepatitis B or C infection	
Other malignancy	Upper aerodigestive tract malignancy
Psychiatric	Depression or mood disorders
	Personality disorders
	Anxiety disorders
	Psychosis

Comorbidities associated with ALD

It is seen that only a small percentage of patients with ALD, who are likely to benefit from OLT, actually undergo transplantation[46]. One of the potential reasons for the low rate of transplantation in these patients is the presence of comorbid medical conditions which might contraindicate transplantation. Comorbid medical conditions maybe either as a direct effect of alcoholism or they may be conditions commonly occurring in alcoholics (Table 3).

Cardiovascular

Patients with alcoholic cirrhosis may have alcohol related heart disease (alcoholic cardiomyopathy), heart disease associated with cirrhosis *per se* (cirrhotic cardiomyopathy), or coincidental heart disease (coronary artery disease, CAD). CAD is more common overt problem than either alcoholic or cirrhotic cardiomyopathy. Alcoholic cardiomyopathy is related to the total lifetime amount of alcohol intake[47]. Clinically resembles idiopathic dilated cardiomyopathy and is the major type of secondary dilated cardiomyopathy in Western world. Whereas idiopathic dilated cardiomyopathy is associated with progressive deterioration, alcoholic cardiomyopathy may reverse on stopping alcohol before severe heart failure develops.

Criteria for the diagnosis of alcoholic cardiomyopathy include the presence of alcohol dependence and the following cardiac findings: (1) Large left ventricular diameter on echocardiography; (2) Left ventricular ejection fraction less than 50% as measured on radionuclide angiography; (3) Normal coronary arteries on coronary arteriography; and (4) Characteristic histological changes in endomyocardial biopsy[48,49].

Alcoholic cardiomyopathy is generally associated with active alcohol intake, hence is uncommon in patients referred for OLT.

Cirrhotic cardiomyopathy is the syndrome of high output heart failure associated with impaired ventricular contractile function seen in patients with both alcoholic and non-alcoholic end stage liver disease[50]. Cirrhotic cardiomyopathy is usually mild or latent in these patients as the associated peripheral vasodilatation reduces the after load of the ventricle. OLT with shunting of large volumes of venous return back to the heart may precipitate overt heart failure and contribute to postoperative mortality[45]. The mechanism of cirrhotic cardiomyopathy involves impaired β adrenergic receptor function, alteration in plasma membrane fluidity and hyper dynamic circulatory state.

CAD is found more often (5.6%-27%) than expected in patients with ESLD being considered for OLT than in the general population. Factors proposed for such finding include: older age, preponderance of males, and frequent concomitant cigarette smoking. Associated diabetes mellitus if present is an important risk factor[50-52].

Management dilemma is posed when a patient with ESLD, who is otherwise a good candidate for OLT, is found to have moderate to severe CAD. Consensus is to treat the CAD before OLT, as OLT poses the risks of myocardial ischemia or infarction particularly in patients with triple vessel disease or left main CAD[51]. If CAD cannot be treated by percutaneous transluminal coronary angioplasty, then coronary artery bypass grafting (CABG) can be considered. Patients with ESLD might experience deterioration of hepatic functions after CABG, including portal hypertensive bleeding and worsening coagulopathy. Prophylactic placement of transjugular intrahepatic portosystemic shunt has been proposed, before CABG. Few patients have had CAD and ESLD treated with both CABG and OLT immediately following each other[51].

Currently in most of the European Transplant centres, echocardiography and electrocardiography are used routinely in pretransplant evaluation. About 50% utilise exercise or dobutamine stress tests. Radionuclide or invasive testing is not routinely undertaken. Although most centres consider cardiomyopathy as a relative contra-indication for OLT, the limits of left ventricular ejection fraction below which OLT is contraindicated is variable from 20%-50%[4]. Routine testing to exclude cardiomyopathy is not justified in asymptomatic patients[52,53].

Myopathy

Approximately half of active alcoholics have a myopathy that is related to alcohol intake, nutritional deficiency and neuropathic damage. Muscle strength is inversely related to the lifetime ingestion of alcohol[54]. Alcohol myopathy usually improves with abstinence and is not a factor for consideration in patient selection or outcome of OLT.

Neurologic

Neurologic disease with fixed deficits may be found in patients with ESLD and long standing alcoholism, and it may be difficult to differentiate it from hepatic encephalopathy, which is reversible following OLT[55]. Korsakoff's psychosis, which is characterised by profound deficits in retentive memory and learning, is a late manifestation of the Wernick-Korsakoff's syndrome, with features of opthalmoplegia, ataxia, and confusion occurring earlier

and is not always recognised. Complete recovery is uncommon. "Alcoholic dementia" is the term used for late stage Korsakoff's psychosis, which is characterised by cognitive impairment, memory dysfunction, and is associated with cerebral atrophy on imaging.

Alcoholic cerebellar degeneration is a form of cerebellar ataxia, which occurs in patients with prolonged and heavy alcohol intake. This is partly caused by nutritional deficiency, affects the stance and gait, and is usually not reversible[55]. Patients having significant cerebral or cerebellar dysfunction usually are not considered for OLT.

Peripheral neuropathy associated with alcoholism usually improves with nutritional therapy and is not a factor influencing the selection or outcome following OLT. Autonomic neuropathy is not uncommon in patients with ESLD of any aetiology, and improves with OLT. Imaging studies of the brain and psychometric testing may be required in patients with atypical hepatic encephalopathy or symptoms suggestive of organic brain dysfunction for differential diagnosis.

Chronic pancreatitis

Acute and chronic pancreatitis, an important clinical problem in alcoholic patients, seldom has an impact in the selection process for OLT. Patients with significant chronic pancreatitis are excluded from consideration for OLT. Chronic pancreatitis is less common in patients with ALD as compared to alcoholics without liver disease (1% *vs* 5%)[56]. Morbidity and mortality associated with pancreatitis following OLT is substantial and any evidence of active pancreatitis is a reason to abandon OLT[55].

Malnutrition

Malnutrition is common in patients with ESLD irrespective of the aetiology; it is one of the factors which leads to consideration for OLT. About half of the patients with alcoholic cirrhosis have protein calorie malnutrition[57]. Factors responsible for malnutrition in these patients include a poor diet, increased catabolism of carbohydrates, proteins and lipids, impaired absorption of nutrients, cholestasis with associated interruption of bile flow, pancreatic dysfunction, bacterial overgrowth and alcohol induced intestinal mucosal injury[58]. Various studies have indicated that the degree of malnutrition affects the outcome following hepatobiliary surgery and OLT, including the stay in intensive care unit, duration of ventilation, hospital stay and mortality after OLT[59-61]. Nutritional support before OLT is important for obvious reasons, and severe malnutrition may require postponement of OLT until a better state of nutrition is achieved[59].

Osteopenia

Long standing alcoholism and ALD is associated with osteopenia and reduced bone mineral density which remains unrecognised until fracture occurs. Spinal and peripheral fractures are common in patients with ESLD. Spinal and forearm osteoporosis is also more often seen in patients with ESLD. Reduced bone mineral density in various studies at various sites range between 10%-42%[62,63]. Factors attributed to osteoporosis in these patients include alcohol induced impairment of osteoblastic function hypogonadism, reduced body mass index and limited physical activity[64,65]. Pain and recurrent fractures particularly vertebral collapse are indications for transplantation in these patients[55]. It is imperative to check serum 25-hydroxyvitamin D levels in patients with ESLD and initiate vitamin D replacement therapy if the levels are low, use oestrogen therapy *via* patch in postmenopausal women, screen for testosterone deficiency in men and administer exogenous testosterone in those with low levels[55]. Treatment with calcium and vitamin D can improve bone mineral density in patients with ALD.

Other liver diseases

Approximately 20%-30% of patients with ALD have chronic hepatitis C virus (HCV) infection and the majority have detectable serum HCV RNA[66]. Diagnosis of concomitant HCV infection in patients with alcohol related cirrhosis has important implications on the outcome of OLT. HCV infection recurs in almost all patients with OLT, and 5%-10% of these would go on to develop ESLD within 3-5 years[67,68]. Patients with ALD can have coexistent chronic hepatitis B virus (HBV) and hemochromatosis. These have important implications in the treatment of these patients following OLT. Patients with HBV infection require antiviral therapy with either immunoglobulin or lamivudine and those with hemochromatosis have reduced survival following OLT, and they may benefit from phlebotomy prior to OLT[69-71].

Hepatocellular carcinoma and ALD

There is increased risk of hepatocellular carcinoma (HCC) in any patient with ESLD, including those with alcohol related cirrhosis. Patients with chronic HCV, chronic HBV and hemochromatosis have highest risk[72,73]. HCC in these patients may be detected during the transplant operation, discovered by the pathologist in the explant histology (incidental HCC) or may be detected in the pretransplant imaging (coincidental HCC). Patients with a lesion less than 3-5 cm in diameter have a good prognosis with OLT as compared to those with a larger and symptomatic lesion[74,75] (Table 4).

Other malignancy

It is seen that patients with ALD undergoing OLT have significantly increased incidence of upper aerodigestive tract cancers as compared to those with non-alcoholic ESLD. These are a major cause for morbidity and mortality following OLT (as described later)[82]. It is important that these patients undergo a thorough pretransplant evaluation to rule out these tumors before OLT and also to have regular evaluation post-OLT[4] (Tables 4 and 5).

LIVER TRANSPLANTATION IN ACUTE ALCOHOLIC HEPATITIS

Many patients with severe AH, whether in the setting of

Table 4 Outcome of post-orthotopic liver transplantation in patients with alcoholic liver disease, combined alcoholic liver disease with hepatitis C virus and hepatitis C virus alone *n* (%)

Study	ALD	ALD + HCV	HCV	Others
Burra *et al*[76]	*n* = 9880	*n* = 1119	*n* = 6672	
Patient survival 1-yr, 3-yr, 5-yr, 10-yr	84%, 78%, 73%, 58%	84%, 75%, 65%, 52%	81%, 72%, 67%,54%	
Aguilera *et al*[77]	*n* = 107	*n* = 60	*n* = 170	
HCC	19 (18)	21 (35)	75 (44)	
Graft loss	35 (33)	25 (42)	95 (56)	
Severe recurrent HCV disease		22/49 (45)	54/122 (45)	
Retransplant	4 (4)	8 (13)	7 (4)	
De-novo tumors	14/107 (13)	2/67 (3)	10/67 (6)	
Rejection	17/100 (17)	9/60 (15)	32/169 (19)	
Patient survival 1-yr, 5-yr, 7-yr	90%, 76%, 67%	86%, 73%, 63%	72%, 49%, 43%	
Graft survival 1-yr, 5-yr, 7-yr	89%, 76%, 67%	83%, 63%, 56%	71%, 48%, 43%	
Mortality	29 (27)	21 (35)	95 (56)	
Cause of death				
Recurrent disease	3 (3)	9 (15)	44 (26)	
Sepsis	7 (6.5)	7 (12)	26 (15)	
De-novo tumors	9 (8)	2 (3.5)	6 (3.5)	
Neuberger *et al*[4]				
HCC (%)	11	26	28	
Yamauchi *et al*[78] Yamanaka *et al*[79]				
Risk of HCC (at 10-yr)	15%-20%	50%-80%		
Khan *et al*[80]	*n* = 14	*n* = 24	*n* = 40	*n* = 42
HCV RNA (Meq/mL)		2.3 ± 1.7	2.7 ± 2.9	2.3 ± 2.6
Necroinflammation	1.8 ± 0.7	3.1 ± 1.1	3.4 ± 1.6	2.9 ± 1.3
Fibrosis	2.9 ± 1.0	3.6 ± 0.7	2.9 ± 0.9	3.4 ± 1.0
Cirrhosis	5 (8.4)	16 (27.2)	10 (16.9)	28 (47.5)
HCC	5 (9)	14 (25.5)	10 (18.2)	26 (47.3)
Size of HCC	1.9 ± 0.8	2.5 ± 0.8	2.5 ± 1.0	2.4 ± 0.9
Donato *et al*[81]				
Relative risk for HCC	4.6	64.7	23.2	

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; ALD: Alcoholic liver disease.

Table 5 Post-orthotopic liver transplantation events-rejection, infection, malignancy, retransplantation and cardiac events

Study	Rejection (%)		Infection (%)		Malignancy (%)		Retransplantation (%)		Cardiac events (%)	
	ALD	Non-ALD	ALD	Non-ALD	ALD	Non-ALD	ALD	Non-ALD	ALD + viral	Non-ALD
Burra *et al*[76]	7.6	10.1	15.5	17.6	13.7/5.4[1]	5.6/2[1]			8	5.3
Pfitzmann *et al*[5]			4.7-6.3[2]		9.4-18.8/3.8[2]				3-11.8[2]	
Wiesner *et al*[83]	Significantly less in ALD *vs* non-ALD		Bacteremia, overall fungemia, and CMV infection, comparable		*De-novo* tumors significantly increased in ALD *vs* non-ALD		3	9		
Bhagat *et al*[84]	23/2[3]	41/4[3]	43[2]	53	29[2]	0	3.6	5.6	7[2]	26

[1]*De-novo* tumors/upper aerodigestive tract tumors; [2]Cause of death; [3]Acute/chronic rejection. ALD: Alcoholic liver disease.

previous normal liver or in those with established cirrhosis, fail to recover even after abstinence and maximal medical treatment. The severe form of AH is associated with 35%-50% mortality at 1 mo following diagnosis. Any treatment for these patients requires identification of that subgroup of patients who have significant risk of death at 1 or 2 mo. Severity of acute AH is best assessed using Maddrey discriminant function (DF), which is a reproducible, objective criterion to predict the risk of early death. This is based on prothrombin time and serum bilirubin concentration (mg/dL). It is calculated using the formula [4.6 × (prothrombin time - control prothrombin time) + serum bilirubin]. DF > 32 indicates high risk of early mortality in the absence of treatment. Spontaneous survival at 1 mo in patients with a DF < 32 is approximately 90%[85,86]. To reduce the probability of early death, patients with a DF > 32 need to be offered treatment. American College of Gastroenterology and various other studies have observed that 2 mo survival of patients of AH with DF > 32 treated with corticosteroids was approximately 80%[86-88]. One simple criterion to identify the population of patients with AH who would benefit from corticosteroid treatment is termed as an early change in bilirubin levels (ECBL), which is defined as an ECBL at 7 d, which is lower than level on the first day of treatment. At 6 mo, patients with ECBL had a significantly higher survival compared to those without ECBL (83% *vs* 23%)[89]. Another treatment which is found to have an effect in

improving survival in the index admission, compared to placebo, is that with pentoxifylline (75.5% *vs* 53.5%). Development of acute renal failure in these patients with acute AH is a bad prognostic criterion. The benefit of pentoxifylline appears to be related to a significant reduction in the risk of developing hepatorenal syndrome[90]. There is insufficient data on the benefits of transplantation in patients with AH. Offering liver transplantation to those patients who are non responders to corticosteroid treatment is still a matter of debate. These patients require alternative strategies of treatment as they have a poor survival. Most transplant centres in United States and Europe require a period of abstinence before considering transplantation which is not possible in these patients. There is limited and mixed experience of transplantation in these patients[91-95].

According to the current consensus in most European and North American transplant centres, patients with acute AH are not considered for liver transplantation[23,96]. A recent French multi-centre pilot study examined the outcomes of transplantation in patients with AH who were corticosteroid non-responders. The selection criteria included first time presenters and acceptance from all members of the transplant MDT. Twenty-two patients were listed with 18 undergoing transplantation following listing. At 6 mo, survival was 83% in transplanted patients in comparison with 44% in patients not transplanted in a case-control group. There was no reported relapse to drinking at 1 year post transplant. This data is as yet only available in abstract form and long term follow-up is required[97].

HEPATITIS C VIRAL INFECTION AND ALD

Prevalence of hepatitis C viral (HCV) infection is seven times higher in patients with ALD than in the general population. About 20%-30% of patients with ALD are infected with HCV, and the rate of progression of liver disease and the long term outcome are worse for these patients as compared to those who are not infected with HCV[55,98]. Although the outcome of patients undergoing liver transplantation for ALD is good with an overall survival of 60% at 10 years, outcome in patients with HCV cirrhosis is impaired by recurrence of disease and progression to cirrhosis[99-101]. The combination of alcohol and HCV infection leads to a rapid progression of disease, with cirrhosis developing earlier than in patients with HCV infection alone[102]. Factors proposed for this accelerated disease course are higher viral load, alterations in the immune response, alcohol induced aggravation of histological lesions, interference in hepatocyte regeneration and ineffectiveness of Interferon in these patients making treatment even more difficult[98,103-105].

A study by Aguilera *et al*[77] compared the post-transplantation outcome in patients with HCV related cirrhosis, alcoholic cirrhosis and cirrhosis of mixed aetiology (HCV and ALD) (Table 4). It is important to know the natural history post-transplantation in this group of patients, to address the expectation of these patients prior to transplantation and the potential complications. About a quarter of patients undergoing transplantation for HCV related cirrhosis had a history of significant alcohol consumption. This partially determined the course of disease prior to transplantation. On the contrary, 36% of patients undergoing OLT for ALD had associated chronic HCV infection. Age at transplantation was lower in the subgroup with mixed aetiology and the Child-Turcotte-Pugh score was higher in patients with alcoholic cirrhosis. The prevalence of hepatocellular carcinoma was more in the two groups of patients with HCV infection compared to the alcohol alone group, re-iterating the oncogenicity of the virus. This has been reported by other studies as well, a combination of hepatitis C and alcohol leading to an increased risk of HCC compared with either entity alone (50% to 80% *vs* 15% to 20% at 10 years)[78,79,81]. Post-transplantation patient survival at 1-, 5- and 7-year was significantly lower in the group of patients undergoing transplantation for HCV related cirrhosis (72%, 49% and 43%) as compared to patients with alcohol related cirrhosis (90%, 76% and 67%) or those with mixed aetiology (86%, 73% and 63%). Histological damage which was assessed by protocol biopsy at 1, 3 and 5 years post transplantation revealed no difference in the incidence of severe recurrent HCV disease or progression of disease, in patients with HCV related cirrhosis and the mixed group. Graft loss was more and graft survival was significantly lower in patients undergoing transplantation for HCV related cirrhosis compared to those with alcohol related cirrhosis or those with mixed aetiology. Despite greater survival, recurrent hepatitis C progressed similarly in patients undergoing transplantation for cirrhosis of mixed aetiology and in those undergoing transplantation for HCV alone. The authors propose that this might be attributed to greater use of antiviral agents in the mixed group compared to HCV alone group (32% *vs* 18%, $P = 0.03$) and younger age of patients in this group who were able to tolerate the treatment[106]. Patients with mixed aetiology for cirrhosis (HCV and alcohol), have more severe liver disease and this is determined by alcohol intake prior to the transplant, post transplantation course of these patients is determined by the interaction between the HCV and the new milieu, where alcohol no longer determines the progression of recurrent disease[77].

Risk of occurrence of HCC was significantly higher in the mixed aetiology group compared to HCV infection alone. HCV infected patients with moderate to heavy alcohol intake had a 1.5-2.5 fold increased risk of HCC compared to alcohol free HCV infected patients[80]. This study also demonstrated that excessive alcohol intake increased the severity of liver disease - it accelerated the degree of hepatic fibrosis, the risk of liver cirrhosis and worsened the clinical outcome of liver disease with higher risk of HCC. HCV replication however was independent of severity of liver disease[80].

Other problems encountered in HCV infected patients with excessive alcohol intake are that if there is early presentation for transplantation, alcohol abuse may not be investigated as in a typical case of alcohol related cirrhosis, thus the follow-up measures to detect relapse

Table 6 Comparison of outcomes of patients with alcoholic liver disease post-orthotopic liver transplantation

Study	Time period	Number of patients	Survival (%)				Relapse (%) any (abusive)	Death due to relapse (%)
			1-yr	3-yr	5-yr	10-yr		
Burra *et al*[76]	1988-2005	ALD-9880	84	78	73	58	33 (11)	4.3
		ALD + HCV-1119	84	75	65	52		18.3
		ALD + HBV-309	89	85	81	64		
		Cryptogenic-2410	78	73	69	61		
Bhagat *et al*[84]	1997-2007	ALD-83	92	86	86	76[1]		
		NASH-71	82	79	75	62[1]		
Gedaly *et al*[22]	1995-2007	ALD-147	96.2	89.6	84.4		19	
Pfitzmann *et al*[5]	1989-2002	ALD-300	96		88	76	19 (8)	4.8
		Non-ALD	97		80	72		
OPTN/SRTR 2006[113]	1996-2005	All causes of cirrhosis	86.9		82.4			
Lim *et al*[101]	1988-1997	ALD-3063	81.9	73.9	67.9		13	
		Viral hepatitis-4267	80.3	71.7	65.3			
Bellamy *et al*[82]		ALD-123	84		72	63[2]	10	
Mackie *et al*[110]	1996-1999	ALD-64	82	82[3]			45.6 (6.5)	
		Non-ALD-335	83	82[3]				
Gerhardt *et al*[114]	1985-1991	ALD-67	90	84[4]	82[4]	76[4]	26 (4.8)	4.5
Lucey *et al*[15]	1985-1989	ALD-45	78	73[3]			4.4	
		Non-ALD-111	70	65[3]				
Kumar *et al*[115]	1982-1988	ALD-73	74				11.5	2
		Non-ALD	67					

[1]9 yr survival; [2]7 yr survival; [3]2 yr survival; [4]2-yr, 3-yr and 4-yr survival. HCV: Hepatitis C virus; HBV: Hepatitis B virus; ALD: Alcoholic liver disease.

and supportive measures to maintain abstinence may not be available[76].

According to European Liver Transplant Registry (ELTR) data, patient survival for ALD patients is superior to those transplanted for HCV infection. Increasing donor age is found to have an adverse influence on patient and graft survival for ALD and HCV patients; it is more significant in HCV patients when the donor age is more than 40 years[107].

OUTCOME OF TRANSPLANTATION IN ALD

Studies have reported similar 1- and 5-year survival rated for patients undergoing OLT for ALD and for other indications, and in most studies alcohol relapse did not influence 1- and 5-year survival rates after OLD for ALD[108-112] (Table 6). The definition of relapse is not clear and this lack of consistent definition explains the varied relapse rates reported in the literature ranging from 7%-95%[108,112].

Heavy drinking has been shown to impair the long term survival (over 5 years) of patients with ALD following OLT[116]. Pfitzmann *et al*[5] retrospectively analysed 300 patients of ALD who had OLT for long term survival and risk factors for alcohol relapse. Recurrent alcohol consumption was observed in 10% of patients, of whom 30% had slipped, abusive drinking was documented in 41% and in the remaining 29%, severity of alcohol consumption was unknown. On multivariate analysis, duration of sobriety of less than 6 mo, poor social support, presence of young children and poor psychosomatic prognosis were associated with significantly increased risk of recurrent alcohol consumption. The overall survival

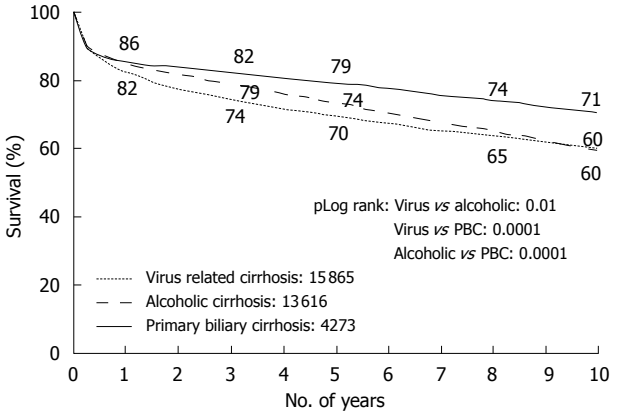


Figure 5 European Liver Transplant Registry (2008) data. One year, 3-year, 5-year, and 10-year survival following orthotopic liver transplantation for three common indications. PBC: Primary biliary cirrhosis.

of patients who underwent OLT for ALD was not statistically different from that of patients who had OLT for other indications. The 1-, 5-, and 10-year patient survival rates for ALD were 96%, 88%, and 76%, respectively as compared to 97%, 80%, and 72%, respectively for patients with other indications for OLT (Figure 5). Significantly better survival rates were observed for patients who remained abstinent when compared to those who resumed drinking after OLT. Further they observed that patients who resumed abusive drinking following OLT had the lowest survival. Recurrent alcoholic liver disease was responsible for the majority of deaths (87.5%) among patients who resumed abusive drinking[5] (Tables 4 and 6).

The impact of alcohol consumption on the outcome of OLT has been reported variedly. Several studies have

reported that recidivism has no significant impact on survival rate[114,117]. These studies did not account for the different patterns of drinking[5]. Recent studies have indicated that resumption of abusive drinking following OLT, leads to significantly reduced survival rates[116]. Patients who resumed heavy drinking have been reported to have 5- and 10-year survival rates of 69.5% and 20.1%, respectively compared to 90.3% and 81.5%, respectively in abstinent patients[5].

Numerous studies have reported that 5-year survival of patients undergoing OLT for ALD is comparable to the survival of patients transplanted for other indications[13,112,113]. According to the ELTR (2008), the overall 1- and 5-year survival of patients with ALD following OLT was 86% and 74%, and 1-year survival exceeded 90% in some centres (Figure 5).

Rejection in patients of ALD post OLT

ALD patients post OLT have reduced incidence of acute cellular rejection. Burra *et al*[76] report histologically proven acute cellular rejection in 14% of patients 23-180 d post OLT. Chronic ductopenic rejection is reportedly less common or the same in the patients receiving OLT for ALD from those for other indications[11,15]. Wiesner *et al*[83] in their study have reported significant decreases in the overall incidence of rejection in patients with ALD post-OLT as compared to those with non-alcoholic liver disease (Table 5).

Retransplantation in ALD

The incidence of retransplantation in patients with primary ALD is less as compared to other indications for transplantation. Wiesner *et al*[83] reported a significantly decreased incidence of retransplantation compared to non alcoholic liver disease recipients (3% *vs* 9%, $P = 0.04$). Retransplantation because of recurrence of disease is much less compared to those with HCV infection (where almost all recipients have recurrent disease at some point post-OLT), again justifying the allocation of scarce resources to patients with ALD (Table 5).

Medical complications

Infections are reportedly more common following OLT in patients with ALD. The incidence of bacterial infections is greater while the incidence of cytomegalovirus infection is similar to those patients transplanted for non-alcoholic liver disease. The incidence of hypertension and new onset insulin-dependent diabetes is again similar[22,115].

De-novo malignancies

Organ transplant recipients are at increased risk for developing *de-novo* malignancy, as they are exposed to prolonged and often lifelong immunosuppressive therapy. The incidence of *de-novo* malignancy reported in various series ranges from 6%-55% at 15 years following liver transplantation[118]. They are an important cause of delayed graft morbidity and mortality. Well documented risk factors for *de-novo* malignancy after liver transplantation include smoking and tobacco usage in any form, alcohol intake, and inflammatory bowel disease. Prolonged immunosuppression in these patients synergizes with known risk factors for malignancy.

Various studies have reported a higher incidence of *de-novo* malignancy in patients with ALD[119,120]. They are at high risk for developing upper aero-digestive tract malignancy. This has an important bearing in the pretransplant evaluation and post transplant follow-up. Oropharyngeal squamous cell carcinoma incidence of 17% has been reported in patients with ALD[121]. An incidence of 4.2% of oropharyngeal and oesophageal malignancies has been reported at 8 to 40 mo post transplantation in patients with ALD[122]. There is an increased incidence of basal and squamous cell carcinoma in these patients[119]. The incidence of oropharyngeal cancers is reportedly 25.5 times higher and the incidence of lung cancer 3.7 times higher for ALD patients[122]. There is no specific recommendation for post-OLT surveillance in these patients. In patients who have had OLT for ALD should have surveillance for upper aerodigestive tract malignancy at 1 year and thereafter annually[123,124] (Tables 4 and 5).

Cause of death

The vast majority (50%-87.5%) of deaths in patients who resume heavy drinking is due to recurrence of ALD and AH[5,82,112]. The cause of death in other patients who were abstinent was malignant tumors, infection, cardiovascular disease and cerebrovascular events. Malignant tumor of the upper aerodigestive tract was seen in patients who resumed heavy alcohol ingestion and in those who were abstinent after OLT[5,122]. Long term survival in the patients of ALD is affected by *de-novo* malignancy and this is the consequence of prolonged exposure to alcohol and tobacco[121-124]. These patients should be advised to discontinue smoking or intake of tobacco in any form.

Quality of life

QOL in all aspects, medical status, social status, employment status, or relationships shows improvement following transplantation for any indication[125]. There are conflicting results on the QOL of recipients of OLT for ALD as regards the return to work following recovery. There are studies proposing that the rate of return to work is as good as in those patients transplanted for any other cause, while there are others indicating that it is less for those transplanted for ALD[108,126]. Overall there is evidence that the QOL and return to work is similar or may be better, in patients transplanted for alcoholic and non-ALD. These patients seem to return to society to lead active and productive lives; however there is evidence that the societal re-integration may be less compared to those transplanted for other causes[127]. Post-transplant scores on QOL are poorer in patients who relapse to harmful drinking[128]. These patients have more sleep disturbances and are more prone to use benzodiazepines[129].

FOLLOW-UP AND RELAPSE

A proportion of patients grafted for end stage ALD

return to alcohol use post transplant. This statement in itself raises objection, concern, emotional responses and a sense of treatment failure[130]. The evidence is much less alarming, though worthy of further scrutiny. In the Dew *et al*[16] meta-analysis, 6 cases per 100 patients per year (PPY) return to any alcohol use post transplant, while less than 3 PPY return to heavy use. This describes cumulative rates of relapse and therefore the incidence rate at 5 years post transplant would stand at 28%. One Spanish centre has published data showing significant reduction in 10-year survival rates for ALD patients who relapse to alcohol use[116].

Transplant centres require assessment candidates to be abstinent at the point of listing and be committed to abstinence post transplant. If no ALD transplant recipients ever returned to alcohol use post-transplant the selection bar would clearly be set too high. If a significant number of grafts were lost due to a return to alcohol use - either directly or through poor treatment adherence - then this may suggest poor stewardship. Less than 5% of grafts are lost at 5-year post-transplant through direct or indirect consequences of alcohol misuse[32].

Criticism has been levelled at methods of monitoring alcohol use post-transplant. Literature has described retrospective case note review, biochemical markers, psychiatric interview, questionnaires and screening tools amongst others[131-133]. Inconsistent and unreliable methodology has been unhelpful in revealing a clear picture of alcohol use post-transplant, problematic use and untoward consequences.

Alcohol use in the non-ALD transplant candidate should not be overlooked. In a prospective study of 208 non-ALD transplant candidates in a UK centre, 80 (39%) met the DSM IV criteria for a lifetime diagnosis of alcohol abuse or dependence, highlighting the need for appropriate screening and assessment of this population[134].

Many transplant centres now have psychiatric/substance misuse specialists following patients up post-transplant in order to provide ongoing relapse prevention and support. This monitoring should be supplemented by appropriate alcohol screening by physicians, and Hepatology nurses as well as with effective biochemical markers. Where relapse has occurred a treatment plan should be effected and engagement with local substance misuse teams arranged. Such services should demonstrate willingness and a flexible response to this patient group.

CONTROVERSIES ABOUT "SLIPS" AND RELAPSES

Addiction specialists distinguish a relapse which is prolonged and harmful drinking behaviour from a minor lapse or slip which is a sporadic drinking event followed by re-establishment of abstinence[5]. It is also accepted that where a person has a diagnosis of dependence to a substance then it is likely that after a period of abstinence, further exposure to the substance provokes the risk of reinstatement, one of the features of dependence in which the person rapidly returns to the previously required level of drug use. This is a common feature of - for example - alcohol or tobacco dependence. Where a person has not been dependent then the risk of reinstatement is less profound and therefore it is argued in addiction treatment settings that with psychological interventions it is possible to modify the individual's behavioural responses to triggers such as cue response cravings, stress and other high risk situations using relapse prevention techniques largely based on cognitive behavioural therapies[135]. Evidence suggests that some of these techniques are of significant benefit[136].

ETHICAL ISSUES

There are medical and ethical concerns about the appropriate use of scarce resources, and the degree of priority given to patients with ALD has always been a controversial issue: (1) should an individual receive the same priority as others for a self inflicted disease; (2) whether the outcome of liver transplantation is as good in patients with ALD as in non-alcoholics; and (3) the possibility of recidivism and its influence on the graft.

The Oregon experiment highlighted the issue of permitting the voting public to select healthcare priorities, and a UK poll also identified the difference in candidate selection, based on seemingly emotional and moral grounds - in the case of the general public - rather than on clinical outcome and utilitarian use of the organ[11,137].

Doubts have been raised about the ethics of a "6-mo rule" of abstinence as a consequence of the lack of evidence of this approach and the "context" of the abstinence[20]. The argument has also been made that if alcohol dependence as an "addiction" carries a neurobiological component (i.e. a genetic influence) then it does not constitute a "self-induced" disorder but a medical one which should be managed accordingly. This argument is limited as it ignores the fact that clinical outcome is the most important factor and therefore if an "addicted" drinker is transplanted the argument would suggest that they may not be able to exert any degree of control over their drinking in the future[138]. In response to this, Berkalovich[139] argues the disease model of alcoholism and therefore advocates treatment of the addiction and treatment of the liver disease. If an ALD patient is as likely to have a favourable long-term prognosis as a non-ALD candidate with transplantation then there is no further issue[140].

FUTURE DIRECTIONS

Certain issues related to liver transplantation in ALD have remained unresolved despite the convincing reports of similar survival in these patients post transplant as compared to those who received transplant for other indications. Areas of future research are many, and these may help in resolving the controversies associated with OLT in these patients. (1) Not all patients who consume alcohol develop alcoholic liver disease. There have been studies indicating genetic predisposition in ALD patients to develop

chronic liver disease as the severity of liver damage is not uniformly related to the amount and number of years of consumption[141]. Studies are needed to further identify these genetic factors so that liver transplantation is taken as a curative procedure in these patients as they acquire a different set of genes in the new liver with different susceptibility even if there is relapse; (2) Though there are studies which have identified risk factors for relapse in patients with ALD, the controversy about the period of abstinence prior to transplant evaluation still continues. It is time to have a consensus about this so that there is uniformity in organ allocation for these patients and the listing criteria are better defined[142]. Comparison of data would be uniform if this period of abstinence is defined and followed; (3) AH is not yet considered as an indication for liver transplantation; however it is known that there is a subgroup of patients who do not respond to medical treatment and that they have a poor prognosis. This is the group where the benefit of liver transplantation is being argued. It is also known that histological recovery from features of AH is different from clinical recovery so whether these patients who have had acute AH are to be uniformly abandoned from listing or can be reconsidered for OLT when the liver disease worsens must be considered. Whether they have a similar outcome to other ALD patients who have not had AH is to be studied in a prospective manner. A blanket approach of contraindication ignores cases such as the young man with first episode liver damage, thus raising issues around age and opportunity; (4) Pretransplant psychological input need not be restricted to assessment and evaluation. Opportunities abound for therapeutic work during the assessment phase, particularly if transplantation is not imminent. Relapse prevention strategies can be woven into appointments and at least one transplant centre has attempted to engage with the transplant candidate and their families at the assessment phase through implementation of sessions of the psychosocial intervention social behavioural and network therapy[141,142]. Initial results appeared favourable and units should be creative in employing their specialist teams to develop and evaluate such approaches; (5) Follow-up of patients of ALD post-OLT as well as the pretransplant assessment necessitates psychiatric and psychosocial evaluation, which is important not only to identify a subgroup of patients with better outcome, but also is important to identify relapse and treat alcoholism in them. Not all transplant centres have a dedicated psychiatrist/addiction specialist to deal with these patients. Treatment of alcohol relapse in patients of ALD post-OLT is still not defined. Further research is required in this field for the treatment of alcoholism and alcohol dependency in these patients. This is important for graft survival; (6) Treatment of ALD before transplantation and considering OLT only once if it fails is important for better utilisation of organs. The concept of better outcome in patients who are not very sick at the time of transplantation was proven wrong in the recent prospective study on immediate listing *vs* delayed transplantation. Future research in the medical treatment of patients with ALD might help in reducing the long list of patients waiting for OLT; (7) *De-novo* malignancies post-transplant are more frequently identified in ALD patients, hence a better surveillance programme is required for these patients so that patient and graft survival is not affected in the long term. Longitudinal studies to determine the timing and frequency of surveillance in these patients are important to avoid delayed morbidity and mortality. Whether the immunosuppression protocol needs adjustment in these patients is an ingredient for further research; and (8) There is no definitive biochemical test to identify alcohol relapse and the tests available have poor sensitivity and specificity. More research is required in this field to identify sensitive tests for detection of harmful alcohol ingestion and the effect on the new liver.

CONCLUSION

ALD is an acceptable indication for liver transplantation as survival of these patients after transplantation is similar to that seen in patients who receive grafts for other causes. Patient selection is important for rationing scarce organs, hence the use of prognostic models for predicting risk of relapse to alcoholism. Rate of graft loss is no greater and rejection of the graft is even less so in patients transplanted for ALD. The disease recurs in a minority of patients but histologically proven disease recurrence is less frequent than with hepatitis C, primary biliary cirrhosis, auto-immune hepatitis, or primary sclerosing cholangitis.

Disease recurrence has little impact on graft survival rates within 7-10 years of transplantation, in contrast with hepatitis C. Abstinence before transplantation evaluation and listing is important to select patients who would benefit the most from transplantation, as some would get better in this period. There should be reservations in listing those patients with a lack of social support, active smoking, psychotic or personality disorders, or a pattern of nonadherence. Pretransplant evaluation and follow-up is a combined effort of clinicians, psychiatrists and substance abuse specialists.

ACKNOWLEDGMENTS

Figures 1-5 are downloaded from the ELTR and UNOS website. These are available for public view, and have been accessed in December 2009. These are incorporated in the manuscript for comparison of data. http://www.eltr.org/publi/results.php3; http://optn.transplant.hrsa.gov/latestData/viewDataReports.asp.

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