



Alcohol-related liver disease and liver transplantation

Musheer Shafqat¹, Ji Hoon Jo², Hyung Hwan Moon², Young Il Choi², Dong Hoon Shin²

¹Department of Surgery, Bach Christian Hospital, Abbottabad, Pakistan

²Department of Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea

Alcohol-related liver disease (ALD) has become the major cause of liver transplantation (LT) in Korea, and is currently the most common cause of LT in Europe and the United States. Although, ALD is one of the most common indications for LT, it is traditionally not considered as an option for patients with ALD due to organ shortages and concerns about relapse. To select patients with terminal liver disease due to ALD for transplants, most LT centers in the United States and European countries require a 6-month sober period before transplantation. However, Korea has a different social and cultural background than Western countries, and most organ transplants are made from living donors, who account for approximately twice as many procedures as deceased donors. Most LT centers in Korea do not require a specific period of sobriety before transplantation in patients with ALD. As per the literature, 8%–20% of patients resume alcohol consumption 1 year after LT, and this proportion increases to 30%–40% at 5 years post-LT, among which 10%–15% of patients resume heavy drinking. According to previous studies, the risk factors for alcohol relapse after LT are as follows: young age, poor familial and social support, family history of alcohol use disorder, previous history of alcohol-related treatment, shorter abstinence before LT, smoking, psychiatric disorders, irregular follow-up, and unemployment. Recognition of the risk factors, early detection of alcohol consumption after LT, and regular follow-up by a multidisciplinary team are important for improving the short- and long-term outcomes of LT patients with ALD.

Keywords: Alcohol use disorder; Liver disease; Liver transplantation

Introduction

Liver transplantation (LT) is the only available treatment option for survival in the cases of liver failure in patients with terminal disease. Repeated and continuous alcohol consumption has been identified as a substantial risk factor for chronic liver disease, and the net effect of alcohol consumption on health is estimated to account for approximately 3.8% of deaths worldwide [1,2].

Alcohol-related liver disease (ALD) has become the major cause of LT in Korea, and is currently the most common cause of LT in Europe and the United States (US). One of the

biggest reasons for the increase in LT in ALD is the decrease in chronic hepatitis B patients in Korea, which is related to the decrease in LT patients with hepatitis C owing to the use of direct-acting agents in Western countries. However, the decrease in hepatitis B and C, which have been the main indications for LT, cannot fully explain the increase in LT in patients with ALD. LT for ALD has several ethical dilemmas. Alcoholism has recently been considered as a chronic and relapsing-remitting neurological disease with a definite biological background, and the change in attitude towards LT in ALD is also one of the reasons why LT has become the main treatment for ALD [3-5].

Received: May 14, 2022; **Revised:** June 17, 2022; **Accepted:** June 17, 2022

Corresponding Author: Young Il Choi, MD, PhD

Department of Surgery, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea

Tel: +82-51-990-6462 Fax: +82-51-246-6093 E-mail: tsojc@naver.com

© 2022 Kosin University College of Medicine

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ALD is one of the major causes of chronic liver disease, accounting for approximately 48% of cirrhosis-related deaths in the US. Persistent alcohol consumption is the main cause of alcoholic steatohepatitis (ASH), cirrhosis, and liver cancer [6].

Despite the environmental and genetic factors associated with alcohol use disorder (AUD), ALD is still regarded as self-harm by some transplant doctors. Transplantation access for LT candidates with ALD is still marginal. Of the potential candidates with ALD, only approximately 5% to 10% of the patients have been selected for LT [7,8].

These results could may at least partially explain why transplant waitlist registrants with ALD present have high Model for End-stage Liver Disease scores, and why a higher proportion of waitlist registrants have severe decompensated complications compared with other patients on the waiting list.

Current status of LT for ALD

According to the United Network for Organ Sharing report, up to 2015, the LT waitlist and LT surgeries for patients with hepatitis C virus (HCV)-related chronic liver disease, the first indication for LT, accounted for 33% and 28%, respectively. Since 2016, ALD (30%) and nonalcoholic steatohepatitis (21%) have accounted for more than half of the total waiting list, and LT surgeries due to ALD and nonalcoholic

steatohepatitis have surpassed HCV. In Europe, LT for alcoholic cirrhosis (AC) increased abruptly from approximately 35% in 1988–1995 to 45% in 1996–2005. Since 2019, AC has become the major cause of LT. Therefore, ALD has become the leading cause of LT in the US and Europe [9,10].

In Korea, the number of patients waiting for an LT increased from 4,279 in 2010 to 5,804 in 2019, and the number of deaths due to the unavailability of a liver for transplantation steadily increased from 631 in 2010 to 972 in 2019 (Fig. 1). Korea is an endemic region for hepatitis B virus (HBV), with approximately 5% of the general population being HBV carriers; however, it has been controlled by a national vaccination program for all neonates in Korea since 1995 and a national screening program for antiviral treatment. Thus, the patients who received liver grafts from deceased donors for ALD has increased sharply, from 34% in 2015 to 51% in 2019, while the number of patients undergoing living donor LT has increased gradually, from 20% in 2015 to 25% in 2019. Similar to Western countries, ALD has pushed HBV as the second causative disease and has become the primary etiology of LT in Korea (Fig. 2) [3,11].

Alcohol-related liver disease

ALD represents a spectrum of liver damage due to repeated and continuous alcohol misuse, from alcoholic fatty liver to more advanced forms, including ASH, liver fibrosis, AC, and

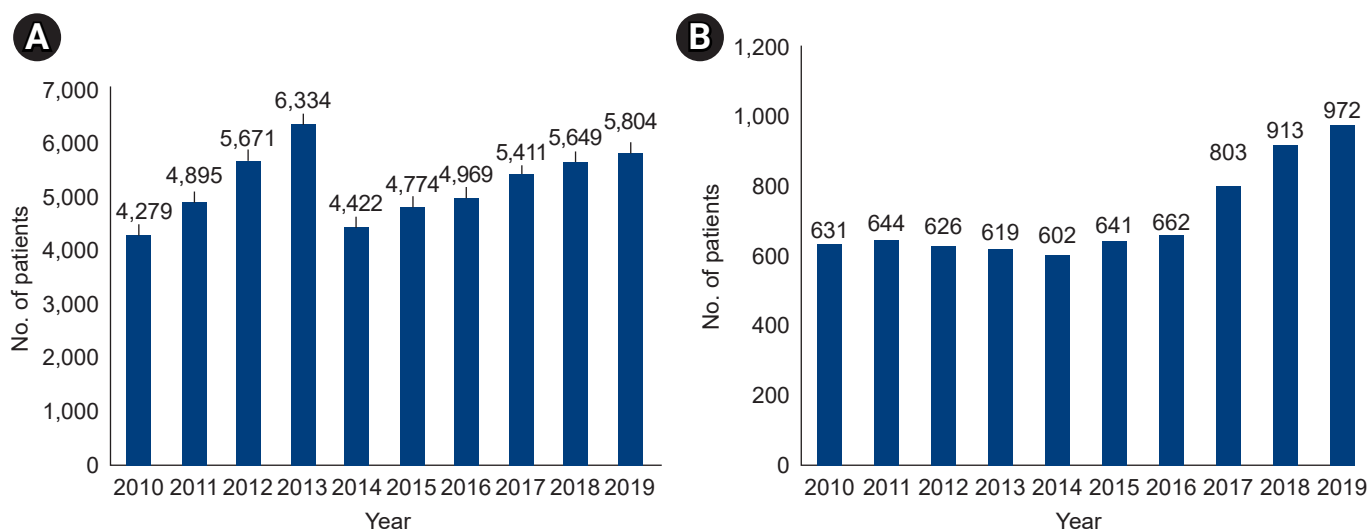


Fig. 1. Liver transplant waiting list (A) and waiting list mortality (B) in Korea from 2010 to 2019. Data are from Korean Network for Organ Sharing [3].

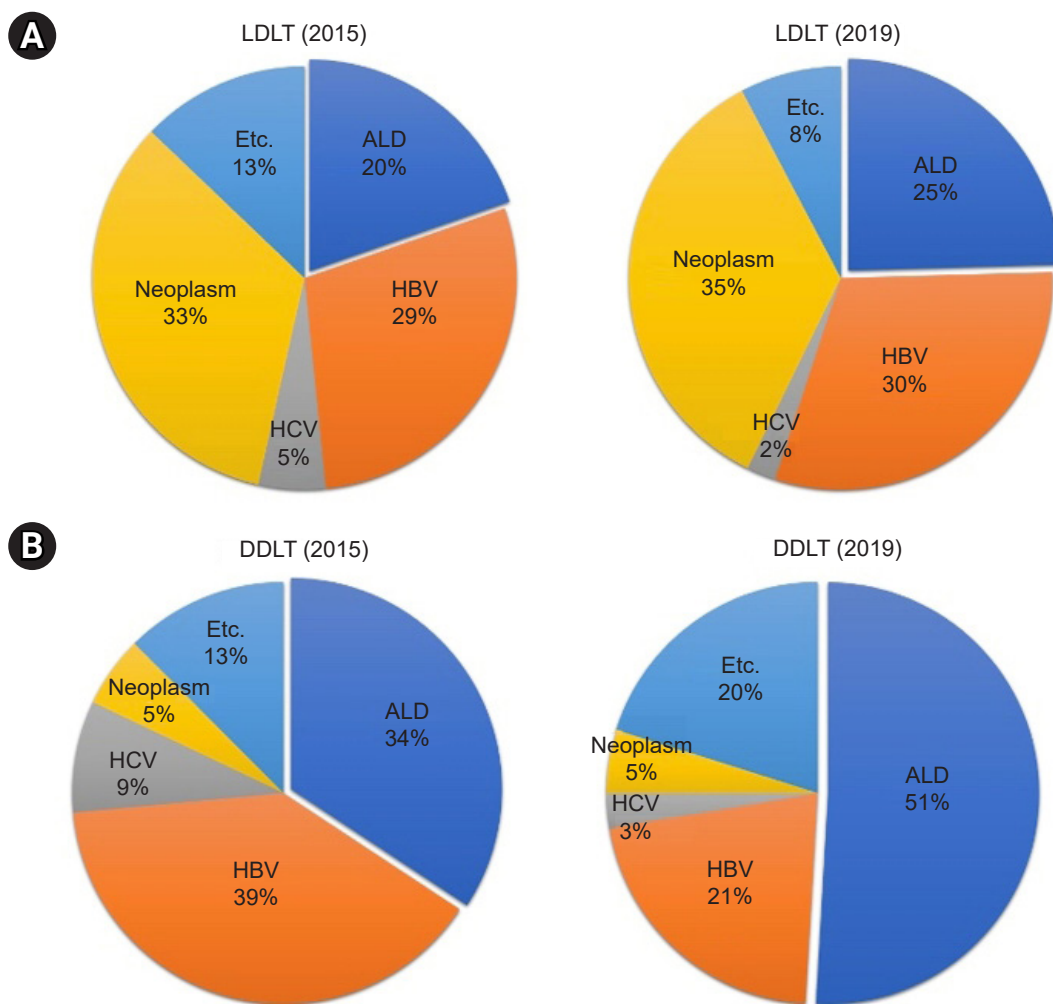


Fig. 2. Changes of etiology for liver disease in liver transplantation in Korea. (A) Living donor liver transplantation (LDLT). (B) Deceased donor liver transplantation (DDLT). HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcohol-related liver disease. Data are from Korean Network for Organ Sharing [3].

severe alcoholic hepatitis presenting with acute-on-chronic liver failure. ALD is one of the major causes of chronic liver disease worldwide, both by itself and as a contributor to the aggravation of chronic viral hepatitis, non-alcoholic fatty liver disease, and other liver diseases [6].

In general, the risk of ALD increases based on the amount of alcohol intake (≥ 30 g/day). The minimum amount required to cause cirrhosis is approximate ≥ 30 g/day in men and ≥ 20 g/day in women. In most studies, alcohol intake of 40–80 g/day increases the risk of liver damage. People who consume more than 60 g of alcohol per day develop steatosis, and some people with steatosis develop ASH, of which 10% to 20% eventually develop cirrhosis. In addition, both

genetic and non-genetic factors can influence both individual susceptibility and the clinical course of ALD [12–14].

Disease spectrum

1. Fatty liver

Fatty liver is the first response to repeated alcohol misuse and is incarnated by the deposition of adipose tissue in the hepatocytes. Macrovesicular steatosis, with its characteristic foamy cytoplasmic appearance, is the early and most common observed pattern of alcohol-induced liver damage from alcohol. There are four major pathogenic factors as follows: (1) increased nicotinamide adenine dinucleotide

synthesis caused by alcohol oxidation; (2) increased hepatic inundation of chylomicrons and free fatty acids; (3) ethanol-mediated blocking of adenosine monophosphate-activated kinase effect, which inhibits peroxisome proliferating-activated receptor α and stimulates sterol regulatory element binding protein-1c to increase adipogenesis and reduce lipolysis; (4) acetaldehyde-induced mitochondrial and microtubules damage, reduced nicotinamide adenine dinucleotide oxidation, and very low-density lipoprotein accumulation, respectively [15-17].

2. Steatohepatitis

ASH is an advanced form of hepatic injury in patients with repeated alcohol misuse and can present as an acute-on-chronic hepatic failure, resulting in rapid deterioration of liver function, and increased mortality. Despite the aggressive therapy, approximately 30% to 50% of patients with severe ASH eventually die [18]. ASH is pathologically determined as the existence of steatosis, hepatocyte swelling, and the inflammatory infiltration of polymorphonuclear neutrophils. ASH is a clinical syndrome that refers to the recent onset of symptoms, such as ascites and/or jaundice in patients with persistent alcohol intake. Although clinical symptoms may appear abruptly, the term “acute” is not recommended, as it is an aggravation of the underlying ALD and usually follows a chronic long course. However, the exact prevalence of ASH remains unknown. According to a study that used the National Inpatient Database in the US, ASH contributed to 0.8% of all hospitalizations in the US, with approximately 325,000 hospitalizations in 2010. The population burden of AC is underestimated and is not clearly known, and there is a higher probability of AC in patients hospitalized for alcohol-related problems. The clinical features of ASH are characterized by severe jaundice and are associated with the risk of other related complications. ASH can occur at any stage of liver disease and up to 80% of patients with severe ASH presenting with underlying AC. Patients with severe ASH are hospitalized for treatment, which can also lead to complications such as hepatic failure and sepsis. Alcoholic fatty livers can cause repeated parenchymal inflammation and cellular damage, which increase the risk of progression to fibrosis and cirrhosis. Various factors can contribute to ASH development, which are as follows: (1) toxic effects of acetaldehyde; (2) lipid peroxidation due to reactive oxygen species production and Deoxy-

ribonucleic acid adduct formation; (3) pro-inflammatory cytokines levels. Repeated alcohol misuse can also result in changes in the colonic microbiota and increased intestinal permeability, resulting in increased serum lipopolysaccharides levels, which induce inflammatory actions in hepatic Kupffer cells [19-21].

3. Cirrhosis

AC is an advanced, chronic form of ALD. Progressive alcoholic steatosis can result in septal fibrosis and cirrhosis, which are characterized by the development of extensive scarring (fibrosis) and regenerative nodules. The development of fibrosis is a major change in ALD as it is an essential prerequisite for the exacerbation of cirrhosis. The progression of fibrosis varies according to the histological lesions of ALD. As with other etiologies, patients with AC are susceptible to decompensation-related complications due to high portal pressure and hepatic failure and are at risk of developing hepatocellular carcinoma [12,22]. A study of patients diagnosed with AC showed that the 1- and 5-year mortality rates were approximately 30% and 60%, respectively. Hepatic encephalopathy is considered the most dangerous sign and symptoms among the complications that define hepatic decompensation [23].

Alcohol use disorder

AUD is the leading cause of cirrhosis in European countries and the US. AUD is a chronic medical condition defined as an unhealthy pattern of alcohol consumption. When alcohol is not consumed, it can cause clinically significant impairment that can include compulsive alcohol quest, positive reinforcement, and negative emotional states. These include alcohol abuse, alcohol dependence, alcohol addiction, and a condition that some people colloquially call alcoholism [2,24].

AUD has become a significant public health concern over the past decade, and its prevalence has increased at an alarming rate. According to an epidemiological survey conducted in the US between April 2012 and June 2013, 12-month and lifetime prevalence rates of AUD were approximately 13% and 29%, respectively. The prevalence rate increased from 8.5% to 12.7% between 2001–2002 and 2012–2013, constituting an increase of approximately 50%. This increase was particularly prominent among minority-race

groups, city dwellers, women, and low-income individuals. AUD affects 10% of the European population [2,25].

AUD diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) requires at least two of the 11 criteria. According to the following DSM-5 criteria, the AUD is classified as follows according to the severity: mild, moderate, or severe (2–3, 4–5, or ≥ 6 , respectively) (Table 1) [26–28]. Addiction specialists consider AUD as a chronic disorder of relapse and remission. For addiction experts, relapses in drinking should be defined by the amount and frequency of alcohol intake. However, most LT centers have an absolute view of alcoholic consumption and define any drinking as relapse [29–31].

Pre-LT management

Treating patients with AUD is extremely challenging both before and after LT. The most important and major treatment plan for patients who undergo LT after surgery is complete abstinence; if alcohol consumption continues even after medical or surgical treatment, the treatment effect is inevitably limited. If there is no improvement in liver function even after complete abstinence, and symptoms of decompensation persist, LT is the best treatment option.

All patients preparing for LT should be screened for AUD before surgery, even if the reason for LT is not ALD. As the role of the pre-LT assessment is to identify the best fit for transplantation, an initial recommendation may be that an individual needs treatment for addiction before a final deci-

sion is made. Establishing abstinence before LT is the most important starting point. The AUD identification test (AUDIT) comprises 10 questions with a scoring system. An AUDIT score of >8 is considered a positive screening test result indicative of the presence of AUD. A score of >20 indicates alcohol dependence, and the patient should be referred to an addiction specialist (Table 2) [28]. Patients with AUD often undergo LT evaluation after hepatic decompensation (i.e., ascites, variceal bleeding, or hepatic encephalopathy) or are managed palliatively without considering a transplant.

1. Behavioral therapy for pre-LT AUD

Behavioral therapy is the mainstay of AUD treatment in LT candidates and recipients. LT programs in many Western transplant centers require regular attendance at alcoholic anonymous meetings after completing behavioral therapy before being put on a waiting list.

2. Pharmacotherapy for pre-LT AUD

The American Psychiatric Association (APA) has suggested the AUD treatment guidelines. This guideline describes several pharmacological agents, including naltrexone, acamprosate, disulfiram, topiramate, and gabapentin. The APA recommends the administration of naltrexone or acamprosate to patients with moderate-to-severe AUD as the first-line treatment. Naltrexone blocks the effects of opioid receptors and suppresses alcohol intake and desire. Drug levels of naltrexone after administration are different in

Table 1. DSM-V diagnostic criteria for alcohol use disorder

1. Do you end up drinking more, or longer, than you intended?
2. Have you more than once wanted to cut down or stop drinking, or tried to, but could not?
3. Do you spend a lot of time drinking alcohol or being sick or getting over other aftereffects?
4. Have you ever wanted a drink so badly that you could not think of anything else?
5. Have drinking or being sick from drinking often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
6. Have you continued drinking even though it was causing trouble with your family or friends?
7. Do you give up or cut back on activities that are important or interesting to you, or give you pleasure, in order to drink?
8. Have you gotten into situations more than once while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
9. Have you continued drinking even though it makes you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
10. Do you have to drink much more than you once did to get the effect you want? Or do your usual number of drinks have much less effect than before?
11. When the effects of alcohol are worn off, do you experience withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or do you sense things that are not there?

DSM-V, Diagnostic and Statistical Manual of Mental Disorders.

Table 2. The Alcohol Use Disorder Identification Test questionnaire

1. How often do you have a drink containing alcohol?
(0) Never (1) Monthly or less (2) 2–4 times per month (3) 2–3 times per week (4) 4+ times per week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
(0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7 or 9 (4) 10 or more
3. How often do you have six or more drinks on one occasion?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
(0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily
9. Have you or someone else been injured as a result of your drinking?
(0) No (2) Yes, but not in the last year (4) Yes, during the last year
10. Has a relative, friend, doctor, or other health worker been concerned about your drinking or suggested that you should cut down?
(0) No (2) Yes, but not in the last year (4) Yes, during the last year

patients with compensated cirrhosis and those with decompensated cirrhosis; therefore, it is not recommended in the decompensated cirrhosis group with severe decompensated complications. Acamprosate has shown efficacy in treating AUD, especially for preventing alcohol relapse in previously sober patients. A study in patients with Child-Turcotte-Pugh (CTP) class A or B liver cirrhosis showed safety outcomes and, although results in the severe cirrhosis group; however, studies on patients with CTP class C liver cirrhosis are limited. Disulfiram is an alcohol-insensitive drug that alters the patient's response to alcohol, resulting in a dispersant and loathe experience. Disulfiram has hepatotoxic effect; therefore, it is not recommended for use in patients with advanced liver disease. The APA also suggests that topiramate or gabapentin should be administered be as the second-line treatment for patients with moderate-to-severe AUD. Topiramate is a Food and Drug Administration (FDA)-approved anticonvulsant that works as a glutamate blocking agent in addition to gamma-aminobutyric acid agonistic effects. The APA recommended its use in cases of intolerance or suboptimal responses to first-line drugs (i.e., naltrexone and acamprosate). Although topiramate causes no direct hepatotoxicity, it exhibits indirect hepatotoxicity because it is metabolized by cytochrome P3A4. Therefore,

it increases the levels of valproic acid and other anticonvulsants, which may cause hepatic injury. Gabapentin is in a class of anticonvulsant medication approved by the FDA for treating epilepsy and nerve pain. The APA recommends gabapentin for patients who show first-line treatment failure or cannot tolerate first-line treatment.

In the future, there may be more drugs related to the treatment of AUD. For example, a randomized controlled trial reported that varenicline, a drug for smoking cessation, reduced binge drinking and usual social alcohol drinking days, and increased smoking cessation compared to with a placebo.

LT for ALD

Although ALD is one of the most common causes of LT in the US and Europe, LT has traditionally been not considered as an option for patients with ALD due to organ shortage and concerns for relapse [10,25,32].

The survival rates of patients at 1, 3, 5, and 10 years after LT for AC are reported to be 84%–89%, 78%–83%, 73%–79%, and 58%–73%, respectively. The overall survival rates were similar to those of LT in patients with HCV cirrhosis or hepatocellular carcinoma. However, the 10-year survival

rate for patients with harmful drinking after LT is 45%–71%, compared with 75%–93% for patients who refrain from drinking or occasionally drink [10,33–37].

Grat et al. [37] reported that there was no difference in the overall survival rate at postoperative 5 years in patients with ALD who underwent LT; however, the survival rate deteriorated beyond the fifth year after transplantation in patients with ALD, and ALD was a risk factor.

Hong et al. [11] reported that the 1-year and 3-year overall survival rates of deceased donor LT (DDLT) for the patients with ALD and HBV were 90.7% and 82.1% in the HBV patients group and 92.1% and 82.3% in the ALD patients group, in Korea, respectively. They reported that there were no significant differences in the 1-year and 3-year overall survival rates between the two groups [11].

The improvement in survival rate after LT in patients with ALD patients differs according to the severity of liver disease, especially in severe AC with CTP grade C decompensated cirrhosis. CTP grade C patients who underwent LT showed significantly higher 1-year and 5-year survival rates compared with the control group; however, there was no significant increase in survival benefits for AC patients with CTP grade A or B compared with the control group [38,39].

Prevalence of alcohol relapse after LT

LT can cure liver disease, but not AUD. Therefore, the LT teams should be aware that patients who have undergone LT for ALD may experience alcohol relapse whenever after surgery. However, the precise proportion of patients with alcohol relapse after LT remains unknown. The prevalence of alcohol relapse varies from 10% to 90% in several studies due to differences in the definition of relapse and follow-up time after LT. As per literature, 8%–20% of patients resume alcohol consumption 1 year after LT, and it gradually increases to 30%–40% at 5 years post-LT. Studies estimate that up to 20%–50% of patients who undergo LT will be readmitted for alcohol-related problems within 5 years after LT, and approximately 10%–15% of the patients resume heavy alcohol consumption [14,29,40–43].

A meta-analysis showed an alcohol relapse and heavy alcohol relapse rate of 22% and 14%, respectively, at a mean follow-up of 24 months after LT. Studies have shown poor outcomes in patients with alcohol relapse after performing LT for ALD compared with patients with no or intermittent

alcohol intake. A meta-analysis by Rustad et al. [44] showed that patients with alcohol relapse had a higher risk of steatohepatitis, rejection, or liver failure, and mortality. The results of this study highlight the importance of examining alcohol use after LT and identifying steps to avoid negative consequences [5,44,45].

Definition of alcohol relapse after LT

The reported definitions of alcohol relapse vary widely, from sobriety to alcohol-related consequences, such as hospital readmissions, or physical, social, and legal consequences. Failure of sobriety is the commonly used definition because it emphasizes the recommendation to abstain from alcohol completely; however, there is no evidence that mild relapses (occasional “slips,” less than once per month) have effects on graft or patient survival. The most effective methods for identifying alcohol relapse post-LT are the clinical interviews and the Alcohol Timeline Followback questionnaire; however, more research on the utility of combining several methods needs to be conducted [32,46].

Some experts stipulate relapse as four or more alcoholic drinks per day or 14 or more total drinks per week for at least 4 weeks [47,48]. Arab et al. [49] suggested a three-stage definition of alcohol relapse according to the relapse severity: (1) mild; (2) moderate (continuous and repeated drinking, at daily and weekly doses within the recommended standards of the National Institute on Alcohol Abuse and Alcoholism); and (3) severe (associated morbidity or mortality, which includes alcohol-induced hepatitis, pancreatitis, hepatic graft loss or other medical problems associated with alcohol recurrence). DiMartini et al. [50] suggested four patterns of alcohol consumption stage depending on the time of relapse, quantity, and duration as follows: (1) minimum drinking over a long period; (2) early relapse that progresses rapidly to moderate consumption; (3) early relapse that progresses to a repeated and continuous harmful drinking; (4) moderate drinking with a late start.

Many LT centers consider even a single drop of alcohol consumption after LT to be a relapse, and addiction experts do not support this definition. Data accumulated over the past decade show that reducing alcohol consumption, whether intoxicated or not, lowers overall morbidity, mortality, and health costs, and improves the psychosocial status. Alcoholism experts define AUD as a chronic disease

that recurs with exacerbation and improvement, and the treatment focuses on changing it from severe to mild [51-53].

Unfortunately, there are few well-designed studies on interventions to improve outcomes in patients with ALD after LT, as the treatment goals of post-LT studies for ALD are still unclear. Mathurin and Lucey [54] proposed that, in order to achieve this goal, future studies should recalibrate the outcome goals of recipients with ALD as either abstinence (the ideal outcome) or low-risk drinking (acceptable outcome).

Six-month abstinence rule

A 6-month abstinence rule has been proposed because of organ shortages and concerns regarding sharing limited resources with patients with self-inflicted conditions who are at risk of alcohol relapse after LT. In this context, pre-LT alcohol abstinence is one of the hottest and most controversial issues. This rule has been a general requirement since 1997. During a national meeting for LT in ALD in 1997, and all transplant professionals agreed that abstinence from alcohol prior to LT is an important prerequisite for selecting patients for LT and most European and US programs

require a definite period of abstinence lasting 6 months (the so-called 6-month abstinence rule) [40,55]. To identify patients with ALD who are eligible for LT, many transplant centers in Western countries require the 6-month rule to be followed before transplantation can be considered. However, unlike the US and Europe, Korea has a different cultural and social background than Western countries, and most organ transplants are made from living donors, which is about twice that of deceased donors. Most transplant centers in Korea do not require a specific period of sobriety before LT either living donor LT or deceased donor LT for patients with ALD. In recent years, more patients with ALD have received transplants from deceased donors in Korea. Of the deceased liver donors in 2012, 18.7% were allocated to patients with ALD, and the proportion was 38.0% in 2017, without the requirement of any abstinence period [3,43].

Although abstinence before transplantation is the most widely studied predictor, it has not been shown to be a significant predictor of recurrence after LT in many studies. Additionally, different cutoffs for pre-transplant abstinence (3 months and 1.5 years) have been found in various studies [56,57].

Table 3. Predictors of alcohol relapse after liver transplantation

First author	Year	No.	Relapse rate (%)	Abstinence predict post-LT relapse	Predictors of alcohol relapse
Jauhar [58]	2004	111	15	No	Family history of alcoholism
Kelly [59]	2004	100	20, harmful	No	Amount of pre-LT consumption, smoking, family support
Perney [60]	2005	61	52	Yes	Younger age, alcohol abuse in first relatives
DiMartini [61]	2006	167	42	Yes	NS
De Gottardi [62]	2007	387	11.9, harmful	Yes	Age >50 yr
Pfizzmann [63]	2007	300	11.9	Yes	Absence of companion, presence of young children
Gedaly [64]	2008	142	19	Yes	Drug abuse
Karim [65]	2010	80	10, harmful	Yes	Female sex
Hartl [56]	2011	120	16	Yes	NS
Egawa [66]	2013	140	22.9	No	Psychological disease history, smoking, Noncompliance with clinic visits after LT
Rice [67]	2013	300	16	Yes	Young age, biliary complication
Deruytter [68]	2013	108	29	No	Family history of alcohol abuse
Rodrigue [69]	2013	118	33.8	No	No hepatocellular carcinoma, smoking, social activity
Grat [37]	2014	97	33.5	No	Younger age
Satapathy [70]	2015	148	10.8, harmful	No	Older age, family support
Saigal [71]	2015	408	9.5	No	Younger age
Skladany [72]	2019	89	26	No	Smoking
Kitajima [57]	2019	190	13.7	No	Complication after LT, alcohol relapse before LT
Chung [43]	2021	129	13.9 (LDLT) 31.7 (DDLT)	No	Smoking

LT, liver transplantation; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; NS, not studied.

The 6-month abstinence rule serves two purposes. First, to give the patient time to demonstrate abstinence (which is thought to be predictive of abstinence after LT) and second, to give the patient an opportunity to recover through medical treatment after abstinence [73].

Risk factors for alcohol relapse after LT

Various predictors of recurrence after LT have been investigated. Many studies are retrospective and used different definitions of alcohol relapse after LT, making comparisons challenging (Table 3) [37,43,56-73]. Several studies have identified the associations between demographic and clinical factors and alcohol relapse after LT. According to the literature, the commonly reported risk factors in the several studies are poor social and familial support, young age, smoking, psychiatric disorder, family history of AUD, previous treatment history for AUD, short abstinence period before transplantation, irregular follow-up, divorce, separation by death, and unemployment [5,43,49,50,61,72,74].

Conclusions

It is a known fact that abstinence is a pivotal factor for improving the long-term prognosis in patients who have undergone LT for ALD, and alcohol relapse is the most serious problem for patients. Few prospective studies have been conducted to reduce recurrence after LT for ALD. It has been considered that continuous intervention before and after LT is extremely important, and this can be achieved by the accurate identification of risk factors for recurrence after LT. In this sense, the key to the main treatment of these patients is the role of the multidisciplinary ALD team before and after surgery. A multidisciplinary team approach in combination with biochemical screening, can identify early recurrence and improves post-LT survival in patients with ALD. Recognition of risk factors, early detection of relapse after LT, and regular follow-up by a multidisciplinary team are essential to improve the prognosis of LT patients with ALD.

Article information

Conflicts of interest

Musheer Shafqat and Young Il Choi are editorial board members of the journal but were not involved in the peer

reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

Conceptualization: YIC. Data curation: YIC. Formal analysis: MS. Investigation: JHJ. Methodology: HHM. Project administration: DHS. Resources: DHS. Software: JHJ. Supervision: JHJ, HHM, DHS. Validation: DHS. Visualization: YIC. Writing - original draft: YIC. Writing - review & editing: MS. Approval of final manuscript: all authors.

ORCID

Musheer Shafqat, <https://orcid.org/0000-0002-0411-6727>

Ji Hoon Jo, <https://orcid.org/0000-0002-7238-0482>

Hyung Hwan Moon, <https://orcid.org/0000-0002-4212-4568>

Young Il Choi, <http://orcid.org/0000-0002-9630-6287>

Dong Hoon Shin, <https://orcid.org/0000-0001-6602-3393>

References

1. Busuttil RW, DuBray BJ. Liver transplantation for alcoholic hepatitis. *Ann Surg* 2017;265:30-1.
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009;373:2223-33.
3. Center for Korean Network for Organ Sharing. Annual report of organ transplantation statistics [Internet]. Cheongju: Center for Korean Network for Organ Sharing; c2022 [cited Jun 17]. https://www.konos.go.kr/board/boardListPage.do?page=sub-4_2_1&boardId=30.
4. Cabezas J. Management of alcohol-related liver disease and its complications. *Clin Drug Investig* 2022;42(Suppl 1):47-53.
5. Chuncharunee L, Yamashiki N, Thakkinian A, Sobhonslidsuk A. Alcohol relapse and its predictors after liver transplantation for alcoholic liver disease: a systematic review and meta-analysis. *BMC Gastroenterol* 2019;19:150.
6. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2020;71:306-33.

7. Veldt BJ, Laine F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002;36:93–8.
8. Watt KD, McCashland TM. Transplantation in the alcoholic patient. *Semin Liver Dis* 2004;24:249–55.
9. Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* 2018;16:1356–8.
10. Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant* 2010;10:138–48.
11. Hong SK, Yi NJ, Kim HS, Ahn SW, Yoon KC, Kim H, et al. Korean patients undergoing deceased donor liver transplantation for alcoholic liver disease have non-inferior survival outcomes than for hepatitis B virus: a real-world experience without minimum abstinence before transplantation. *J Korean Med Sci* 2017;32:919–25.
12. Zakhari S, Li TK. Determinants of alcohol use and abuse: impact of quantity and frequency patterns on liver disease. *Hepatology* 2007;46:2032–9.
13. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut* 1997;41:845–50.
14. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012;57:399–420.
15. Baraona E, Lieber CS. Alcohol and lipids. *Recent Dev Alcohol* 1998;14:97–134.
16. You M, Considine RV, Leone TC, Kelly DP, Crabb DW. Role of adiponectin in the protective action of dietary saturated fat against alcoholic fatty liver in mice. *Hepatology* 2005;42:568–77.
17. Ji C, Chan C, Kaplowitz N. Predominant role of sterol response element binding proteins (SREBP) lipogenic pathways in hepatic steatosis in the murine intragastric ethanol feeding model. *J Hepatol* 2006;45:717–24.
18. Torok NJ. Update on alcoholic hepatitis. *Biomolecules* 2015;5:2978–86.
19. Chedid A, Mendenhall CL, Gartside P, French SW, Chen T, Rabin L. Prognostic factors in alcoholic liver disease. VA Cooperative Study Group. *Am J Gastroenterol* 1991;86:210–6.
20. Niemela O, Juvonen T, Parkkila S. Immunohistochemical demonstration of acetaldehyde-modified epitopes in human liver after alcohol consumption. *J Clin Invest* 1991;87:1367–74.
21. Thurman RG. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. *Am J Physiol* 1998;275:G605–11.
22. Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. *Br Med J (Clin Res Ed)* 1981;282:263–6.
23. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010;51:1675–82.
24. Tarli C, Mirijello A, Addolorato G. Treating alcohol use disorder in patients with alcohol associated liver disease. *Semin Liver Dis* 2022;42:138–50.
25. Shipley LC, Kodali S, Singal AK. Recent updates on alcoholic hepatitis. *Dig Liver Dis* 2019;51:761–8.
26. Grant BE, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry* 2015;72:757–66.
27. Goldstein RB, Chou SP, Smith SM, Jung J, Zhang H, Saha TD, et al. Nosologic comparisons of DSM-IV and DSM-5 alcohol and drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *J Stud Alcohol Drugs* 2015;76:378–88.
28. Moehring A, Rumpf HJ, Hapke U, Bischof G, John U, Meyer C. Diagnostic performance of the Alcohol Use Disorders Identification Test (AUDIT) in detecting DSM-5 alcohol use disorders in the General population. *Drug Alcohol Depend* 2019;204:107530.
29. Tome S, Lucey MR. Timing of liver transplantation in alcoholic cirrhosis. *J Hepatol* 2003;39:302–7.
30. O'Brien CP, McLellan AT. Myths about the treatment of addiction. *Lancet* 1996;347:237–40.
31. Vaillant GE. The natural history of alcoholism and its relationship to liver transplantation. *Liver Transpl Surg* 1997;3:304–10.
32. Addolorato G, Bataller R, Burra P, DiMartini A, Graziadei I, Lucey MR, et al. Liver transplantation for alcoholic liver disease. *Transplantation* 2016;100:981–7.
33. Singal AK, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013;95:755–60.
34. Jain A, DiMartini A, Kashyap R, Youk A, Rohal S, Fung J. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. *Transplantation* 2000;70:1335–42.
35. Faure S, Herrero A, Jung B, Duny Y, Daures JP, Mura T, et al. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. *J Hepatol* 2012;57:306–12.

36. Cuadrado A, Fabrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2005;11:420–6.
37. Grat M, Lewandowski Z, Grat K, Wronka KM, Krasnodebski M, Barski K, et al. Negative outcomes after liver transplantation in patients with alcoholic liver disease beyond the fifth post-transplant year. *Clin Transplant* 2014;28:1112–20.
38. Poynard T, Barthelemy P, Fratte S, Boudjema K, Doffoel M, Vanlemmens C, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis by a case-control study and simulated controls. *Lancet* 1994;344:502–7.
39. Vanlemmens C, Di Martino V, Milan C, Messner M, Minello A, Duvoux C, et al. Immediate listing for liver transplantation versus standard care for Child-Pugh stage B alcoholic cirrhosis: a randomized trial. *Ann Intern Med* 2009;150:153–61.
40. Leong J, Im GY. Evaluation and selection of the patient with alcoholic liver disease for liver transplant. *Clin Liver Dis* 2012;16:851–63.
41. Gaglio PJ Jr, Gaglio PJ Sr. Complications in patients with alcohol-associated liver disease who undergo liver transplantation. *Clin Liver Dis* 2012;16:865–75.
42. Perut V, Conti F, Scatton O, Soubrane O, Calmus Y, Vidal-Trecan G. Might physicians be restricting access to liver transplantation for patients with alcoholic liver disease? *J Hepatol* 2009;51:707–14.
43. Chung HG, Sinn DH, Kang W, Choi GS, Kim JM, Joh JW. Incidence of and risk factors for alcohol relapse after liver transplantation for alcoholic liver disease: comparison between deceased donor and living donor liver transplantation. *J Gastrointest Surg* 2021;25:672–80.
44. Rustad JK, Stern TA, Prabhakar M, Musselman D. Risk factors for alcohol relapse following orthotopic liver transplantation: a systematic review. *Psychosomatics* 2015;56:21–35.
45. Choudhary NS, Saraf N, Dhampalwar S, Saigal S, Gautam D, Rastogi A, et al. Poor outcomes after recidivism in living donor liver transplantation for alcohol-related liver disease. *J Clin Exp Hepatol* 2022;12:37–42.
46. DiMartini A, Day N, Dew MA, Lane T, Fitzgerald MG, Magill J, et al. Alcohol use following liver transplantation: a comparison of follow-up methods. *Psychosomatics* 2001;42:55–62.
47. Iruzubieta P, Crespo J, Fabrega E. Long-term survival after liver transplantation for alcoholic liver disease. *World J Gastroenterol* 2013;19:9198–208.
48. Dew MA, DiMartini AE, Steel J, De Vito Dabbs A, Myaskovsky L, Unruh M, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl* 2008;14:159–72.
49. Arab JP, Izzy M, Leggio L, Bataller R, Shah VH. Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation. *Nat Rev Gastroenterol Hepatol* 2022;19:45–59.
50. DiMartini A, Dew MA, Day N, Fitzgerald MG, Jones BL, deVera ME, et al. Trajectories of alcohol consumption following liver transplantation. *Am J Transplant* 2010;10:2305–12.
51. Kline-Simon AH, Litten RZ, Weisner CM, Falk DE. Posttreatment low-risk drinking as a predictor of future drinking and problem outcomes among individuals with alcohol use disorders: a 9-year follow-up. *Alcohol Clin Exp Res* 2017;41:653–8.
52. Laramée P, Leonard S, Buchanan-Hughes A, Warnakula S, Daep-pen JB, Rehm J. Risk of all-cause mortality in alcohol-dependent individuals: a systematic literature review and meta-analysis. *EBioMedicine* 2015;2:1394–404.
53. Witkiewitz K, Pearson MR, Hallgren KA, Maisto SA, Roos CR, Kirouac M, et al. Who achieves low risk drinking during alcohol treatment? An analysis of patients in three alcohol clinical trials. *Addiction* 2017;112:2112–21.
54. Mathurin P, Lucey MR. Liver transplantation in patients with alcohol-related liver disease: current status and future directions. *Lancet Gastroenterol Hepatol* 2020;5:507–14.
55. Testino G, Burra P, Bonino F, Piani F, Sumberaz A, Peressutti R, et al. Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: an Italian position statement. *World J Gastroenterol* 2014;20:14642–51.
56. Hartl J, Scherer MN, Loss M, Schnitzbauer A, Farkas S, Baier L, et al. Strong predictors for alcohol recidivism after liver transplantation: non-acceptance of the alcohol problem and abstinence of <3 months. *Scand J Gastroenterol* 2011;46:1257–66.
57. Kitajima T, Nagai S, Segal A, Magee M, Blackburn S, Ellithorpe D, et al. Posttransplant complications predict alcohol relapse in liver transplant recipients. *Liver Transpl* 2020;26:379–89.
58. Jauhar S, Talwalkar JA, Schneekloth T, Jowsey S, Wiesner RH, Menon KV. Analysis of factors that predict alcohol relapse following liver transplantation. *Liver Transpl* 2004;10:408–11.
59. Kelly M, Chick J, Gribble R, Gleeson M, Holton M, Winstanley J, et al. Predictors of relapse to harmful alcohol after orthotopic liver transplantation. *Alcohol Alcohol* 2006;41:278–83.
60. Perney P, Bismuth M, Sigaud H, Picot MC, Jacquet E, Puche P, et al. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease?

- Transpl Int 2005;18:1292-7.
61. DiMartini A, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transpl* 2006;12:813-20.
62. De Gottardi A, Spahr L, Gelez P, Morard I, Mentha G, Guillaud O, et al. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. *Arch Intern Med* 2007;167:1183-8.
63. Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nussler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2007;13:197-205.
64. Gedaly R, McHugh PP, Johnston TD, Jeon H, Koch A, Clifford TM, et al. Predictors of relapse to alcohol and illicit drugs after liver transplantation for alcoholic liver disease. *Transplantation* 2008;86:1090-5.
65. Karim Z, Intaraprasong P, Scudamore CH, Erb SR, Soos JG, Cheung E, et al. Predictors of relapse to significant alcohol drinking after liver transplantation. *Can J Gastroenterol* 2010;24:245-50.
66. Egawa H, Nishimura K, Teramukai S, Yamamoto M, Umeshita K, Furukawa H, et al. Risk factors for alcohol relapse after liver transplantation for alcoholic cirrhosis in Japan. *Liver Transpl* 2014;20:298-310.
67. Rice JP, Eickhoff J, Agni R, Ghufuran A, Brahmabhatt R, Lucey MR. Abusive drinking after liver transplantation is associated with allograft loss and advanced allograft fibrosis. *Liver Transpl* 2013;19:1377-86.
68. Deruytter E, Van Steenkiste CV, Treppe E. Liver transplantation for alcoholic liver disease: a retrospective analysis of recidivism, survival and risk factors predisposing to alcohol relapse. *Acta Gastroenterol Belg* 2013;76:282-90.
69. Rodrigue JR, Hanto DW, Curry MP. The Alcohol Relapse Risk Assessment: a scoring system to predict the risk of relapse to any alcohol use after liver transplant. *Prog Transplant* 2013;23:310-8.
70. Satapathy SK, Eason JD, Nair S, et al. Recidivism in liver transplant recipients with alcoholic liver disease: analysis of demographic, psychosocial, and histology features. *Exp Clin Transplant* 2015;13:430-40.
71. Saigal S, Choudhary NS, Yadav SK, Saraf N, Kumar N, Rai R, et al. Lower relapse rates with good post-transplant outcome in alcoholic liver disease: experience from a living donor liver transplant center. *Indian J Gastroenterol* 2016;35:123-8.
72. Skladany L, Adamcova Selcanova S, Koller T. Alcohol use relapse following liver transplantation for alcoholic liver disease. *Ann Transplant* 2019;24:359-66.
73. Choudhary NS, Saraf N, Mehrotra S, Saigal S, Soin AS. Recidivism in liver transplant recipients for alcohol-related liver disease. *J Clin Exp Hepatol* 2021;11:387-96.
74. Lim J, Curry MP, Sundaram V. Risk factors and outcomes associated with alcohol relapse after liver transplantation. *World J Hepatol* 2017;9:771-80.