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EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Hepatology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
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MINIREVIEWS

Risk factors and outcomes associated with alcohol relapse after liver transplantation

Jane Lim, Michael P Curry, Vinay Sundaram

Jane Lim, Department of Medicine, Cedars Sinai Medical Center, Los Angeles, CA 90048, United States

Michael P Curry, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA 02215, United States

Vinay Sundaram, Division of Gastroenterology and Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

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Correspondence to: Vinay Sundaram, MD, MSc, Assistant Medical Director, Division of Gastroenterology and Comprehensive Transplant Center, Cedars-Sinai Medical Center, 8900 Beverly Blvd, Suite 250, Los Angeles, CA 90048, United States. vinay.sundaram@cshs.org
Telephone: +1-310-4236000
Fax: +1-310-4230849

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Abstract

Alcoholic liver disease (ALD) is the second most common indication for liver transplantation (LT) in the United States and Europe. Unlike other indications for LT, transplantation for ALD may be controversial due to the concern for alcohol relapse and non-compliance after LT. However, the overall survival in patients transplanted for ALD is comparable or higher than in patients transplanted for other etiologies of liver disease. While the rate of alcohol use after liver transplantation does not differ among various etiologies of liver disease, alcohol relapse after transplantation for ALD has been associated with complications such as graft rejection, graft loss, recurrent alcoholic cirrhosis and reduced long-term patient survival. Given these potential complications, our review aimed to discuss risk factors associated with alcohol relapse and the efficacy of various interventions attempted to reduce the risk of alcohol relapse. We also describe the impact of alcohol relapse on post-transplant outcomes including graft and patient survival. Overall, alcohol liver disease remains an appropriate indication for liver transplantation, and long-term mortality in this group of patients is primarily attributed to cardiovascular disease or *de novo* malignancies rather than alcohol related hepatic complications, among those who relapse.

Key words: Cirrhosis; Relapse prevention; Recidivism

Core tip: There are no established risk factors or scoring systems to predict alcohol relapse after transplantation for alcoholic liver disease. Studies regarding the "6-mo rule" demonstrated heterogeneous findings, suggesting that this rule is not a reliable predictor of relapse.

Comorbid psychiatric conditions, lack of social support, and tobacco use are consistently associated with alcohol relapse. Scoring systems have been proposed, but have not been validated. Alcohol relapse may be associated with graft rejection and graft loss, though reduction in long-term survival may be attributed to cardiovascular disease and *de-novo* malignancies rather than alcohol-related hepatic complications.

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INTRODUCTION

Alcohol use disorder affects nearly 10% of the general population in both the United States and Europe and is one of the most frequent causes of liver cirrhosis in the Western world[1]. After hepatitis C virus (HCV) infection, alcoholic liver disease (ALD) is the second most common indication for liver transplantation (LT) in the United States and Europe[2,3]. According to the OPTN/SRTR 2015 annual report, 21% of liver transplantation was for alcoholic liver disease[4].

Unlike other indications for LT, transplantation for ALD may be controversial because of the concern regarding relapse and medication non-compliance after transplantation[5]. The exact proportion of ALD patients who drink alcohol after LT is unclear and is reported to range anywhere between 7%-95%[6-8]. The broad range of percentages reported in the literature is because there are no standardized definitions for alcohol relapse[6-8]. Interestingly, the rate of alcohol use after LT does not differ between patients transplanted for other etiologies of liver disease, though recipients transplanted for ALD tend to drink in greater quantities[9,10]. In terms of patterns of alcohol use, there are varying frequencies given the different definitions and follow-up periods, but in general approximately 12%-33% of liver recipients for ALD relapse to abusive or harmful amounts of drinking[11-14] and 6%-26% relapse to occasional slips after transplantation[12,14,15]. Furthermore, the overall survival rate for patients transplanted for ALD is comparable or higher than those of patients transplanted for non-ALD[2,3,10,16]. Still, separate studies have identified harmful and excessive amounts of alcohol use to be associated with increased rates of graft rejection and failure[10,15,17-19]. Due to these potential adverse complications, our aim was to discuss risk factors associated with alcohol relapse after transplantation, the efficacy of interventions attempted to prevent relapse, and the post-transplant outcomes associated with alcohol relapse[5].

Definitions

There are no standardized definitions or classification criteria to describe alcohol consumption after transplantation. Terms that have been used in the literature include recidivism or relapse[7,15-17,19]. Quantification of alcohol consumption after LT can also be described using terms such as abstinence, occasional slip, harmful drinking and excessive drinking, though the definitions of these terms are variable (Table 1)[8,20,21]. Lucey *et al*[22] defines harmful drinking as consumption of 4 or more drinks in one day or drinking for 4 or more days in succession, whereas a slip is defined as consumption of a limited amount of alcohol, followed by immediate measures to re-establish abstinence. De Gottardi *et al*[11] defined harmful drinking as alcohol consumption greater than 40 g/d that was associated with the presence of alcohol-related damage, such as histologic features of alcoholic liver injury on biopsy. The Diagnostic and Statistical Manual of Mental Disorders Version Ⅳ defined alcohol abuse as meeting one of the following criteria during a 12 mo period: Use which causes failure to fulfill major role obligations at work, school or home, use which causes a hazardous situation, use which causes legal problems or use continuing in the setting of recurrent social or interpersonal problems[23,24]. Faure's study used the World Health Organization definition where excessive alcohol consumption was > 20 g and > 30 g/d for women and men[10].

"The 6 mo rule"

Many centers require 6 mo of abstinence to be listed for liver transplantation. The 6 mo rule has two presumed purposes: To allow patients to recover from their liver disease and preclude the need for liver transplantation and to identify patients who are likely to remain abstinent after liver transplantation[1]. Nonetheless, there are conflicting findings as to whether this length of abstinence is needed to reduce the risk of relapse[11,25-27]. There have been several studies which have found that duration of abstinence less than 6 mo is associated with alcohol use and harmful drinking (Table 2)[11,28,29]. Additionally, Tandon *et al*[30] calculated that for every additional month of pre-LT abstinence there was a 5% decrease in the adjusted relapse rates. This is contrasted by other studies that have shown that the 6-mo rule is not a strong indicator of future drinking[26,27,31]. Based on the conflicting outcomes, the 6-mo rule may not reliably predict post-transplant relapse.

Furthermore, achieving 6 mo of abstinence is not always feasible, particularly for patients with severe alcoholic hepatitis that is refractory to treatment[32,33]. In fact, certain professional societies suggest that the 6-mo rule should not be required in patients where the expected mortality of the disease would not allow for a 6-mo waiting period[1,18,34]. Additionally, survival outcomes are superior among patients with severe alcoholic hepatitis that is refractory to corticosteroids and subsequently undergo OLT, as compared to those receiving standard of care[34-37]. As demonstrated by Mathurin *et al*[34] patients with severe alcoholic hepatitis who underwent OLT had a significantly greater cumulative 6 mo survival of 77% compared to

Table 1 Definitions of alcohol use after liver transplantation

Study	Term	Definition
Lucey *et al*[21]	Harmful drinking	Consumption of 4 or more drinks in one day or drinking for 4 or more days in succession
	Occasional slip	Consumption of a limited amount of alcohol, followed by immediate procedures to re-establish abstinence
De Gottardi *et al*[11]	Harmful drinking	Consumption greater than 40 g/d that is associated with the presence of alcohol-related damage, such as histologic features of alcoholic liver injury on biopsy
Diagnostic and Statistical Manual of Mental Disorders Version Ⅳ	Alcohol abuse	Meeting one of the following criteria during a 12 mo period: Use which causes failure to fulfill major role obligations at work, school or home, use which causes a hazardous situation, use which causes legal problems or use continuing in the setting of recurrent social or interpersonal problems
World Health Organization	Occasional consumption	Men: < 20 g/d Women: < 30 g/d
	Excessive consumption	Men: > 20 g/d Women: > 30 g/d

23% for controls who did not receive transplantation (P < 0.001).

PATIENT FACTORS ASSOCIATED WITH RELAPSE

Age

Like the 6-mo rule, age has an inconsistent association with alcohol relapse after LT. A few studies have found that younger age is associated with alcohol relapse after LT and that the category of patients that relapsed were significantly younger compared to those that did not[14,26,38]. One study found that age < 45 years was associated with increased risk of relapse and another found an association between relapse and age < 40 years[15,38]. These findings are contrasted by other studies that found no association between age and alcohol relapse[8,27]. Furthermore, two larger studies determined that age is not an independent risk factor associated with alcohol relapse[11,15]. Based on the heterogeneity of these findings, we believe that age is not a reliable predictor of risk of alcohol relapse.

Social support

Lack of social support is an extrinsic factor that has consistently been associated with an increased risk of relapse for patients transplanted for ALD[13,15,31,39]. ALD patients who resumed alcohol use post-LT were more likely to be divorced or separated from their partners compared to those that remained abstinent, and multiple studies found that the lack of a spouse or life partner is a predictor of alcohol relapse[8,13,15,31]. One study also suggested that marriage is protective against binge drinking[13]. Therefore, it is important to ensure that patients with ALD have a strong support system during LT evaluation.

Comorbid psychological conditions

The presence of psychiatric comorbidities or previous diagnosis of a mental illness has been found to be an important intrinsic risk factor for increased risk of relapse after LT[11,13,31]. Multivariate analysis showed that a pre-LT diagnosis of a psychiatric disorder (anxiety or depressive disorder) at the time of listing was independently associated with a significantly increased risk of harmful levels of alcohol relapse, which is defined as consumption of greater than 40 g/d[11]. Another study also determined that a prior diagnosis of a mental illness was significantly associated with harmful drinking, which was defined in the study as consumption of greater than 140 g of ethanol per week[31]. Furthermore, prior treatment for co-morbid psychiatric disorders is a potential risk factor for alcohol relapse[40]. Evaluation for comorbid psychiatric conditions during the LT evaluation period may potentially help identify ALD patients that are at higher risk of both alcohol relapse and harmful drinking after transplantation.

Employment

In a cross-sectional study of organ transplant patients, only 37.5% of liver transplant patients were employed post-transplant[41]. Furthermore, among liver transplant recipients, those transplanted for ALD are significantly less likely to be employed both before and after transplant compared to transplant recipients for non-ALD[9]. A total of 29% of transplant recipients with ALD and 59% of those with non-ALD worked pre-transplantation, *vs* 33% of those with ALD *vs* 80% of non-ALD at 3 years post-transplantation (P < 0.00001)[9]. Furthermore, ALD patients that were previously employed were less likely to return to work compared to patients transplanted for non-ALD[8]. Despite the low proportion of ALD patients that work pre and post-transplant, employment status does not appear to be significantly associated with the risk of alcohol relapse after transplantation[8,26,27,31].

Cigarette smoking

Studies have found cigarette smoking to be associated with alcohol relapse after transplant for alcoholic cirrhosis[17,31,40,42]. Kelly *et al*[31] demonstrated in univariate analysis that pre-transplant tobacco use was a predictor of harmful alcohol drinking in the post-transplant period. This was not a significant finding when subjects were

Table 2 Risk factors associated with alcohol relapse

Risk Factor	Ref.	Study design	Sample size	Results
Abstinence less than 6 mo pre-LT	Perney *et al*[26] (2005)	Retrospective	*n* = 61	Associated with severe relapse to heavy drinking[1]
	De Gottardi *et al*[11] (2007)	Retrospective	*n* = 387	Associated with relapse
	Pfitzmann *et al*[15] (2007)	Retrospective	*n* = 300	Associated with relapse
	Tandon *et al*[30] (2009)	Retrospective	*n* = 171	For every 1-mo increment increase in pre-transplant abstinence, there was a 5% decrease in the adjusted relapse rate
	Karim *et al*[29] (2010)	Retrospective	*n* = 80	Associated with relapse and is an independent risk factor for relapse
	Satapathy *et al*[42] (2015)	Retrospective	*n* = 148	Associated with alcohol relapse
	Osorio *et al*[28] (1994)	Retrospective	*n* = 43	No association
	Jauhar *et al*[27] (2004)	Retrospective	*n* = 112	No association
	Björnsson *et al*[8] (2005)	Retrospective	*n* = 103	No association
	Addolorato *et al*[25] (2013)	Retrospective	*n* = 55	No association
	Egawa *et al*[40] (2014)	Retrospective	*n* = 140	No association
Abstinence < 1 yr pre-LT	Kelly *et al*[31] (2006)	Retrospective	*n* = 100	No association with harmful relapse[2]
	Gedaly *et al*[79] (2008)	Retrospective	*n* = 142	Independent predictor of relapse
Age	Perney *et al*[26] (2005)	Retrospective	*n* = 61	Alcohol relapse group was younger compared to the non-relapse group
	Pfitzmann *et al*[15] (2007)	Retrospective	*n* = 300	Age < 40 yr of age was associated with relapse, but was not an independent risk factor
	Karim *et al*[29] (2010)	Retrospective	*n* = 80	Age < 50 yr of age approached clinical significance for alcohol relapse
	Rice *et al*[14] (2013)	Retrospective	*n* = 300	Alcohol relapse group was younger compared to the non-relapse group
	Grąt *et al*[38] (2014)	Retrospective	*n* = 97	Younger age < 45 associated with relapse
	Satapathy *et al*[42] (2015)	Retrospective	*n* = 148	Older patients had lower likelihood of alcohol relapse
	De Gottardi *et al*[11] (2007)	Retrospective	*n* = 387	Age > 50 yr associated with relapse
	Jauhar *et al*[27] (2004)	Retrospective	*n* = 112	No association
	Björnsson *et al*[8] (2005)	Retrospective	*n* = 103	No association
Social support	Kelly *et al*[31] (2006)	Retrospective	*n* = 100	Lack of partner associated with harmful alcohol relapse[2]
	Pfitzmann *et al*[15] (2007)	Retrospective	*n* = 300	Absence of life companion associated with increased risk of alcohol relapse
	DiMartini *et al*[13] (2006)	Prospective	*n* = 167	Marriage is protective against binge use
	Rodrigue *et al*[39] (2013)	Retrospective	*n* = 118	Limited social support associated with alcohol relapse
	Egawa *et al*[40] (2014)	Retrospective	*n* = 140	Marital status associated with alcohol relapse and harmful relapse[3]
	Satapathy *et al*[42] (2015)	Retrospective	*n* = 148	Support from immediate family (spouse, parent or child) was highly correlated with reduced risk of alcohol relapse
Marital status	Björnsson *et al*[8] (2005)	Retrospective	*n* = 103	No association
Psychiatric condition	De Gottardi *et al*[11] (2007)	Retrospective	*n* = 387	Associated with relapse
	Karim *et al*[29] (2010)	Retrospective	*n* = 80	Associated with relapse
	Kelly *et al*[31] (2006)	Retrospective	*n* = 100	Previous diagnosis of a mental illness associated with harmful drinking[2]
	DiMartini *et al*[13] (2006)	Prospective	*n* = 167	History of depressive disorder associated with alcohol relapse
	Egawa *et al*[40] (2014)	Retrospective	*n* = 140	A history of treatment for psychological diseases other than alcoholism before LT is associated with risk of alcohol relapse but not harmful drinking[3]
	Jauhar *et al*[27] (2004)	Retrospective	*n* = 112	Comorbid psychiatric condition had no association with relapse
Employment	Jauhar *et al*[27] (2004)	Retrospective	*n* = 112	No association
	Perney *et al*[26] (2005)	Retrospective	*n* = 61	No association
	Kelly *et al*[31] (2006)	Retrospective	*n* = 100	Previous occupation not associated with harmful drinking
	Egawa *et al*[40] (2014)	Retrospective	*n* = 140	Post-LT occupational status not associated with alcohol relapse
	Satapathy *et al*[42] (2015)	Retrospective	*n* = 148	Employment status at time of transplant was not associated with alcohol relapse
Cigarette smoking	Pageaux *et al*[17] (2003)	Retrospective	*n* = 128	Occasional and heavy drinkers were more likely to be cigarette smokers compared to abstinent patients
	Kelly *et al*[31] (2006)	Retrospective	*n* = 100	Median cigarette use per day was higher in harmful alcohol relapse group
	Rodrigue *et al*[56] (2013)	Retrospective	*n* = 118	Associated with alcohol relapse
	Egawa *et al*[40] (2014)	Retrospective	*n* = 140	Cigarette smoking after LT associated with alcohol relapse
	Satapathy *et al*[42] (2015)	Retrospective	*n* = 148	Active cigarette smoking at time of LT associated with alcohol relapse
Non-compliance with clinic visits	Egawa *et al*[40] (2014)	Retrospective	*n* = 140	Associated with alcohol relapse and harmful relapse[3]
Pre-LT substance abuse or alcohol treatment	DiMartini *et al*[13] (2006)	Prospective	*n* = 167	Prior alcohol rehabilitation was associated with relapse
	Gedaly *et al*[79] (2008)	Retrospective	*n* = 142	Participation in rehabilitation was associated with relapse
	Jauhar *et al*[27] (2004)	Retrospective	*n* = 112	Substance abuse treatment before LT had no association with relapse
	Björnsson *et al*[8] (2005)	Retrospective	*n* = 103	No association

[1]Alcohol consumption of more than 21 units per week for males and 14 units per week for females; [2]Alcohol consumption greater than 140 g of ethanol per week; [3]Alcohol consumption greater than 40 g per day that was associated with the presence of alcohol-related damage. LT: Liver transplantation.

divided into no smoking, prior smoking or active smoking categories[31]. Additionally, ALD patients who drank both occasionally and heavily after LT were more likely to be smokers compared to those who remained abstinent[17]. Independent of alcohol relapse, cigarette smoking is an important risk factor for recipient morbidity and mortality[20,31,43,44]. Long-term consequences of cigarette smoking include hepatic artery thrombosis, cardiovascular disease and new onset malignancy of the aerodigestive tract[43,44]. History of tobacco use was also found to be associated with poorer survival after LT from cardiovascular disease or *de novo* non-hepatic cancer[20,31,43,44].

Noncompliance with clinic visits

Egawa *et al*[40] found noncompliance with clinic visits after LT, defined as 3 absences without notice, to be associated with both alcohol relapse and harmful drinking. In the study population, most patients underwent living donor liver transplantation, due to scarcity of deceased donors in Japan[40]. Furthermore, a cross-sectional study found that those who missed clinic appointments had lower adherence to immunosuppressive medications after liver transplant for any etiology ($P < 0.001$). In the study, non-adherence to immunosuppressive medications was liberally defined as any missed doses of transplant medications[45]. This finding is significant because strict adherence to immune suppressant agents is a very important factor in long-term outcome after liver transplant[46]. In multivariate analysis, missing physician appointments was the only independent factor associated with non-adherence to immune suppressants. Survey respondents who missed clinic visits were more than 4.7 times as likely to be non-adherent with immune suppressants compared to those who did not miss clinic visits (OR = 4.7, 95%CI: 1.5-14.7, $P = 0.008$[45]).

HCV infection

HCV infection and ALD often co-exist and approximately 8%-10% of liver transplantation performed was for mixed HCV and ALD cirrhosis[47]. Aguilera *et al*[48] compared post-transplantation outcomes among patients transplanted for alcoholic cirrhosis, mixed alcoholic cirrhosis and HCV and HCV alone. Interestingly, there was no significant difference in rate of alcohol relapse between the mixed HCV and alcoholic cirrhosis group (8%) and the alcoholic cirrhosis group (18%). Alcohol relapse also does not affect liver histology or liver functions tests differently in recipients with concomitant HCV *vs* ALD alone. Additionally, rates of rejection and graft loss were not significantly different between the mixed HCV and ALD and ALD groups. While recurrence of HCV is a major cause of reduced survival in patients transplanted for HCV cirrhosis, 5-year survival was comparable between the mixed HCV and ALD group (73%) and alcoholic cirrhosis group (76%)[49,50]. Though further studies are warranted, based on these studies, presence of HCV does not appear to result in greater risk of alcohol relapse or worse post-transplantation outcomes.

Scoring systems to predict alcohol relapse

The two main scoring systems in the literature for alcohol relapse after LT are the High Risk Alcoholism Relapse (HRAR) Scale and the Alcohol Relapse Risk Assessment (ARRA). The High Risk Alcoholism Relapse Scale was designed and piloted in the male veteran population and consists of 3 variables: Duration of heavy drinking, number of drinks per day and number of prior alcoholism inpatient treatment experiences[51]. Each item is scored 0-2 and possible score ranges from 0 to 6. A HRAR score greater than 3 is associated with high risk of alcohol relapse[11].

The HRAR Scale has yet to be validated and thus far two studies did not find the HRAR score to be associated with post-OLT alcohol use[40,52]. In terms of the ARRA, this tool found 9 domains to be significantly predictive of alcohol relapse. This scoring system includes both intrinsic and extrinsic risk factors of alcohol relapse. The intrinsic factors include low motivation for alcohol treatment and poor stress management skills. The extrinsic factors include limited social support, engagement in social activities with exposure to alcohol and lack of nonmedical behavioral consequences. The remaining factors are absence of hepatocellular carcinoma, dependence on tobacco and ongoing alcohol use after diagnosis of liver disease. Groups in ARRA Ⅲ and Ⅳ (with 4-6 and 7-9 out the 9 factors) had significantly higher rates of alcohol relapse and were more likely to return to pre-transplant levels of drinking[39]. The ARRA scale has not been validated by other studies.

The Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) was developed from a comprehensive literature review of psychosocial factors found to predict outcomes in liver, lung and heart transplant patients[53]. The SIPAT has been evaluated by one prospective study in liver, lung, kidney and heart transplant recipients. While mortality and organ failure was not associated with SIPAT scores, secondary medical and psychosocial outcomes such as rejection episodes, hospitalizations, infections and psychosocial decompensation were predicted by SIPAT[54]. The SIPAT has not yet been studied separately in liver transplant patients. In conclusion, there are no validated scoring systems to predict risk of alcohol relapse after LT at this time.

INTERVENTIONS TO PREVENT RELAPSE

Relapse prevention and psychosocial therapy

Studies have been conducted regarding relapse prevention before and after OLT. Erim *et al*[55] conducted a study that demonstrated that patients who received 6 mo of pre-LT psycho-educational therapy had significantly less alcohol recidivism during the pre-transplant waiting period. Björnsson *et al*[8] evaluated the effectiveness of active addiction treatment prior to transplant and demonstrated that active addiction treatment during the

pre-LT period may reduce the risk of relapse after LT by more than 50% (from 48% to 22%). In the study, 19 out of 40 (48%) patients transplanted before the start of structured management had resumed alcohol compared to 13 (22%) out of 58 after this intervention that did not (P = 0.002). No treatment was offered in the post-operative period. In a retrospective study, Addolorato *et al*[25] evaluated the use of an alcohol addiction unit (AAU) that was integrated within the transplant center. Post-LT patients either followed up with an addiction specialist at the transplant center or were offered addiction counseling by a provider outside the transplant unit. Patients who followed up in the AAU received multimodal treatment with counseling and pharmacologic treatment. Counseling involved 30-min sessions that emphasized craving evaluation and identification of risk factors for alcohol relapse. Out of 92 cirrhotic liver transplant recipients the alcohol relapse rate was remarkably lower in recipients managed by the alcohol addiction unit within the transplant center (16.45%) compared to patients managed by psychiatrists not affiliated to liver transplant units (35.1%).

Rodrigue *et al*[56] found that patients who had received substance abuse treatment before LT did not differ in alcohol relapse compared to patients who did not (30% *vs* 39%, P = 0.20). Interestingly, he discovered that patients who received substance abuse treatment both before and after transplant had significantly lower rates of alcohol relapse (16% *vs* 41%) compared to patients who received substance abuse treatment only before transplant (45%) or those who did not receive any substance abuse treatment (41%). While more studies are needed to evaluate relapse prevention strategies, follow-up with addiction specialists integrated with a transplant unit and a combination of pre and post-transplant interventions may be more efficacious[56].

Pharmacological interventions

Several medications are approved for alcohol dependence, but only baclofen has been studied in a randomized control trial (RCT) in patients with alcoholic cirrhosis[57,58]. Baclofen is a gamma amino butyric acid receptor agonist that works by reducing craving for alcohol. In a RCT, a total of 84 patients with both alcohol use dependence and liver cirrhosis were randomized to receive baclofen 10 mg three times daily or placebo for 12 wk. Baclofen demonstrated significant efficacy in promoting alcohol abstinence and reducing alcohol relapse. There were no serious side effects reported and no patients discontinued the medication during the study[58]. Furthermore, the baclofen study group displayed a significant decrease in alanine aminotransferase, gamma-glutamyl transferase, bilirubin and international normalized ratio values compared to placebo. It is theorized that the improvement in liver function tests was due to the significant reduction of alcohol intake in the baclofen group[58]. Baclofen has yet to be studied in the decompensated patient and post-LT population.

Other drugs that are currently approved for alcohol dependence include disulfiram, naltrexone and acomprosate, however these have not been studied in the post-transplant population. Additionally, both disulfiram and naltrexone are not ideal options for ALD patients due to their risk of hepatotoxicity[59-62].

Disulfiram was one of the first drugs approved for alcohol dependence and is an irreversible inhibitor of aldehyde dehydrogenase (ALD)[60,63,64]. If alcohol is consumed while taking disulfiram, acetaldehyde levels will increase and result in a disulfiram reaction of hypotension, flushing, nausea and vomiting that may deter patients from drinking alcohol[63]. Naltrexone is an antagonist of κ-and μ-opioid receptors and increases dopamine release in the mesolimbic system, which may help reduce alcohol craving[65]. The long acting intramuscular formulation of naltrexone may be less hepatotoxic because it does not undergo first pass metabolism by the liver, but both the oral and intramuscular formulations currently carry a black-box warning for liver damage[59,62]. Another anti-craving medication, acamprosate, is an N-methyl-D-aspartate glutamate receptor antagonist with an unclear mechanism of action. It is not metabolized by the liver and is not associated with liver toxicity[66]. Furthermore, a preliminary study suggested that 1 d of administration was well tolerated in patients with Child-Pugh class A and B cirrhosis[67]. More studies are needed to establish its efficacy in patients transplanted for alcohol liver disease and its safety profile with repeated administration.

Other promising pharmacologic agents to reduce alcohol relapse include topiramate and ondansetron[59]. Topiramate is only partially metabolized by the liver (22%) and is primarily excreted by the kidneys[68]. Ondansetron is a serotonin (5-HT3) receptor antagonist that is thought to downregulate dopaminergic neurons, reducing the reward pathway for alcohol[69]. It has been shown to be more effective than placebo in increasing total days of abstinence and percentage of abstinent days[70]. Its major side effect was QT prolongation, which was a dose related complication[71]. More studies are needed to evaluate the efficacy and safety profiles of topiramate and ondansetron in post-liver transplant patients[68,70].

Consequences of alcohol use on allograft outcomes

Graft rejection, graft loss and recurrent alcohol cirrhosis are feared complications of alcohol relapse after transplant for ALD patients. It has been suggested that alcohol relapse may lead to reduced compliance associated with a significantly increased graft rejection rate[14,17,72]. Pageaux *et al*[17] demonstrated that that while there was no significant difference in graft rejection rates between abstinent, occasional drinkers or heavy drinkers, the rejection episodes observed in the heavy drinker category were related to poor compliance to immunosuppressant medications. Therefore, alcohol consumption after LT may be a marker of medication non-adherence and can potentially predict risk of graft rejection. Overall, graft

loss from recurrence of ALD is uncommon, but multiple studies have shown that alcohol use after transplant is associated with an increased risk of graft loss and advanced allograft fibrosis[14,17,72-74]. In a study by Rice *et al*[14] any alcohol relapse increased the risk of graft failure, but upon subdivision by drinking pattern, a single slip or intermittent relapse was not associated with graft failure, but continuous heavy drinking was significantly associated with decreased graft survival. In terms of histopathology, patients with alcohol relapse were more likely to have advanced fibrosis (stage 3 or higher) compared to those that remained abstinent[14]. In the study, 20.8% of patients had a single slip and 33.3% of patients relapsed to continuous heavy drinking[14]. Multiple studies have demonstrated that patients with heavy post-transplant drinking were more likely to have more fatty changes and severe fibrosis[17,48]. Still, these histologic findings may also be explained by nonalcoholic hepatitis, given the fact that metabolic syndrome is common among post-LT patients[75].

Survival

The overall survival rates of patients transplanted for ALD are comparable or higher than the survival rates of patients transplanted for other etiologies[2,3,10,16]. According to an article by Dumortier, survival after liver transplant for ALD is 92.6% at 1 year, 88.5% at 3 years, 84.3% at 5 years and 73.4% at 10 years, which is comparable to that of patient's transplanted for other etiologies of cirrhosis[20]. While occasional slips are not associated with reduced survival, relapse to abusive or harmful levels of drinking is associated with increased mortality in ALD patients[15]. Interestingly, mortality after LT for ALD is rarely due to recurrent alcoholic cirrhosis. According to DuMortier *et al*[20], only 3% of deaths were related to alcohol cirrhosis after transplant and only 0.7% of the patients transplanted for alcoholic cirrhosis died from recurrent alcoholic cirrhosis. This finding was consistent with another study where only 1 (1%) death was related to alcohol relapse whereas the majority of deaths were attributed to cancer[27]. Björnsson *et al*[8] also found that deaths in the group of patients that resumed alcohol use were not directly related to alcohol use. While alcohol use itself does not reduce post-transplant survival, recurrent alcoholic cirrhosis does significantly reduce post-transplant survival. One-, 5-, 10- and 15-year survival was 100%, 87.6%, 49.7% and 21.0%, respectively, for patients with recurrent alcoholic cirrhosis *vs* 100%, 89.4%, 69.9% and 41.1%, respectively, for the patients without recurrent alcoholic cirrhosis ($P < 0.001$)[76]. Furthermore, Cuadrado *et al*[72] found no difference in 1 or 5 year survival in those who were abstinent *vs* those with alcohol relapse, but the study did find a remarkably worse 10 year survival in patients with alcohol use of more than 30 g/d (45.1% *vs* 85.5%). This difference in long-term mortality did not appear to be related to liver failure, graft rejection, infection rate or metabolic disturbances, but was attributed to a higher frequency of deaths from *de novo* malignancy and cardiovascular events[72]. Therefore, the major long-term causes of mortality in patients transplanted for ALD appear to be due to cardiovascular disease and *de novo* malignancy rather than related to alcohol use[10,20,38,72,76].

CONCLUSION

Overall, ALD is a good indication for liver transplantation. Patients transplanted for ALD have comparable survival rates to patients transplanted for other etiologies of liver disease[2,3,10,16].

Based on this review article, consistent predictors of alcohol relapse include comorbid psychiatric conditions, social support and tobacco use[11,13,15,29,31,40,77,78]. While the 6-mo rule is a common prerequisite for LT listing, it is not a reliable predictor of alcohol relapse[8,27,28]. It is also not feasible for some patients, particularly those with severe alcoholic hepatitis that is refractory to medical management[34]. Furthermore, scoring systems to predict relapse such as the HRAR and ARRA have been proposed but have yet to be validated by other studies.

Additionally, participation in an addiction unit integrated within a transplant center was found to be efficacious in reducing alcohol relapse after LT, but further studies are still needed to reproduce this finding[25]. Rodrigue *et al*[56] did not find pre-LT treatment of substance abuse disorders to significantly impact relapse post-LT, but patients who received both pre-and post-transplant substance abuse treatment were significantly less likely to drink post-transplant. Therefore, continuous addiction treatment may play an important role in this population.

Multiple drugs have been approved for alcohol dependence, but the majority has not yet been studied in patients transplanted for ALD[57,58]. Baclofen appears to be the most promising pharmacologic agent in promoting abstinence post-transplant and was shown to have a good safety profile in patients with advanced liver disease. Further research is needed to determine whether baclofen can reduce alcohol relapse in ALD patients in the post-transplant period. Acamprosate, topiramate and ondansetron are also promising agents because of their lower risk of hepatotoxicity, but further research is needed[59,66,67].

Lastly, alcohol relapse is associated with increased rates of graft rejection[14,17,72]. This is thought to be due to the association between alcohol use and non-adherence to immunosuppressive agents[14,17,72]. While occasional slips do not impact graft loss, a harmful or excessive amount of alcohol use post-LT has been found to be associated with an increased rate of graft loss and advanced fibrosis[14,17,48]. Heavy drinkers were also noted to have more fatty changes and steatohepatitis compared to those who remained abstinent, though this finding may be confounded by nonalcoholic steatohepatitis[14,17,72,73,75]. Overall, survival in ALD patients is comparable or higher compared to those transplanted for other etiologies of liver disease[2,3,10,16]. Long-term survival at 10 years was found to be significantly lower in those

that resumed alcohol use, but this was attributed to mortality from *de novo* malignancies and cardiovascular events rather than due to liver failure[72,75].

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