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Review

Updates in Liver Transplantation for Alcohol-Related Liver Disease

Michael J Eiswerth, Joel Wedd *

Department of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University, Richmond, VA, USA; E-Mails: michael.eiswerth@vcuhealth.org; joel.wedd@vcuhealth.org

* **Correspondence:** Joel Wedd; E-Mail: joel.wedd@vcuhealth.org

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Abstract

The prevalence of alcohol use disorder (AUD) and alcohol-related liver disease (ALD) has increased in the last two decades. ALD is currently the most common indication for both waitlist additions and liver transplant (LT) in the United States, including alcohol-associated cirrhosis, alcohol-associated hepatitis (AH), and acute-on-chronic liver failure (ACLF). ALD also has a significant global disease burden. LT in ALD is a complex paradigm that poses both medical and ethical challenges, requiring a multidisciplinary approach to management. Furthermore, the scope of liver transplantation for alcohol use is expanding. Here we review updates in LT for ALD pertinent for the practicing clinician. We will discuss current practice patterns, treatment strategies, and outcomes.

Keywords

Liver transplant; alcohol-related liver disease; alcohol-associated hepatitis; cirrhosis, and alcohol use disorder

1. Introduction

Alcohol-related liver disease (ALD) is one the leading causes of liver-related morbidity and mortality worldwide and the leading cause of liver transplantation in both the United States and Europe [1-4]. The healthcare burden of ALD is increasing, although identifying the exact prevalence of ALD worldwide is challenging [5]. One recent study from the World Health Organization found that 46.9% of all chronic liver diseases globally were related to alcohol [6]. Alcohol use has continued to increase internationally since the COVID pandemic [7]. Concurrently, hospitalizations and hospital re-admissions for alcohol-associated hepatitis (AH) and alcohol-related cirrhosis have increased [8]. As hospitalizations for ALD have risen, so have the number of liver transplants (LT) for ALD. As of November 2024, 37% of all wait list registrations in 2024 for liver transplantation in the United States according to the Organ Procurement & Transplant Network (OPTN) are for ALD [9].

ALD occurs across a spectrum including acute presentations such as AH and acute-on-chronic liver failure (ACLF) which warrant unique transplant considerations. LT listings have continued to rise for AH and have quadrupled in individuals under 40 between 2003 and 2018 [10, 11]. This phenomenon was accelerated by the COVID-19 pandemic with one study reporting a 7% increase in LT listing for ALD during the pandemic [11]. There are multiple components that impact the management and changing landscape of ALD that we will review in this article (Figure 1).

Figure 1 Schema of liver transplant for alcohol-related liver disease. LT (liver transplant), ALD (alcohol-related liver disease), AUD (alcohol use disorder).

2. Ethical Principles for Liver Transplant and How They Impact Transplant Decisions for Alcohol

As the number of liver transplants performed for ALD has continued to rise, the scarcity of donor grafts available for transplant remains a limiting factor. Given this scarcity, societal concerns and ethical considerations for both the individual (beneficence, futility, and non-malfeasance) and society (distributive justice, utility, and rationing) are key considerations guiding organ selection, allocation, and policy. Beneficence, the obligation to act in the benefit and in support of the patient, is a central principle for healthcare professionals [12].

This is weighed against medical futility, in which treatment will not provide benefit or improve a patient's condition as well as medical non-malfeasance, which is the obligation to not harm a patient. Beyond the scope of the individual under consideration for liver transplantation, societal factors are considered to maintain equitable and fair treatment. Distributive justice dictates that every person should have the same level of material goods and services [13]. Utility is a principle that maximizes value and the greatest benefit for the most individuals. Competing principles like utility are weighed against rationing, in which the degree of a scarce resource such as organ grafts dictates the rigidity of criteria for transplant candidacy.

LT in ALD is historically controversial. Past discussion included questioning how "deserving" of a liver transplant these individuals are, but the advances in understanding of alcohol use disorder (AUD) as a medical entity shifted this landscape. Given this, ethical principles require the consideration of LT in this patient population without discrimination [14]. Weighing the medical necessity and good for the patient against futility and societal good guide organ allocation. Living donor liver transplantation (LDLT) is also used in the treatment of ALD and carries its own unique ethical considerations. An individual acting as a living donor must have the capacity to make medical decisions and have a comprehensive understanding of the risks and benefits [15]. LDLT can be a lifesaving measure but carries both medical and psychological risk to the donor.

3. Changing Approach to Transplant for Alcohol

LT in ALD as a treatment modality has inherent challenges including bias and ethical considerations, but perception among transplant centers globally about the use of transplant for ALD is changing. From a historical perspective, many transplant centers were previously reluctant to use LT in ALD, considering ALD a "self-inflicted" disease process [16]. A commonly used sobriety standard, the six-month rule, is controversial with cited weaknesses including arbitrary duration and limited specificity and positive predictive value [17-19]. Multiple meta-analyses and reviews suggest the period of abstinence prior to LT for AH does not indicate the likelihood of returning to alcohol after LT [20, 21]. This waiting period is also detrimental for those with severe AH, which portends an extremely poor three-month prognosis. The six-month rule was challenged by a 2011 pilot study by Mathurin, *et al.* [22], which selected patients for LT after failure of medical therapy and showed a better cumulative six-month survival rate compared to those not selected for early LT. The survival benefit was consistent at two-year follow-up. Current practice patterns vary by institution, but there is a growing number of centers that do not require six months of abstinence prior to LT listing and an increase in candidacy acceptance for very recent alcohol use and AH. In one recent survey of transplant directors and centers in the United States, 66% reported that their center had an established criteria for listing an individual for LT with less than 6 months of sobriety [23]. Patient

selection is key in this setting, as there are patients with non-severe AH and with chronic ALD who will recover liver function with treatment of AUD and alcohol cessation without LT.

4. Benefit of Liver Transplant for ALD

In patients with severe ALD who do not respond to medical therapy, the only therapeutic intervention associated with a long-term survival benefit is LT [24]. The determination of disease severity is crucial in clinical practice. Prior studies and survival models did not show a survival benefit for LT in patients with ALD who have intermediate or low disease severity as defined by the Child-Turcotte-Pugh (CTP) score [25-27]. Despite this, one study reported that an estimated 95% of patients with ALD who meet the American Association for the Study of Liver Diseases (AASLD) guideline criteria for LT evaluation are not referred to a transplant center [28]. This identifies one of the current challenges in the management of patients with ALD: selection of patients who should be evaluated for LT across the spectrum of its presentations including AH, decompensated cirrhosis, and ACLF.

In current practice in the United States, the model for end-stage liver disease (MELD) score guides prognosis and triages the allocation of organ allocation. Liver transplant has an established survival benefit with a MELD score of 15 or greater [29] in alcohol-related cirrhosis. AH, a subset of ALD, carries a poor short-term prognosis, supporting consideration for LT. In 1978, the Maddrey discriminant function (MDF) was created to assess disease severity, short term mortality, and appropriateness for initiating corticosteroids in AH [30]. Current literature comparing the MELD to the MDF score in identifying 30-day mortality found the MELD had an 86% specificity with an 81% sensitivity, while that of the MDF was 86% and 48% respectively [31]. This is now reflected in current American College of Gastroenterology (ACG) guidelines which recommend the use of the MELD score for clinicians to stratify disease severity, predict short-term mortality, and guide corticosteroid treatment [32]. In AH, MELD > 20 indicates severe disease [33] and has prognostic value when followed up to 1,287 days [34]. The natural history of non-severe AH defined as MELD < 20 is not well understood but carries a one-year mortality as high as 20% [35]. The implication of poor short-term mortality outcomes in severe AH compared to mild-to-moderate AH has helped guide the changing clinical practice of early evaluation and listing for liver transplantation in severe AH.

5. Healthcare Disparities in Patients with ALD

Gender disparities in liver transplantation for ALD impacts healthcare outcomes. As recently as 2008, women were 30% less likely to undergo LT [36]. Women were further disadvantaged by MELD-based LT allocation [37]. Prior iterations of the MELD score have underestimated disease severity and created a disparity in equity and access to treatment for women [38]. Specifically, they disadvantaged women by using creatinine as a surrogate for renal function, because lower muscle mass results in lower creatinine and overestimates renal function in women. Given the higher incidence of ALD in males compared to females, a successful implementation of a MELD score in this setting would not necessarily grant liver transplant to men and women in an equal number but rather provide a fair and equitable opportunity to receive a liver transplant irrespective of gender, prioritizing the sickest patients without bias. The current MELD 3.0 was created to address this gender disparity and includes extra points for females to offset the creatinine-based disadvantage.

Racial disparities and health inequities in ALD is another important consideration. Disparities between ethnic groups can be attributed to multiple components. A distinction should be made between disparities in access to the transplant waitlist compared to outcomes once listed for LT. As opposed to waitlisted patients, national databases for patients at any point prior to transplant listing are lacking, limiting the ability to study access to the liver transplant waitlist. Equitable access to liver transplantation may vary by transplant center. In one study Non-Hispanic Black patients had less access to the liver transplant list than Non-Hispanic White patients, but once listed their disparities in outcomes diminished [39]. Non-Hispanic Black patients have discordant liver-related outcomes compared to Non-Hispanic White patients in ALD. Non-Hispanic White patients have higher ALD related mortality, but Non-Hispanic Black patients have higher all-cause mortality, increased comorbidities, and lower rate of liver transplant [40, 41]. Prior studies have also reported genetic variance and risk factors among ethnic groups including fatty liver disease allele burden [42]. What is less clear however, are the impacts of healthcare disparities in different groups of patients with ALD once listed for transplant. One United Stated based study concluded that Hispanic, Asian, and American Indian individuals have higher waitlist mortality than non-Hispanic White patients [43], but this requires further research.

6. Waitlist Survival for Patients with ALD

Deaths on the liver transplant waitlist are a benchmark in the allocation of deceased organ donation [44]. Almost 20% of patients listed for LT either die or become too ill for LT on an annual basis [45]. The mismatch in supply and demand in LT magnifies the current challenges faced by clinicians. In one large retrospective study, 17.4% of patients with ALD listed for LT died or became too sick for LT compared to 19.6% of those listed for non-ALD indications [46]. ALD specific risk factors for waitlist mortality include hyponatremia and chronic kidney disease stage III or worse [47]. Another key metric that has been studied in waitlisted patients is functional status. Functional status is defined as an individual's ability to perform daily activities required to meet daily needs, fulfill usual roles, and maintain health and well-being [48]. Multiple recent studies demonstrate that poor performance and functional status are associated with higher mortality in patients with cirrhosis and those awaiting liver transplantation [49, 50]. Individuals with ALD have worse functional status than other indications for LT, which impacts waitlist mortality and outcomes [51]. Frailty is associated with progression of liver disease and death in patients with cirrhosis [52] and is affected by both malnutrition and sarcopenia. Sarcopenia has a high prevalence in ALD of 80% in patients with alcohol-related decompensated cirrhosis [53].

7. Post-Transplant Outcomes

Post-transplant outcomes for ALD compare favorably to other indications for LT. Current literature supports that the survival of patients with ALD who receive a LT has improved to 90% at one-year post-transplant, and that graft survival in LT recipients with ALD is as high as 73% at five years post-transplantation [54, 55]. This same study by Bergsmark *et al.* compared these post-transplant survival rates in ALD to that of a non-ALD post-transplant cohort. They found a similar one-year post-transplant survival of 90%, and an 83% five-year post-transplant survival in the non-ALD group, while ALD and non-ALD groups compared similarly at 10 years with the ALD post-transplant group having a 63% survival compared to 62% in the non-ALD group [54]. In one recent

large study which evaluated United Network for Organ Sharing (UNOS) registry data from 2002 to 2016, five-year post-liver transplant survival in ALD was 79% compared to 80% in non-ALD with similar risk for graft failure between the two groups [56]. When evaluating early LT for AH specifically, one multicenter United States study demonstrated a three-year survival rate of 84% [57]. This is an encouraging result although early LT for AH is only offered at select transplant centers. There is global variability in the utilization of LDLT in AH. LDLT is not commonly done in the United States, in which many patients have high MELD scores and high urgency for LT evaluation. This allows for high priority for deceased donor liver transplantation in the United States MELD-based system. International studies for LDLT in AH have shown promising results. In one study out of Korea showed 92.1% one-year post-transplant survival in LDLT [58] while another study from India showed 84.5% one-year post-transplant survival [59].

Critically ill patients with ACLF are another important subset of individuals with ALD who undergo LT. In a recent study from France, individuals with ALD who presented with ACLF and underwent LT had a 94% one-year survival, although only 69 of the 200 patients enrolled in this study ultimately were listed for transplant and only 50 were successful transplanted [60]. In an American study of LT for ACLF, one-year survival ranged from 82%-88.2%, which depended on the degree of ACLF [61]. One limitation of this registry-based study however is the inability to account for post-LT recidivism. Notably, ACLF criteria also varies globally, and should be kept in mind when comparing these outcomes.

8. Pre- and Post-Transplant Alcohol/Addiction-Specific Treatment

Patient selection for LT requires a thorough evaluation of medical comorbidities, substance use, psychological issues, and social support to ensure that there are no factors present which may preclude a successful LT and post-LT course [62]. In ALD, there is an increased incidence of the psychiatric diagnosis alcohol dependence, and evaluation by clinicians with mental health and addiction experience is important in both making a psychiatric diagnosis and formulating a treatment plan [63-65]. One distinct aspect of AUD is concurrent psychiatric conditions that may accompany or overlap with it. Anxiety disorders are the most prevalent psychiatric conditions in the United States, and studies report that between 20-40% of patients treated for anxiety disorders have AUD [66, 67]. Mood disorders are important to evaluate and treat in AUD, notably major depressive disorder. The prevalence of major depressive disorders in patients with AUD are estimated to be between 27-40% [68, 69]. AUD is also associated with increased risk for other substance use disorders [70] and increases risk of overdose [71]. Post-traumatic stress disorder (PTSD) and sleep disorders are other conditions which can both overlap with AUD and require simultaneous evaluation and treatment.

Treatment of AUD requires a mechanistic understanding by the provider and is an essential aspect of ALD management. Alcohol dependence can be characterized by dysregulation of both reward and antireward systems [72, 73]. Alcohol intoxication causes the release of dopamine and endogenous opioids into the ventral striatum, associated with reward valuation [74-77]. Ongoing exposure to alcohol impacts the basal ganglia, ultimately mediating compulsive behaviors and increases risk of relapse [78]. The disruption of this reward system can then lead to withdrawal, a state associated with anxiety, stress, and medical instability.

AUD in ALD should be managed by a multidisciplinary team integrating addiction specialists, which improves rates of abstinence; the intervention with the greatest impact on survival [79]. Tobacco cessation is recommended to those with tobacco use disorder, as it decreases risk of relapses [80]. Pharmacologic therapies are also available and are associated with a reduced risk of disease progression in those with alcohol-related cirrhosis [81]. There are multiple pharmacologic therapies supported by both AASLD and ACG guidelines for the treatment of AUD. Therapies that are currently Federal Drug Administration (FDA) approved for the treatment of AUD include naltrexone and acamprosate, which are both first line agents as well as disulfiram. Disulfiram, however, has significant hepatotoxicity and is not recommended in the treatment of ALD. Naltrexone previously had a black box warning regarding its use in cirrhosis, but this was removed in 2013 and can be used in the treatment of AUD in patients with advanced liver disease. Acamprosate does not undergo hepatic metabolism but must be renally dosed. Second line agents include topiramate, gabapentin, and baclofen. Relapse prevention medications have not been shown to interact with immunosuppressive medications in transplanted patients and can be used in this patient population [82].

Abstinence and relapse prevention is not only an important aspect of care in pre-transplant ALD, but post-transplant as well. Identifying risk factors for post-transplant recidivism has an impact on long-term outcomes. Definitions of return to alcohol can be variable by amount of alcohol consumed: a slip is an unplanned or short-term return to use of alcohol whereas a relapse is return to harmful alcohol use with abandonment of a treatment plan. Current literature suggests that post-transplant rates of a slip of any kind can vary between 30-50% [83]. Rates of relapse, however, for individuals' post-LT for ALD are estimated to be between 10-26% [84]. When early LT for AH challenged the 6-month rule, recidivism rates in those who underwent early LT became a point of clinical and research interest (Table 1).

Table 1 Overview of published trials using LT in ALD.

Authors	Sample Size (patients)	Median Sobriety Period	Survival Outcomes	Recidivism Definition	Post-LT Alcohol Consumption	Comments
Mathurin *et al.* 2011 [22].	26	None required	6-month survival: 77% 2-year survival: 71%	>30 grams of alcohol daily use	Slip: 11.5% Relapse: 7.6%	Prospective multicenter study
Singal *et al.* 2012 [85]	184	None reported	5-year survival in AH: 80% 5-year survival in alcohol-related cirrhosis: 78%	Not defined	None reported	Retrospective analysis of UNOS database. Evaluated cohorts with AH & alcohol-related cirrhosis
Ahn *et al.* 2013 [58]	126	6 months	1-year survival: 92.1% 3-year survival: 88% 5-year survival: 85.8% 10-year survival: 83.7%	Did not differentiate between a slip and relapse	7.9% returned to alcohol use post-LT	Retrospective, single-center study evaluating LDLT for AH
Im *et al.* 2016 [86]	9	None required	6-month survival: 89%	Relapse defined as ≥4 standard sized drinks in a day or ≥1 drink four days in a row	Relapse: 1.11%	Retrospective, single-center study
Lee *et al.* 2018 [57]	141	55 days	1-year survival: 94% 3-year survival: 84%	Relapse ≥100 days of use or binge drinking (>6 units per day for men, 4 units per day for women or >4 days/week)	Relapse: 11%	Retrospective study across 12 centers

Choudhary *et al.* 2019 [59]	39	4 months	1-year survival: 84.5%	Moderate consumption: 1-20 units (10 grams of ethanol)/day or Heavy consumption: >20 units per day	Relapse (combined moderate and heavy use): 8.1%	Retrospective, single-center study evaluating LDLT for AH
Lee *et al.* 2019 [56]	9,438	Not reported	1-year survival: 91% 5-year survival: 79% 10-year survival: 63%	Not defined	Not reported	Prospective, multicenter, national (US) cohort study
Musto *et al.* 2024 [87]	344	None reported. 110 patients underwent LT within 6 months of last drink	1-year survival: 93.7% 3-year survival: 89.6% 5-year survival: 86%	Defined as ≥4 drinks in a sitting for >3 months	Any post-LT alcohol use: 28.7% Relapse: 20.8%	Single-center retrospective study

In one study, the 10-year survival rate for patients with post-LT recidivism was 45.1% compared to 85.5% in those with sustained abstinence [88]. The interval time to returned alcohol consumption also has a significant impact on outcomes. Post-LT alcohol consumption within 12 months of transplant is associated with higher three and five-year mortality compared to those who are abstinent [89]. Patterns of return to alcohol use after LT are complex, and their effects on post-LT outcomes are not well defined. One study compared post-LT slips to relapses and found no statistical difference in mortality or other outcomes, although the number of patients and interval of follow up was a limitation [87]. Further studies are warranted to evaluate this gap in the literature. One systematic review of predictors for alcohol recidivism found that psychiatric co-morbidities were the strongest predictors, including anxiety and schizophrenia but interestingly did not find a significant impact of depression on recidivism rates [90]. Lack of social support is another factor that is strongly predictive of recidivism [82]. In one study from Poland, younger women were found to have higher risks of recidivism and higher rates of relapse [91].

9. Conclusions

In this review, we have discussed findings from recent studies and highlighted emerging practice patterns in liver transplant for ALD. ALD is now the most common indication for LT in both the US and Europe and is increasing globally, while attitudes and perceptions around LT in ALD are changing. Early LT in severe AH improves survival and has promising long term outcomes. The integration of multidisciplinary care models has improved care in transplant medicine, and current post-transplant mortality in ALD mirrors that of other indications for LT.

With the advent of direct alcohol biomarkers, further research is needed to quantify alcohol consumption and its impact on clinically relevant outcomes in liver transplant. Future studies should be directed at assessing the degree of alcohol consumption and its impact on outcomes such as LT waitlist mortality, post-LT alcohol relapse rates, graft dysfunction, and patient survival.

Abbreviations List

AASLD	American Association for the Study of Liver Diseases
ACG	American College of Gastroenterology
ACLF	acute-on-chronic liver failure
AH	alcohol-associated hepatitis
ALD	alcohol-related liver disease
AUD	alcohol use disorder
CTP	Child-Turcotte-Pugh
FDA	Federal Drug Administration
LDLT	Living donor liver transplant
LT	liver transplant
MDF	Maddrey discriminant function
MELD	model for end-stage liver disease
OPTN	Organ Procurement & Transplant Network
PEth	Phosphatidylethanol
PTSD	Post-traumatic stress disorder
UNOS	United Network for Organ Sharing

Author Contributions

Michael Eiswerth: Conceptualization, writing - original draft, formal analysis, writing - review and editing. Joel Wedd: Conceptualization, writing - original draft, formal analysis, writing - review and editing. Final approval. Corresponding author.

Competing Interests

The authors have declared that no competing interests exist.

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