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REVIEW

Liver transplantation in alcoholic liver disease current status and controversies

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Abstract

Alcoholic cirrhosis remains the second most common indication for liver transplantation. A comprehensive medical and psychosocial evaluation is needed when making a decision to place such patients on the transplant list. Most transplant centers worldwide need a minimum of 6 mo of alcohol abstinence for listing these patients. Patients with alcohol dependence are at high risk for relapse to alcohol use after transplantation (recidivism). These patients need to be identified and require alcohol rehabilitation treatment before transplantation. Recidivism to the level of harmful drinking is reported in about 15%-20% cases. Although, recurrent cirrhosis and graft loss from recidivism is rare, occurring in less than 5% of all alcoholic cirrhosis-related transplants, harmful drinking in the post-transplant period does impact the long-term outcome. The development of metabolic syndrome with cardiovascular events and *de novo* malignancy are important contributors to non liver-related mortality amongst transplants for alcoholic liver disease. Surveillance protocols for earlier detection of *de novo* malignancy are needed to improve the long-term outcome. The need for a minimum of 6 mo of abstinence before listing makes transplant a nonviable option for patients with severe alcoholic hepatitis who do not respond to corticosteroids. Emerging data from retrospective and prospective studies has challenged the 6 mo rule, and beneficial effects of liver transplantation have been reported in select patients with a first episode of severe alcoholic hepatitis who are unresponsive to steroids.

Key words: Alcoholic liver disease; Liver transplantation; Transplant evaluation; Recidivism; Six months rule; Alcoholic hepatitis

Core tip: Alcoholic cirrhosis remains the second most common indication for liver transplantation. Due to effective immune suppression regimens, graft loss and recurrent alcoholic liver disease rarely leads to mortality. However, the development of non-hepatic disorders such as malignancy and metabolic syndrome contributes to long-term morbidity and mortality. Although recidivism does impact long-term survival, data on the accuracy of 6 mo rule in predicting recidivism are scanty and controversial. Emerging data on the beneficial role of liver transplant provides a ray of hope for select patients with alcoholic hepatitis.

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INTRODUCTION

In the United States, about 60% of the general population admits to alcohol use, and about 8%-10% report heavy drinking (2 or more drinks per day)[1]. One drink is equivalent to 12 oz. of beer (4%-5% weight by volume or w/v), 6 oz. of wine (8%-10% w/v), and 2 oz. of hard liquor or whiskey (45% w/v). Of the various factors responsible for liver disease, the most important are the duration and amount of alcohol consumed. Pooled data from several epidemiological studies report a minimum intake of 30 g/d of alcohol in women and 50 g/d in men, consumed over at least 5 years is required to cause liver cirrhosis[2]. The prevalence of and the mortality rates from cirrhosis parallel the prevalence rates of alcohol consumption in the population globally. Several host and environmental factors increase the risk of development of liver disease, such as gender (women are more prone), hard liquor compared to wine, binge drinking (5 or more drinks at one time), drinking on an empty stomach, genetic factors such as *PNPLA3* gene polymorphisms, concomitant hepatitis C virus (HCV) infection, and obesity[3,4].

Alcohol remains the third most common preventable cause of death after smoking and hypertension. Alcohol-related mortality affects the young and middle-aged population, with loss of the most productive life years. Although cirrhosis is the fourth leading cause of death in the US in people aged between 45 and 54 years of age, the mortality rate rises with increasing age reaching as high as 31 per 100000 amongst people in the age group of 75-84 years. Liver-related complications from alcohol contributes to 4% in mortality and 5% in disability adjusted life years (DALY) globally with the highest impact in Europe where similar figures are 7% and 12% respectively[5]. This huge disease burden has an economic impact of about 125 billion Euros annually in Europe, accounting for 1.3% of the gross domestic product. In 2006, the estimated total economic cost of excessive alcohol consumption in the US amounted to $223.5 billion. Of the $223.5 billion, 72.3% ($161.3 billion) represented the costs related to lost productivity, secondary to impaired productivity at work (45.9%) and lost productivity due to alcohol-related deaths (83180; 40.3%). In addition, another 11% ($24.6 billion) is lost due to increased healthcare costs, the largest expenditures coming from specialty treatment for alcohol abuse and dependence (43.4%), and hospitalizations due to medical conditions related to excessive drinking (20.8%). The remainder of the expenditure was due to the costs associated with the criminal justice system ($21 billion) and motor vehicle crashes ($14 billion)[6]. These figures are probably underestimates due to inaccuracies in death certificate reports, since the mention of alcohol as contributing cause of death may have social and legal implications.

Alcohol abstinence remains the cornerstone in the management of patients with alcoholic liver disease with the potential for improvement in liver histology, complications, and survival. However, complete reversibility of liver function usually does not occur once cirrhosis sets in. The use of corticosteroids and/or pentoxifylline in patients with severe alcoholic hepatitis provides about 50% survival benefit; nearly 20%-25% of such patients succumb to their illness despite treatment with these drugs. Thus, the curative management options for patients who are non-responsive to drugs and/or abstinence are limited, with the exception of liver transplantation (LT), a definitive treatment option for patients with cirrhosis and end-stage liver disease. In this article, we review the current status and special considerations on the use of LT for alcoholic cirrhosis and controversies and emerging data on liver transplantation for patients with severe alcoholic hepatitis that is non-responsive to pharmacological therapies.

LIVER TRANSPLANTATION FOR ALCOHOLIC CIRRHOSIS

LT is a definitive treatment option for patients with cirrhosis and ESLD. Over the last two decades, advances in technical aspects of the operative procedure, intraoperative and postoperative care, and immunosuppression protocols have led to graft and patient survivals of over 90% at one year after LT[7,8]. Currently, LT is an accepted treatment modality for ESLD patients who have an estimated 1 year survival of less than 10%[9]. The excellent graft and patient outcomes of patients transplanted for alcoholic cirrhosis have encouraged physicians and the transplant communities to more readily refer these patients for liver transplant evaluation[8-10]. Alcoholic liver disease remains the second most common indication for LT, accounting for approximately 40% of all primary transplants in Europe and about 25% in the United States[8,11]. However, in spite of the encouraging data, disparities remain on the referral pattern of patients with alcoholic cirrhosis. In one study, only 21% patients were found to qualify for LT based on the current American Association for Study of Liver Diseases (AASLD) guidelines[12].

Evaluation of alcoholic cirrhosis patients for liver transplantation

Evaluation for LT of a patient with alcoholic liver disease requires a multidisciplinary approach, with important contributions from psychiatrists and addiction specialists. However, the overall evaluation process of a patient with alcoholic cirrhosis for LT is similar to that of a patient with non-alcoholic cirrhosis, including the indications and contraindications for LT. However, there are certain specific issues that need to be addressed during the evaluation process, which will be briefly discussed.

Evaluation for alcohol use

The first step is to obtain a detailed and accurate history from the patient and the relatives and friends, of alcohol use to ascertain that the patient meets the criteria

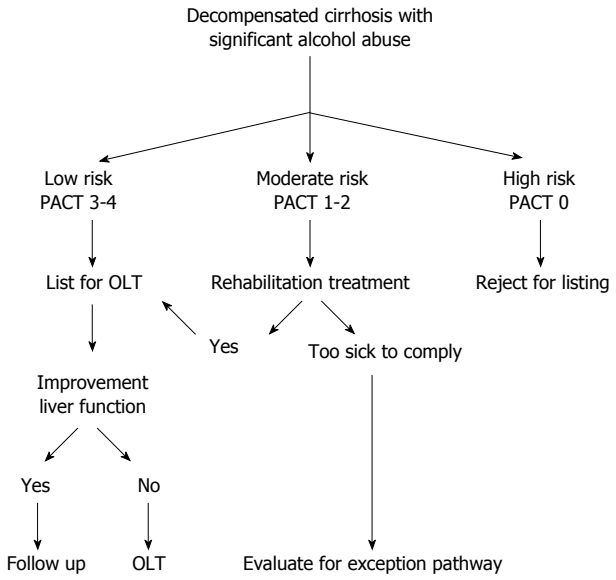

Figure 1 Psychosocial evaluation of patients with alcoholic cirrhosis awaiting listing for liver transplantation. OLT: Optical line terminal; PACT: Psychosocial Assessment of Candidacy for Transplantation.

for the diagnosis of alcohol-related cirrhosis[13]. Patients with alcohol dependence (tolerance to alcohol with use of increasing amounts, withdrawal symptoms, failed abstinence attempts, craving, and eye opener to avoid a hangover) should be identified, as these patients would often require rehabilitation treatment to maintain abstinence. As noted above, the history of alcohol use should be confirmed with relatives or friends since self-reported use of alcohol is often inaccurate. In one study, 18 of 82 alcoholic cirrhotic with a Department of Motor Vehicle record of driving under the influence (DUI) were not discovered on patient self-report[14]. Apart from the amount of alcohol use, it is mandatory to determine the date of the last drink in order to assess the duration of abstinence. A consensus conference in 1997 stated the need for minimum abstinence duration of 6 mo prior to listing a patient for LT (6 mo rule)[15]. The concept behind this rule was to allow the full benefit of abstinence on the liver functions, as studies have shown that the maximum benefit of abstinence is observed within the first 3-6 mo[16]. AASLD recommends that patients who continue to have significant liver disease despite 6 mo of abstinence should be considered and evaluated for LT[17].

Medical evaluation

A careful assessment should be made of the effects of alcohol on other organs including the presence of cardiomyopathy, chronic pancreatitis, Wernicke's encephalopathy, alcohol-related dementia, peripheral neuropathy, and upper aero-digestive malignancies as these can affect LT candidacy[18]. For example, patients with memory loss or confusion may be misdiagnosed as hepatic encephalopathy, instead of Wernicke's encephalopathy or alcohol dementia. Similarly, patients may have narcotic dependent due to chronic pancreatitis or may have poor performance status due to peripheral neuropathy that is unrelated to the liver disease. These issues need to be addressed as they have a negative impact on LT outcome. Therefore, detailed cardiac and neurological assessment should be done in alcoholic cirrhotic to assure their LT candidacy. Although, malnutrition does not impact outcome after LT, malnourished patients are known to have greater length of hospital stay and consume more hospital resources compared to well-nourished patients[19]. Therefore, nutritional status should be assessed and malnourished patients should receive supplementation for optimizing their nutritional status.

Psychosocial evaluation

Although psychosocial evaluation is mandatory for all transplant candidates, it is more important in alcoholic cirrhotic. Psychosocial Assessment of Candidacy for Transplantation (PACT) scale is a common tool used at most centers for evaluating candidates for all types of transplants[20]. This scale is used to assess social support, psychological health, life style factors, and patients' understanding of the transplant process including the follow up process after transplantation. Alcohol and substance abuse are only one part of this scale. Patients with intermediate risk for recidivism are recommended to undergo rehabilitation treatment before being considered for LT (Figure 1).

The data on the impact of rehabilitation treatment in maintaining abstinence are scanty, especially with respect to whether this treatment needs to be administered as out-patient sessions or as an in-patient intensive treatment for 2-3 wk followed by outpatient sessions. In a randomized study, motivational enhancement therapy (MET, $n = 46$) was beneficial compared to treatment as usual (TAU, $n = 45$) in reducing the amount and frequency of drinking prior to transplantation[21]. In this study, MET consisted of intensive 50-min sessions every month for 7 sessions along with Alcoholic Anonymous (AA) attendance. By contrast, TAU comprised of intensive outpatient treatment and community *AA* referral. However, compliance with the treatment was an issue since the average number of sessions in the MET group was only 3.8 instead of 7 as was proposed initially[21]. There are many reasons for failed adherence to rehabilitation treatment, the most important being inability to attend these sessions due to sickness from liver disease. These patients could be considered for exceptional pathway after multidisciplinary assessment and discussion (Figure 1). A randomized controlled trial on 84 alcoholic cirrhotic on the use of baclofen in maintaining abstinence and reducing hospital readmission rates has provided encouraging results[22]. It was observed that a higher proportion of patients maintained abstinence with baclofen compared to placebo (71% *vs* 29%, $P = 0.0001$) and had a longer mean duration of abstinence (62 d *vs* 31 d, $P = 0.001$). Further, there was improvement in liver function in patients treated with baclofen as compared to patients receiving placebo[23].

Detection of relapse to alcohol use (recidivism)

While awaiting LT, patients should be followed regularly and closely to confirm abstinence as patients not complying with this recommendation should lose their listing status. At each visit, physicians should perform detailed history, urine drug screening, serum nicotine in recent or current smokers, and blood ethanol or other markers of alcohol use. In one study, random blood alcohol screens reduced recidivism by 37%[24]. Methanol testing is more sensitive and detects recent alcohol use when blood ethanol levels are normal[25]. Gamma glutamyltransferase (GGT) is a more sensitive test (70%) than aminotransferase for chronic heavy alcohol use. However, it is not specific in the pre-transplant setting as it may be elevated in cirrhotic patients[5]. Carbohydrate-deficient transferrin (CDT) is an FDA approved marker for alcohol abuse. Moderate to heavy alcohol use reduces the carbohydrate content of transferrin molecule synthesized by the liver[26]. Its performance in detecting alcohol use is better when combined with GGT, with sensitivity of 90% and 75% in males and females respectively[26]. However, since CDT levels are impacted by the severity of liver disease, its use is limited in the pre-transplant setting. Further, CDT levels are affected by smoking and need to be adjusted for total transferrin levels in females[27]. New biomarkers using metabolites of alcohol such as ethyl glucuronide (eTG) are under investigation. Urine eTG is extremely sensitive and can detect alcohol level as low as 10 ng/mL and may become falsely positive with the use of alcohol-containing medications and hand sanitizers. In one study, a cut-off level of 0.5 mg/L, as detected by liquid chromatography-mass spectroscopy (LC-MS), is 89% sensitive and 99% specific with a negative predictive value of 99% and positive predictive value of 89%. Increasing the cut-off level to 1 mg/L did not improve the specificity but decreased the sensitivity to 75%[28]. In this study, combining UeTG with CDT could accurately diagnose 93% of patients with recidivism. UeTG may be falsely negative in patients with urine infection especially with *E. coli* as this metabolite of alcohol may be degraded by the bacterium[29]. Ethyl sulfate (EtS) another metabolite of alcohol is not affected by bacterial degradation and its simultaneous measurement in the urine can overcome this limitation[30]. However, the short-term window for positivity limits the use of these markers in routine clinical practice after the last heavy alcohol use: a few hours for BAL and methanol, and 4-5 d for UeTG and EtS[28]. In this regard, hair analysis for ethyl glucuronide is useful since the metabolite remains in hairs for one month[31]. A cut off level of 7 pg/mg of hair sample is a strong indicator of regular alcohol use, and a cut off level of 30 pg/mg can be accurately diagnose heavy drinking[32]. Other markers such as phosphatidyl ethanol, acetaldehyde, Cytochrome P-450 (CYP) E, mono amino oxidase-B, 5-tryptophol, and fatty acid ethyl ester are experimental and unavailable for clinical application at the present time[33].

Recidivism after liver transplantation for alcoholic cirrhosis

Recidivism is reported in 10%-60% of transplant recipients for alcoholic liver disease[34-37]. The large variation in prevalence rates of recidivism is perhaps due to different definitions used, with some defining recidivism as any alcohol use while others only include harmful drinking, defined as 2 or more drinks per day, which is reported in 15%-20% patients. Recidivism rates across different studies are also affected by the duration of follow up. In a pooled analysis from 50 studies evaluating recidivism after liver transplantation, the rates of any alcohol use after LT were 5.7% per 100 person years, and 2.5% per 100 person years risk for harmful drinking[38]. DiMartini *et al*[39] reported on the patterns of alcohol use after LT. Nearly 45% patients reporting some alcohol use (26% rare slips and 19% harmful drinking). Of those with harmful drinking, about 1/3rd each reported early start (within 2-3 years after LT) with subsequent decline, continued harmful drinking throughout, and late start (after the first 3 years and then persisting with alcohol use).

Data on the accuracy of 6-mo pre-transplant abstinence in predicting recidivism are scanty and controversial. In a systematic review of 22 studies reporting predictors of recidivism, only 2 of the 11 studies evaluating this variable reported it to be an accurate predictor of recidivism[40]. Social and family support, preexisting psychiatric comorbidities, polysubstance use, unsuccessful attempts at rehabilitation, younger age at LT, and family history of alcoholism emerged as the strongest predictors for recidivism[40]. In another study based on the duration of drinking, the number of daily drinks consumed, and the number of previous alcoholism treatments, the high-risk alcoholism relapse (HRAR) score (ranging from 0-6) was calculated and compared with 6-mo abstinence in predicting recidivism. HRAR emerged as a stronger predictor of abstinence with 79%, 69%, and 54% agreement between HRAR and 6 mo abstinence for low, moderate, and high HRAR groups respectively[41]. The impact of pre-transplant motivational enhancement therapy on recidivism could not be assessed in a randomized study due to the small sample size[21].

Outcomes of patients transplanted for alcoholic cirrhosis

The patient survival rates after LT for alcoholic cirrhosis based on data from different parts of the world have been reported to be 81%-92%, 78%-86%, and 73%-86% at 1, 3, and 5 years respectively[8,11,42]. There is improvement in the quality of life, mood status and cognitive functioning, with no difference compared to patients transplanted for non-alcoholic cirrhosis[43,44]. Patients were able to return to society and lead active and prolific lives, irrespective of the indication for transplantation[34,45].

Concomitant alcohol abuse and HCV infection is observed in about 14% of individual with chronic liver disease[3]. The data on outcomes in HCV positive drink-

Table 1 Studies on recidivism and its impact on liver graft and liver related death

Ref.	Total No.	Median FU year	Percent recidivism	Percent graft loss alcohol related	LRD as percent of all deaths
Conjeevaram *et al*[55]	68	3.5	8	38	38
Cuadrado *et al*[52]	99	8.25	26	0	NR
Pageaux *et al*[94]	121	4.5	21	1	12
Lucey *et al*[35]	50	5.25	33[1]	6	6
Pfitzmann *et al*[95]	300	7.5	7	50	88
Schmeding *et al*[51]	271	10	27	0	NR
Dumortier *et al*[78]	305	5.25	12	2	8

[1]Any use of alcohol in this study was reported as recidivism. Other studies defined recidivism as heavy drinking defined with variable amount of alcohol use across different studies. LRD: Liver related death.

ers are scanty and conflicting. Studies using transplant registries from the United States and Europe, suggest worse survival outcomes compared to HCV negative alcoholic cirrhosis[11,46,47], although a study from a single European center reported similar outcomes[48]. It should be noted that in the latter study, patients received antiviral therapy more often compared to patients with HCV cirrhosis alone, which may explain the difference in the outcome[48]. Unfortunately, such information is lacking in data collected from registries. Further, HCV positive drinkers may have been misclassified in the registry databases due to lack of information on the amount of alcohol use. Further studies using data from single or multiple centers with detailed information on these variables are needed to examine post-transplant outcomes of alcoholic cirrhosis and concomitant HCV infection.

Relapse to harmful drinking affects long-term patient survival. Compared to abstinent patients transplanted for non-alcoholic liver diseases, the survival rates in patients with recidivism to harmful drinking are similar initially but become worse after 5-10 years (45%-68% *vs* 75%-86%)[49-52]. The proportion of patients dying from liver-related cause in patients transplanted for alcoholic cirrhosis varies from 6%-88% in various series (Table 1). Graft loss from recurrent disease related to alcohol use is rare[53,54]. Rates of graft loss due to recidivism are 0%-6% in most series except two studies from the same institution which reported 38% and 50% graft loss related to alcohol use (Table 1)[35,55]. Harmful drinking in the early phase of post-transplant period is more significant in terms of the impact on liver graft. In one study, graft loss and liver-related mortality occurred in 72% and 45% respectively in patients with early onset harmful drinking compared to 45% and 0% amongst those who were abstinent, had rare slips, or later use of harmful drinking[56]. Recurrent cirrhosis and graft loss accounts for about 3% of the original cohort of transplant recipients for alcoholic cirrhosis[57]. It is unclear whether certain genetic factors in the donor liver play a protective role despite recidivism to harmful drinking in these patients who were originally genetically predisposed to alcohol-related liver injury. However, once recurrent cirrhosis sets in, the outcome is worse compared to patients with a functional graft (30% ± 17% *vs* 75% ± 6% survival at 10 years, $P = 0.045$)[57].

With the introduction of effective immune suppression regimens, which protect the liver graft, non-hepatic disorders including metabolic syndrome and malignancies have become more important causes of patient mortality after LT for alcoholic liver disease. Registry analyses from Europe and United States have shown that cardiovascular causes and *de novo* malignancies were significantly over-represented in patients who had undergone transplantation for ALD *vs* recipients without ALD[11,47]. Although, the metabolic syndrome is seen frequently on long term follow up after LT, patients transplanted for alcoholic cirrhosis are particularly prone to this complication followed by patients transplanted for non-alcoholic steatohepatitis-related ESLD[58,59]. The development of the metabolic syndrome is a risk factor for cardiovascular death in patients who survive the first year after LT[60].

The development of *de novo* malignancy in LT recipients was recognized as early as 1972[61]. About 5%-15% of patients receiving liver transplantation develop *de novo* extrahepatic malignancy. Skin cancer accounts for 30%-50% followed by post-transplant lymphoproliferative disorders (PTLD) and solid organ cancers[62,63]. The risk is higher compared to the general population for skin as well as solid organ cancers with standardized incidence ratio of about 15 and 2-2.5 respectively[64,65]. The risk increases with time to as high as 19% and 34% at 10 and 15 years post-transplant respectively[64]. The risk for *de novo* malignancy is 1.5-2 folds higher in transplant recipients for alcoholic liver disease compared to transplants for non-alcohol-related etiologies[66-69]. Patients transplanted for alcoholic cirrhosis are at a unique risk for the development of upper aero-digestive cancers with about 10-fold higher risk compared to transplants for other indications[68-70]. Intensive screening for head and neck cancers prior to transplant does not seem to be cost effective, with only 0.17% prevalence of this cancer in one study that evaluated 581 patients with alcohol-related cirrhosis[71].

The use of immune suppression post-transplantation is believed to be the major mechanism for the development of *de novo* malignancy[62,63]. Other risk factors are older age, male gender, and Epstein Barr virus reactivation or infection for lymphoproliferative malignancy, and exposure to sun for non-melanoma skin cancer[63,72,73]. The mechanisms involved in predisposing alcohol-related

transplant patients to malignancy are poorly understood. Oncogenic properties of acetaldehyde, a metabolite of alcohol, and the inhibition of DNA methylation have been blamed[74]. Smoking both pre and post-transplant increases the risk for upper aerodigestive cancers in patients transplanted for alcoholic cirrhosis[62,63]. In one study, 60% of the 202 LT recipients analyzed reported a life time history of smoking, with 54% using both alcohol and tobacco in the pre-transplant period. Of those who quit, 20% patients had a relapse to smoking in the post-LT period[75]. In another study, a higher proportion of transplanted patients had a positive smoking history compared to transplants for non-alcoholic diseases (82% *vs* 45%, $P = 0.001$), with a higher mean number of cigarettes smoked by alcoholics (25 *vs* 16 cigarettes per day, $P = 0.001$)[76].

The development of malignancy has a significant impact on patient survival, with about 38% and 53% risk of death at 1 and 5 years after diagnosis[68]. *De novo* malignancy accounts for 30%-40% of all deaths in LT recipients who survive the first year after transplantation[77,78]. Implementation of intensive surveillance protocols in the post-transplant period has been shown to improve survival by detection of these cancers at an early stage[79,80]. Patients should be instructed to use sun screens when exposed to sun, come for annual physical checkup including skin and ENT examinations, and avoid use of nicotine and alcohol. Intensive protocols have included annual chest X-ray, urine examination, CT chest, abdomen and pelvis, mammography, PAP smear, in addition to standard guidelines for colonoscopy screening. With such a protocol, the overall survival in the surveillance group showed significant improvement (11.3 years *vs* 3.1 years, $P = 0.001$)[79]. However, clear guidelines for other cancers including the frequency of work-up have not been developed.

A higher occurrence of neurological complications has been reported in patients transplanted for alcoholic liver disease, resulting in greater resource utilization[81,82]. These include profound confusion in the early postoperative period, and structural injury from prolonged alcohol use which remained unrecognized before transplant[83,84]. Therefore, detailed and accurate pre-transplant assessment for neurological issues is needed in patients with alcoholic-related cirrhosis, as alluded to earlier in the pre-transplant evaluation section.

LIVER TRANSPLANTATION FOR ALCOHOLIC HEPATITIS

Alcoholic hepatitis is a distinct clinical syndrome seen in patients with chronic and active alcohol use with a potential for mortality of 40%-50% in patients with untreated severe disease. Alcoholic hepatitis occurs in 35%-40% of patients with chronic excessive alcohol use, and represents about 0.2% (20 of every 1000) hospital admissions in the United States[85,86]. The true prevalence is difficult to assess as many patients remain undiagnosed and only 10%-35% of alcohol-related cirrhotic may have changes consistent with alcoholic hepatitis on liver biopsy[87]. The incidence rates of ALD-related deaths decreased from 6.9/100000 persons in 1980 to 4.4/100000 persons in 2003. The age- and sex-adjusted alcoholic liver disease related mortality (per 100000 persons) decreased from 6.3 to 4.5 in Caucasians, 11.6 to 4.1 in African Americans, and 8.0 to 3.7 in the "other" race groups[88]. Overall, the incidence of alcoholic hepatitis is about 7%-10% in mild illness and 40%-50% with severe disease[85-89]. Although, mortality from alcoholic hepatitis has decreased over the last decade as with alcoholic cirrhosis, patients with alcoholic hepatitis and concomitant HCV infection remain at a higher risk of death with 20%-25% higher mortality as compared to alcoholic hepatitis patients without HCV infection[86]. One of the possible reasons may be fear of physicians and gastroenterologists in using corticosteroids for the treatment of alcoholic hepatitis in the presence of HCV infection[90]. More studies are needed aimed at generating guidelines for managing alcoholic hepatitis patients who also have HCV infection.

The available treatment options that include the use of corticosteroids and/or pentoxifylline achieve about 50% survival benefit, with the likelihood of mortality in about 20%-25% patients[85,89]. With the current lack of available pharmacological options for patients with non-response to steroids, there remains an unmet need for the development of newer and more effective drugs. These patients generally do not qualify for LT because of the requirement of 6 mo of abstinence demanded by most transplant centers worldwide. This requirement cannot be met by alcoholic hepatitis patients who do not respond to steroids since by definition they were drinking up until at least 3 wk prior to getting sick. Further, there are other ethical concerns and controversies involved in the use of LT for these patients such as: (1) public opinion that this disease is self-inflicted; (2) shortage of donor livers and the view that they should be allocated to more deserving patients; and (3) the risk of recidivism after LT[91]. The other side of the argument is that pre-transplant abstinence of 6 mo is not a strong predictor of recidivism. Further, patients transplanted for alcoholic cirrhosis with histological changes consistent with alcoholic hepatitis on explants have been shown to have similar post-LT survival compared to patients without such histological changes[87]. An obvious ethical question is whether severe alcoholic hepatitis patients who do not respond to treatment should be left to their fate to die or should be considered for LT as suggested by the French consensus group[91].

The same group took the lead and challenged the 6 mo abstinence rule in a prospective case control study. In this study, 26 patients (mean age 47 years, 58% males) with a first episode of severe alcoholic hepatitis (median MELD 30[22-47]) who did not respond to steroids were recruited from four different centers in Europe (2006-2010) and received LT as a life-saving option. The patients underwent detailed and rigorous psychosocial evalua-

tion by the resident team, hepatologist, anesthesiologist, and surgeon and LT was approved only if all four teams cleared the patient. The median duration between declaring a patient as non-responder to steroids (Lille score ≥ 0.45) and receipt of LT was 9 (1-13) d[92]. Compared to the 26 matched patients who did not receive LT (control group), patients receiving LT had a significantly better outcome at 1 mo (77% ± 9% *vs* 25% ± 8%, $P < 0.001$) and at 2 years (73% ± 8% *vs* 23% ± 8%, $P < 0.001$). Patients receiving LT had survival similar to patients responding to steroid treatment (78% ± 8% *vs* 83% ± 4%, $P = 0.33$)[92]. As can be seen, the majority of deaths in the control group occurred within the first month, indicating the importance of transplanting these patients early without waiting for the 6 mo abstinence requirement**.** Three patients resumed alcohol intake at 720, 740, and 1145 d after LT. The first two patients reported harmful drinking of 30 g/d and > 50 g/d of alcohol respectively, while the 3rd patient was consuming a lower amount, about 10 g/wk. However, recidivism in this study was self-reported which is known to be frequently inaccurate[92]. None of the patients lost the graft due to alcohol use. However, three of the 6 deaths in this study were due to invasive fungal infections. This is unlikely to be due to pre-existing infections as all these patients were undergoing daily rigorous infection work-up prior to LT. Prospective studies are required to evaluate strategies of immune suppression for preventing fungal infections. The authors concluded that LT should be considered as a salvage option in select patients with severe alcoholic hepatitis who do not respond to steroids. With the strict selection of patients, only about 2%-3% of the original cohort with alcoholic hepatitis was amenable to this treatment modality[92]. In the United States, nearly 50000 patients with alcoholic hepatitis are admitted annually. Considering that about 20% of these patients have severe disease, which translates to about 200-300 patients who may qualify for LT as a therapeutic option. However, any amendment in the guidelines for liver transplantation in patients with alcoholism may have an adverse impact on public preferences for liver-transplant allotment and may decrease willingness to donate. However, this has not occurred in response to transplantation being offered to patients with fulminant hepatic failure due to self-inflicted acetaminophen poisoning, or in intravenous-drug users with acute hepatitis B virus infection. Before implementing this in routine practice, with the potential of adversely affecting the liver donor pool, more data are needed on larger patient populations. Until then, there is a ray of hope for patients with a first episode of alcoholic hepatitis who do not respond to steroids and have excellent psychosocial support systems.

Similar findings were reported in a retrospective study using the UNOS database. In this study, 55 patients (mean age 51 years, 76% males) received LT (2004-2010) for a listing diagnosis of alcoholic hepatitis (median MELD 24[16-34]). The results were compared with 165 patients (matched for age, gender, UNOS region, MELD score, and donor risk index), transplanted for alcoholic cirrhosis. There was no difference in the respective outcomes at 1, 3, and 5 years for liver graft survival (87% *vs* 84%, $P = 0.58$, 82% *vs* 77%, $P = 0.47$, and 75% *vs* 73%, $P = 0.97$) and patient survival (93% *vs* 88%; $P = 0.33$, 87% *vs* 81%, $P = 0.33$, and 80% *vs* 78%, $P = 0.91$)[93]. A higher proportion of alcoholic hepatitis patients had concomitant HCV infection compared to the alcoholic cirrhosis controls (27% *vs* 7%, $P = 0.02$). After controlling for HCV and other recipient and donor factors, the graft and patient survival was not different, with OR (95%CI) of 0.82 (0.41-1.63) and 0.7 (0.33-1.54) respectively[93]. Since patients with alcoholic hepatitis have underlying alcoholic cirrhosis in about 60%-70% cases, the outcomes were also compared based on the explant diagnosis. A total of 46 patients with an explant diagnosis of alcoholic hepatitis were compared with 138 patients with an explant diagnosis of alcoholic cirrhosis, again the outcomes were similar. Moreover, 11 patients with a listing as well as explant diagnosis of alcoholic hepatitis compared to 33 patients with a listing and explant diagnosis of alcoholic cirrhosis had equivalent outcomes[93]. None of the patients died or lost their graft secondary to alcohol use. However, in addition to the drawbacks of a retrospective study, this study was limited by the lack of information on alcohol drinking history.

SUMMARY AND FUTURE PERSPECTIVES

In conclusion, alcoholic cirrhosis remains the second most common indication for LT. Although, outcomes are excellent in general, recidivism does impact long-term survival. Graft loss and recurrent alcoholic liver disease rarely leads to mortality. However, the development of metabolic syndrome and *de novo* malignancy contribute to the majority of deaths in the long term. The emerging data on the beneficial role of LT provides a ray of hope for select patients with alcoholic hepatitis with the following characteristics: (1) first episode of severe alcoholic hepatitis; (2) failure to respond to pharmacological approach; and (3) excellent psychosocial support. However, certain unsettled issues need to be resolved. These include: (1) The current discrimination for transplant evaluation and transplant listing of patients with alcoholic cirrhosis; (2) physician and center based barriers to liver transplant evaluation and listing; (3) accurate predictors independent of pre-transplant sobriety duration for post-transplant relapse to heavy drinking; (4) genetic factors in the donor graft that may protect the recipient from recurrent disease despite relapse to heavy drinking; (5) simple and accurate biomarkers for use in clinical practice to detect recidivism with a long window period; (6) cost-effective surveillance protocols for early detection of *de novo* malignancy after liver transplantation; (7) creation of a prospective database on the outcome of LT in patients with a first episode of acute alcoholic hepatitis; and (8) development of better immune suppression regimens in these patients, especially

in reducing invasive fungal infections.

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