Review

Liver transplantation for alcoholic liver disease

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Liver transplantation for alcohol-associated liver disease: The changing landscape

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Abstract

Alcoholic liver disease(ALD) is considered as a growing public health issue with universally increasing disease burden. Various genetic and environmental factors play role in its etiology. ALD recently has become the major indication for Liver Transplantation (LT). Most LT programs select their candidates by adhering to six months of alcohol abstinence policy. Nevertheless, early liver transplantation (ELT) has become a subject of research, both in Europe and the United States, as an effective and lifesaving option among highly selected severe alcohol-associated hepatitis (SAH) patients. ELT is a promising way in the management of ALD, perhaps changing clinical practice for carefully selected patient groups.

Keywords: Liver transplantation; alcohol-associated liver disease; alcohol-associated hepatitis.

Introduction

Alcohol-associated liver disease (ALD) encompasses a range of mild to moderate and severe disorders related to alcohol consumption, beginning with hepatic steatosis, often presenting as alcohol-associated hepatitis (AH), and, with continued alcohol use, progressing to alcohol-associated cirrhosis (AC).[1] Both severe AH (SAH) and AC are associated with increased mortality, with SAH having mortality rates of up to 50% and individuals with AC facing a median survival time as short as one to two years.[2] ALD is the most common etiology of liver cirrhosis in the United States (U.S.). It has recently emerged as the leading reason for liver transplantation (LT), driven by rising rates of alcohol use disorder (AUD) and the limited number of treatment options.[3]

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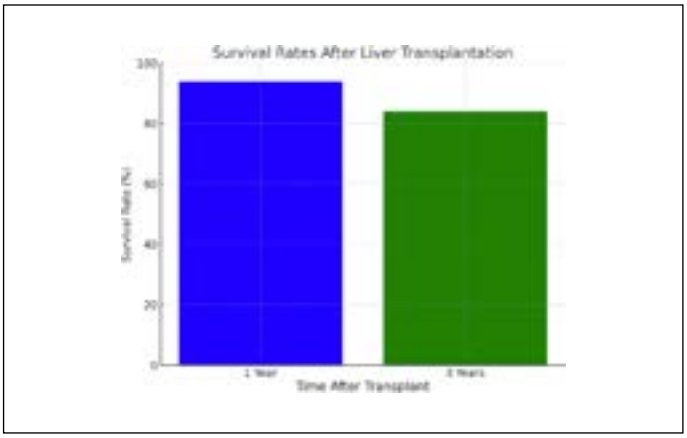

Figure 1. Survival rates after liver transplantation.

The x-axis represents time/year; the y-axis represents survival rate/%. Lee et al.[6]'s retrospective study, including 147 patients who had ELT for SAH, showed that the predominant portion of the patients were alive at one year (94%) (represented with blue in the chart) and three years (84%) (represented green in the cart), comparable to the patients who underwent LT for other indications.

Individuals who develop ALD due to excessive alcohol consumption are expected not to consume alcohol after LT due to the risk of relapse following the procedure, and this expectation is reflected in the patient selection process. Therefore, most transplant programs implement a six-month alcohol abstinence requirement before LT,[4] commonly called the six-month rule. There are patients with end-stage ALD who do not respond to treatment, and the fact that LT is subject to the traditional six-month sobriety rule in most LT programs negatively affects a subset of the patient population who may benefit from LT. This situation brings the six-month sobriety rule into question and warrants new research related to the topic.

In 2011, early LT (ELT) for AH, published by Mathurin et al.,[5] questioned the entire algorithm for this indication worldwide. The accretive six-month survival rate (±SE) was lower in patients who received standard LT compared to patients who received ELT (23±8% vs. 77±8%, $p<0.001$). This study showed that ELT for ALD may be an applicable and life-saving treatment option for carefully selected patients with AH. Another landmark retrospective study, including 147 patients who had ELT for SAH, showed that the predominant portion of the patients were alive at one year (94%) and three years (84%), comparable to the patients who underwent LT for other indications (Fig. 1).[6] This study

showed that the duration of pre-LT alcohol sobriety and post-LT alcohol relapse risk were not associated.[7] After interrogating the six-month rule, which had no significant impact on the risk of post-LT alcohol relapse and survival rates, ELT could be considered a novel approach to managing ALD in carefully selected patients.

Epidemiology and Disease Burden of ALD

ALD is a significant public health issue that has serious effects on the global disease burden, as evident from an increasing number of deaths and disability-adjusted life years (DALYs), especially in the U.S.[8] One of the leading five causes of death and disability worldwide is excessive or harmful alcohol use, which carries with it 2.5 million mortalities and 69.4 million DALYs per year.[9]

There are many interrelated reasons behind ALD being a global burden with a greater impact than expected, including insufficient public policies on alcohol intake regulation, limited perception of disease extent, delayed specialist consultation, inadequate funding for ALD research, inadequate use of existing AUD medications, and, most recently, the COVID-19 pandemic (with up to a 477% increase in online sales of alcoholic beverages recorded in the U.S.).[10] It is estimated that ALD will cost $880 billion from 2022 to 2040, including 355$ billion in direct healthcare-associated expenses and $525 billion in lost workforce and economic consumption.[11] The COVID-19 pandemic has been shown to cause a notable increase in alcohol use across the globe and, therefore, played a role in an increase in ALD.[12,13]

COVID-19 Pandemic

The COVID-19 pandemic has led to a rise in ALD and a 50% increase in LT waiting list additions.[14,15] During COVID-19, there was a remarkable spike in the all-cause mortality rate due to ALD, with a quarterly rate rise of 11.2% as opposed to 1.1% before the pandemic.[10]

According to Johns Hopkins data, advanced care referrals across hospitals to the hospital's tertiary-care hepatology unit from January 2020 to December 2022 found that most referrals were for ALD.[16] The data revealed increased requests from intensive care units, indicating a rise in the severity of ALD cases throughout the COVID-19 period.[16] ALD has divided the pandemic into early, middle, and later periods, with the early period associated with increased alcohol use, the middle period related to restricted access to treatment, and the later period, or the post-COVID period, witnessing difficulty in managing the downstream effects.[17] Social isolation, psychiatric comorbidities, loss of jobs and wages, and increased psychosocial stressors led to a rise in alcohol consumption, resulting in increased rates of hospitalization, mortality related to ALD, LT, and economic burden.[12]

Gender

According to data from 2016, women are less affected by ALD than men (women: 5,909,000 DALYs; 95% CI: 4,653,000–6,423,000; men: 15,568,000 DALYs; 95% CI: 14,230,000–19,125,000), with a significant portion of these lost years of life due to early mortalities rather than disability.[8] The proportional distribution of alcohol use among women and men worldwide is 32% for women and 54% for men.[18]

Although men consume more alcohol than women, the rate of alcohol use by women has recently increased.[18] Studies show that women develop ALD even if they consume less alcohol than men, in addition to when they consume the same amount as men.[19] Gender differences, such as differences in the alcohol absorption process, first-pass metabolism, hormonal disparities, lower body water levels, and reduced levels of gastric alcohol dehydrogenase (ADH) activity, make women especially sensitive to ALD.[20,21]

Age

ALD has become increasingly common and predominantly affects young adults, specifically the population between the ages of 20 and 45.[8,18] Age-specific analysis showed a considerable rise in crude mortality rates among different age categories, especially within the younger age range of 25 to 34 years, which was associated with an average increase of 11.12% between 2006 and 2022, and 35–44 years, showing an average increase of 17.2% between 2018 and 2022.[22]

Per-person alcohol consumption, and consequently, the prevalence of ALD, generally diminish with age in Europe and the U.S. However, a recent rise in alcohol consumption has been reported in individuals over 65.[23] Reasons for this observation may include an increase in life expectancy or the loss of spouses leading to solitude and depression, which in turn increases AUD in this population.[23]

Race and Ethnicity

Sixty-one percent of the American population drinks alcohol, and 10–12% of this 61% are heavy drinkers.[1] The approximate prevalence of ALD in the U.S. is 2–2.5%.[24] In the U.S., the prevalence of ALD was greatest in Hispanic individuals (4.5%), followed by White (3.1%) and Black (1.4%) patients. Combined risk ratios of ALD prevalence indicate a risk of 1.64 (95% CI: 1.12–2.39) for Hispanics compared to White individuals and a risk of 0.59 (95% CI: 0.35–0.87) for Black individuals compared to White individuals.[25] Significant clinical distinctions in the incidence and manifestation of ALD among different ethnicities were observed in one study.[26] Additionally, Hispanic individuals were diagnosed with ALD at a remarkably younger age than Caucasians and African Americans; therefore, ethnic identity was found to be a factor affecting the age at which individuals present with alcohol-associated hepatic steatosis and AH.[26] Phospholipase domain-containing protein 3 (PNPLA3) polymorphism (i.e., rs738409) has been shown to increase the risk for the spectrum of ALD.[27]

In Europe, AUD is the main contributor to liver cirrhosis, and ALD is the foremost factor behind alcohol-related deaths in adults.[28] Over the past three decades, liver cirrhosis mortality rates have diminished in most Western European countries, whereas they have risen in several Eastern European countries, as well as in the United Kingdom, Ireland, and Finland.[29] ALD is also on the rise in various regions across Asia.[30] Alcohol consumption is increasing more rapidly in China than in any other part of the world.[31] Central Asia has reported the largest quantity of AC DALYs per 100,000 individuals, totaling 546.0 DALYs per 100,000 individuals (435.1 DALYs per 100,000 women and 655.0 DALYs per 100,000 men).[30] Eastern Europe reported the second greatest proportion of liver cirrhosis DALYs attributed to alcohol intake, with a rate of 456.1 DALYs per 100,000 individuals.[28]

Risk Factors for ALD

ALD is a multifactorial disease in which a combination of genetic and environmental factors influences its onset and development. These factors affect liver damage, ALD phenotype, and disease progression.[32] A closer look at genetic factors shows that the PNPLA3 gene is a risk factor for AC, in addition to HCC (especially in ALD patients).[33] An

increased number of G alleles aggravates the risk of developing AC, and shorter exposure to heavy drinking enhances the possibility of alcoholic cirrhosis.[33] Additionally, genetic variations in genes responsible for the production of important enzymes that metabolize alcohol, such as ADH, ALDH, and CYP2E1, are known to influence people's vulnerability to alcohol abuse; however, these enzymes' impact on the progression of ALD remains a subject of debate.[34]

The paramount environmental risk factor for ALD is alcohol consumption. According to the Centers for Disease Control and Prevention (CDC), one alcoholic drink contains half an ounce or 13.7 g of pure alcohol, which is equal to 12 oz of beer (5% alcohol), 8 oz of malt liquor (7% alcohol), 5 oz of wine (12% alcohol), or 1.5 oz of 80-proof hard liquor (40% alcohol).[1] Consuming 30 to 50 grams of alcohol daily for more than five years can cause ALD.[1] Steatosis may develop in 90% of patients who consume over 60 grams of alcohol per day, and cirrhosis may develop in 30% of patients who consume over 40 grams of alcohol per day for an extended period.[1]

The CDC defines at-risk drinking as exceeding 14 drinks per week or more than four drinks on a given occasion for men, and no more than seven drinks per week or more than three drinks at a time for women and people aged 65 and older.[1] Clinically significant drinking for liver toxicity is defined as consuming more than 21 drinks per week for men and more than 14 drinks per week for women. This history is important in distinguishing metabolic dysfunction-associated steatotic liver disease (MASLD) from alcohol-associated steatohepatitis.[1]

Gut microbiota composition and function, particularly bile acid physiology, are impaired by harmful alcohol consumption patterns.[35] In individuals with significant liver fibrosis, alterations in gut bacteria occur simultaneously with liver damage. These bacterial changes persist as long as the person continues to consume alcohol, eventually leading to AH.[35]

Environmental risk factors that contribute to the progression of ALD in individuals with alcohol abuse include gender, obesity, alcohol use patterns, nutritional plan, non-sex-related genetic factors, and tobacco use.[36,37] Smoking worsens the impact of alcohol, increasing the risk of severe ALD and AC. Smokers who consume a pack or more per day have a risk three times greater than that of nonsmokers, and smoking also facilitates the onset of HCC in those with AC.[38–40]

Obesity is considered a separate risk factor for ALD and is believed to exacerbate the severity of alcoholic steatohepatitis in individuals consuming heavy alcohol (>50 g/day).[41] Elevated body mass is also a risk factor for AH, potentially leading to a combination of alcoholic and non-alcoholic steatohepatitis.[42] A study showed that MASLD is already present in as many as 75% of individuals who are above normal weight and in more than 90% of people with high-grade obesity.[43,44]

The deleterious effects of ALD are exacerbated by comorbid diseases such as obesity and MASLD, accelerating the rate of liver disease progression.[21] Similarly, patients who have already developed AC and also have comorbid conditions, including AUD, obesity, diabetes mellitus (DM), and viral hepatitis, face an elevated risk of HCC.[33] A study showed that the normalized incidence of HCC was elevated in men (4.0, 95% CI: 3.5–4.6) and women (2.1, 95% CI: 1.6–2.7) with type 2 DM compared to the general population.[45]

Coinfection with viral hepatitis B and C is also a significant enhancer of ALD. Despite a distinct segregation between viral hepatitis deteriorated by alcohol and the inverse situation, differentiating between the two is often challenging and primarily based on predominant histological changes.[46] Research shows that individuals with hepatitis C frequently consume alcohol, and those who do have an elevated risk of fibrosis.[47,48] Additionally, alcohol accelerates liver disease progression through increased oxidative stress, cytotoxicity, immune system impairment, and decreased response to antiviral therapy.[46]

Moreover, iron plays a role in advancing ALD. Since ethanol increases iron absorption, a greater quantity of iron reaches the liver, enhancing pro-oxidant effects, stimulating ferritin synthesis, and activating hepatic stellate cells, leading to inflammation and fibrosis.[49]

Diagnosis of ALD

ALD is usually diagnosed through clinical evaluation and laboratory tests; nonetheless, diagnosing ALD may be challenging, as patients may underestimate their alcohol consumption. Additionally, early stages of ALD are characterized by hepatic steatosis, and clinical findings may be absent.[9] A diagnosis of ALD can also be corroborated through physical examination (PEx), laboratory findings, imaging, and histological studies.[50] New biomarkers, scoring systems, and imaging techniques have been critical in diagnosing and managing ALD.[50]

Taking an accurate history of alcohol consumption is important. Well-structured, approved screening instruments, such as the Alcohol Use Disorders Identification Test (AUDIT).[51] (Recommendation Grade A1) or the CAGE (Cut down, Annoyed, Guilty, Eye-opener) Questionnaire,[52] help in detecting both harmful alcohol use and dependence.[53] Signs and symptoms of ALD include nausea, vomiting, right upper quadrant abdominal pain, fatigue, weakness, anorexia, jaundice, fever, abdominal distension or increased abdominal girth with ascites, hepatomegaly, and edema in the lower extremities.[54] Signs of chronic alcoholism include spider veins, palmar erythema, gynecomastia, parotid hypertrophy, Dupuytren's contracture, and fetor hepaticus.[54] The severity of the disease is the main determinant of PEx findings in patients with ALD; therefore, PEx findings can range from being entirely normal to displaying physical signs of cirrhosis with severe decompensation.[9] Unfortunately, almost no symptoms appear in patients with early-stage ALD, leading to most cases being diagnosed too late.[55]

For laboratory tests, 70% to 80% of patients have an aspartate transaminase (AST)/alanine transaminase (ALT) ratio that is at least twice as high as in healthy individuals; therefore, this ratio is often used to detect ALD.[56] Regardless of the etiology, similar findings can also be observed in patients with advanced cirrhosis.[46] Among biochemical tests, mean erythrocyte volume, aminotransferases, and γ-glutamyl transferase (GGT) are sensitive tests; however, they are not specific for cirrhosis patients.[57] Carbohydrate-deficient transferrin (CDT) combined with GGT has approximately 75%–90% sensitivity.[56] Nevertheless, CDT levels may be confounded by worsening disease conditions and ongoing smoking.[58]

Another noninvasive diagnostic method is transient elastography, or Fibroscan® (FS). Currently, FS is the most validated noninvasive tool for diagnosing advanced liver fibrosis and cirrhosis in ALD.[59] In a prospective study directly comparing tests, both the Enhanced Liver Fibrosis test (ELF) and FS demonstrated high diagnostic accuracy for identifying advanced liver fibrosis (AUROC values of 0.90 or greater using biopsy as a reference) in alcoholic patients from primary and secondary care settings.[60]

Diagnostic methods such as ultrasound, CT, and MRI are valuable for identifying ALD and ruling out other causes of liver dysfunction.[61] In the context of AUD, heterogeneous steatosis and transient perfusion changes on CT and MRI are indicative of SAH.[61] Before establish-

ing a final diagnosis of ALD, it is essential to exclude other factors contributing to liver disease, including chronic viral hepatitis, autoimmune hepatitis, hemochromatosis, and drug-induced liver damage.[9] Sometimes, a liver biopsy may be required if the diagnosis is uncertain, to clarify the condition, or if there is concern for dual pathology.[62] Unless clinical, analytical, and imaging findings are inconclusive, liver biopsy is not routinely recommended in individuals in the early or late stages of ALD.[37,63]

Lastly, biomarkers of alcohol consumption play a significant role in diagnosing ALD, as they can assist in the diagnostic process and support recovery efforts.[53] Ethyl sulfate, phosphatidyl ethanol (PEth), and ethyl glucuronide (EtG) are biomarkers used in AUD/ALD, and their levels remain unaffected by the presence of liver disease.[64]

Liver Transplantation in ALD

ALD is the primary indication for LT, comprising 40% to 50% of all LTs in economically advanced countries.[65] LT is an efficient and currently broadly accepted treatment for end-stage ALD, but some controversy remains, partially due to social stigma and concerns about recidivism.[66] In the U.S., ALD became the leading indication for LT, surpassing HCV in 2016.[67] In another study, ALD was the predominant liver disease etiology for LT in the U.S. by 2017, with one- and five-year patient and graft survival rates comparable to those of other LT indications.[68]

End-stage ALD can be classified into two primary subcategories: AC and SAH.[69] Currently, refractory AH is considered an indication for LT in carefully selected patients, taking into account factors such as their social status, psychosocial background, awareness of the disease, lack of prior treatments for AUD, and absence of additional substance misuse, among others.[70] Clinical markers for LT assessment in ALD include decompensated cirrhosis with a MELD score ≥15 or the onset of a new HCC, which are similar to other cirrhosis etiologies.[71] In cirrhotic patients, a rising MELD score corresponds to greater liver dysfunction and a higher risk of mortality within three months.[72]

AH is an acute manifestation of ALD and is associated with 30–40% mortality at 28 days.[73] Patients with SAH and acute-on-chronic liver failure have been shown to benefit from LT in terms of survival.[68,74] Currently, there are limited treatment options for SAH patients who do not respond to steroid treatment and have a Lille score >0.56.[75] Patients with SAH who do not respond to steroids have a three-month mortality rate of 70%, and those with hepatorenal syndrome face a mortality rate of ≥ 90%, unless they undergo LT.[76,77]

LT for ALD has traditionally been considered only in patients who remain sober for at least six months. The reasoning was to allow time to assess whether liver function could improve, potentially preventing the need for LT.[6] Additionally, due to social and ethical concerns surrounding the allocation of limited organs, most patients with SAH who do not respond to medical therapy are unlikely to survive long enough to meet this criterion.[66] Patients unresponsive to medical treatment underwent ELT for SAH within stringent and carefully defined protocols, leading to an obvious survival improvement and acceptable alcohol consumption rates following LT.[78] Studies, including the seminal Franco-Belgian study[5] and subsequent research replicated by the U.S. ACCELERATE-AH consortium,[6] have demonstrated that ELT can provide a remarkable survival benefit in meticulously selected patients with SAH who do not improve with treatment. ELT has been shown to yield survival outcomes similar to LT for other indications, with six-month survival rates ranging from 77% to 100%.[66]

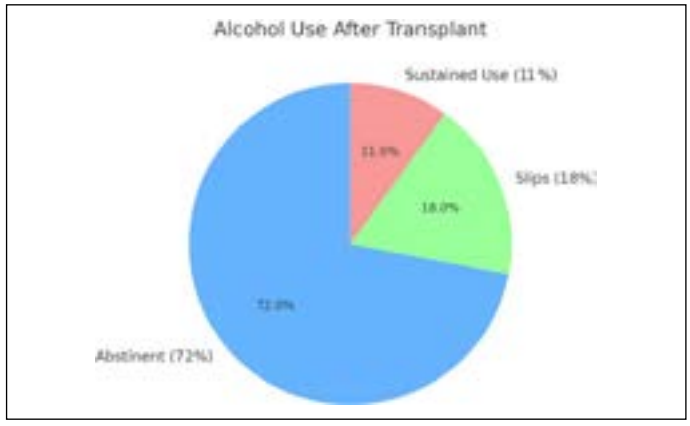

Figure 2. Alcohol use after transplant.

According to Lee et al.[6] study following hospital discharge after LT with a median follow-up of 1.6 years, within 141 LT recipients who were released to home, 101 (72%)(represented blue in the chart) had no evidence of alcohol consumption after LT, 25 (18%)(represented green in the chart) had slips only, and 15 (11%)(represented pink in the chart) had continued consumption.[1]

According to a cohort study, following the six-month rule did not result in improved survival rates for patients, allografts, relapse-free outcomes, or risky relapse-free outcomes (Appendix 1).[78] In this study, with significant follow-up at three years after LT and eight years of patient enrollment in the ELT program, comparable results were observed between ELT and standard LT patients, supporting the ongoing expansion of ELT in the U.S.[78] Based on a retrospective analysis by Lee et al.[6] mortality rates without transplant reached as high as 70% within six months, whereas ELT substantially lowered mortality to 10% (Appendix 1).

In a retrospective study of 209 patients with ALD, including those with AH and acute and chronic rejection episodes, researchers found that the graft rejection rate over a median follow-up period of more than four years was higher among abstinent patients compared to those who relapsed to alcohol consumption (2.24 vs. 0.75 episodes/year, $p<0.01$).[79]

The only treatment that has been proven to improve long-term outcomes for AH is complete abstinence from alcohol,[80] but the origin of the six-month abstinence requirement before LT is not entirely understood.[68] Current guidelines from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, UNOS, and the French Consensus Conference indicate that the requirement of six months of complete alcohol abstinence before LT should no longer be considered an absolute criterion for determining a patient's eligibility for the procedure.[63,81–84] Although lower relapse rates may be associated with longer abstinence, the predictive value of the six-month rule is not validated.[6] Rigid abstinence rules exclude patients at low risk of relapse from transplant evaluation.[85] Figure 2 shows the rates of patients who return to alcohol use following LT.

Instead of the six-month rule, factors independently predicting alcohol relapse include inadequate social support, coexisting psychiatric diseases, tobacco use (and other substance use), and non-compliance.[86] One frequently noted risk factor for alcohol relapse is younger age (Fig. 3).[6] Patients in both the pre- and post-LT periods require consultation with a multidisciplinary team, including psychiatrists and addiction specialists, counseling services, and participation in support groups.[87] A multidisciplinary approach, combined with blood, urine, and hair tests, allows for the early detection of recurrences and improves survival outcomes.[88]

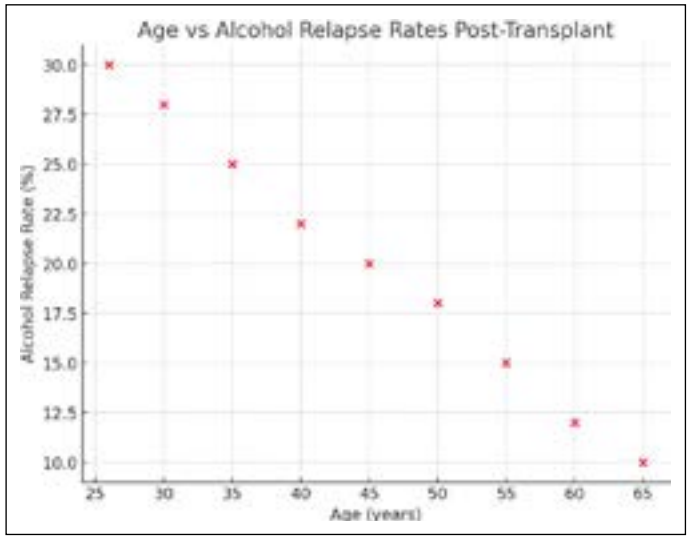

Figure 3. Age vs alcohol relapse rates post-transplant.

The x-axis represents age/years; the y-axis represents alcohol relapse rate/% (For example in age 35 relapse rate is 25%). According to Lee et al.[6] study, in multivariable analysis, only younger age was associated with alcohol following LT (p=0.01).[1] Younger age has been recognized as a potential predictor for alcohol consumption following LT and has been found to be an association in cohorts examining alcohol consumption after LT for ALD.[1] These results emphasize the value of meticulous patient assessment, and characteristics (age, amount of alcohol consumed prior to LT) that might help to optimize selection to improve prediction of alcohol consumption following LT and outcomes.[1]

Patients should be assessed for metabolic complications by the multidisciplinary team prior to LT. It is essential that hypertension, dyslipidemia, obesity, and diabetes be diagnosed and managed appropriately to improve long-term survival among LT recipients.[89] Among the most prevalent complications following LT, with a 44%–58% rate, is metabolic syndrome (MS).[89] MS, along with immunosuppressive treatment, is regarded as a key risk factor for the emergence of cardiovascular disease (CVD) in LT patients.[89]

CVD accounts for 19%–42% of all mortalities independent of graft failure and up to 50% of hospital readmissions in the first 90 days following LT. Additionally, approximately 40% of all mortalities in the first 30 days following LT are due to heart-related causes.[89,90] Transplant centers approach cardiac assessment in diverse ways.[90] Before LT, cardiac risk classification is based on the evaluation of the following criteria: first, the candidate's age and sex characteristics; second, the screening of the cardiovascular system to rule out significant systolic or diastolic left ventricular dysfunction, pulmonary hypertension, and coronary artery disease; and third, the assessment of comorbidities such as DM and renal impairment.[91] A minimum of an electrocardiogram and transthoracic echocardiogram must be performed on all LT candidates as part of cardiac assessment.[92]

The rates of LT for SAH have risen in recent years, but ELT continues to be restricted and offered at a limited number of centers in the U.S.[93,94] However, more centers are adopting ELT.[7] The shift in LT allocation to acuity circles has highlighted the importance of listing the most critically ill patients (and those among them with the best outcomes), as these individuals are expected to receive LT earlier with the most optimal donor grafts.[95] AH patients meet these criteria, as they are typically younger than other candidates, have MELD scores >30, and have fewer comorbidities.[95]

Conclusion

Now, the clinical landscape of chronic liver disease includes LT for AH. It presents a compelling dilemma for clinicians who must balance applying this procedure to benefit carefully selected AH patients while maintaining fairness in donor access.[95] Identifying patients at increased risk of relapse through multidisciplinary assessment of risk factors is crucial. The goal is to intervene early, both before and after LT, to prevent or at least mitigate the impact of alcohol relapse following LT.[96] This objective is central to the ethical issue of prioritizing graft allocation for patients who have the greatest need and the potential for long-term graft survival.[96] LT for SAH is comparable to other etiologies of chronic liver disease in terms of graft and patient survival when careful selection practices are applied.[97]

The approach to LT differs significantly from one region to another.[98] In the Western world, more than 90% of LTs are performed using deceased donor LT (DDLT).[99] In contrast, in the Eastern world, living donor LT (LDLT) is more developed.[100] The common challenge in both Western and Eastern regions is that the demand for organs exceeds the supply, leading to efforts focused on increasing the number of available donor sources. Medical professionals have improved LT practices by advancing procurement techniques, surgical methods, and clinical management.[101]

Lastly, it should be kept in mind that LT for ALD is associated with an increased susceptibility to de novo solid organ cancer, skin cancer, and lymphoproliferative disorders, all of which significantly affect survival outcomes.[102–104]

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Appendix 1. Studies regarding early liver transplantation for alcoholic liver disease with key point

Category	Findings		
	Lee et al.[104]	**Lee et al.[6]**	**Herrick-Reynolds et al.[79]**
Study	Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis	Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis	Evaluation of Early vs Standard Liver Transplant for Alcohol-Associated Liver Disease
Type of the study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Patient population	43 patients had LT. They divided into 2 groups: Group 1, SAH as first liver decompensation; Group 2, alcohol-associated cirrhosis with 6 months sobriety.	147 patients with SAH received ELT.	Among 163 ALD patients involved in this study, 88 (54%) received ELT and 75 (46%) received SLT.
Survival rates	6 months survival rate was 100% for first group compared to 89% for second group (p¼ 0.27).	1-year survival: 94%, 3-year survival: 84%	Both recipients of ELT and SLT had similar 1-year patient survival (94.1% vs 95.9%)
Alcohol relapse rates	Alcohol relapse rates were comparable: 23.5% for first group compared to 29.2% for second group (p>0.99).	25% experienced alcohol relapse at 1 year, with 10% showing sustained alcohol consumption. Within three years, ongoing alcohol use increased to 17%.	1-year relapse-free survival of 80.4% for ELT was similar to published posttransplant relapse rates for ALD of about 20%
Impact of ELT on mortality	100% 1-year survival in Group 1 exhibited that ELT is vital in SAH; its mortality is up to 70% in 6 months.	Without transplant, mortality reached up to 70% within 6 months. ELT significantly reduced mortality to 10%.	There is no association between compliance to the 6-month rule and superior patient survival, allograft survival, or relapse-free survival among chosen patients.
Pre-transplant corticosteroid use	35.3% in Group 1 were treated with steroids for AH; 5.9% were treated with pentoxifylline; 58.8% were not treated either.	54% of patients received corticosteroids for acute AH prior to transplant	42% ELT group and 1% SLT group P<.001 were treated with steroids prior to LT.
Abstinence duration pre-transplant	Duration of sobriety at LT– days – median 40 for Group1, 522 for group 2.	Median duration of abstinence prior to LT was 55 days	Sobriety at time of LT, median (IQR) d is 66.5 for ELT 481.0 for SLT.
Risk factors for relapse	Patient data were assessed for characteristics which have been noted as potential risk factors for post-LT alcohol relapse in previous studies.	Younger age and shorter durations of abstinence were linked to higher rates of alcohol relapse post-LT.	In this study, they discovered a connection between early relapse and patient survival; this modifiable risk factor offers a new aim for post-LT treatments.
Post-transplant alcohol monitoring	Post-LT, patients were followed at the same time intervals: weekly for the first month, biweekly for months 2 and 3, monthly for months 4 to 6, every 6 to 8 weeks thereafter until 1 year.	72% of patients remained abstinent after LT; alcohol use was monitored through direct questioning and random toxicology testing in some centers.	Relapse was identified through patient follow-up visits, with laboratory screening used only as clinically necessary.
Psychosocial evaluation criteria	Patients underwent rigorous psychosocial assessments, including family support evaluation and commitment to lifelong abstinence.	Data are collected about psychosocial profiles (eg, previous illicit drug use, family history of AUD, past alcohol-associated legal issues, and rehabilitation attempts history)	Committee reached a consensus and added patients to LT list after evaluated the lack of effectiveness of treatment, degree of social support, insight into hazardous alcohol consumption history and commitment to sobriety.
Selection for ELT	Strict criteria were applied for patient selection: SAH, failure of medical therapy, absence of severe comorbidities, and strong social support.	Above 18 years of age, presentation with clinically diagnosed acute SAH, no prior diagnosis of chronic liver disease or episodes of AH, and LT before 6 months of alcohol sobriety were including the study criteria.	

Appendix 1 (cont). Studies regarding early liver transplantation for alcoholic liver disease with key point

Category	Findings		
	Lee et al.[104]	**Lee et al.[6]**	**Herrick-Reynolds et al.[79]**
Alcohol use and mortality link		Ongoing alcohol consumption post-LT rose the likelihood of death by 4.59 times	The relationship between patient and allograft survival and relapse is nuanced and influenced by the severity of alcohol consumption.
Comparison of relapse in different groups	Alcohol relapse was 23.5% in the ELT group, in comparison to 29.2% in patients with cirrhosis.	This study was retrospective, did not have a control group for comparison, and did not address long-term outcomes.	They researched the relationship of ELT with these survival outcomes by comparing it with the SLT group.
Long-term follow-up	Their research showed the need for meticulous monitoring of relapse at any time post-LT.	Patients were followed up regularly, with visits decreasing in frequency over time (per week for 1 month, bi-weekly for 3 months, monthly thereafter)	With substantial follow-up at 3 years after LT, as well as 8 years of enrolling patients in the ELT program, similar outcomes for patients who received ELT and those who received SLT support the continued expansion of ELT in the US.

LT: Liver transplantation; ELT: Early liver transplantation; AH: Alcohol-associated hepatitis; SAH: Severe alcohol-associated hepatitis; SLT: Standard liver transplantation; AUD: Alcohol use disorder.