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Chapter

Liver Transplantation in Patients with Alcohol-Associated Liver Disease: Current Strategies and Future Perspectives

Federica Invernizzi and Marta Cilla

Abstract

Patients with alcohol-related liver disease (ALD) who receive a liver transplant (LT) reach a one-year post LT survival of 80–85%. The rule of abstinence from alcohol for 6 months before transplantation has been applied widely, but few data support the use of this rule as the only criterion for selecting LT candidates. Today, many liver transplant centers try to balance the duration of abstinence against the risk of death associated with the severity of ALD. Since 2011, an increasing number of papers suggests that transplantation without a specific period of abstinence (early LT) among patients with severe and nonmedical-therapy responder alcoholic hepatitis is an effective therapeutic strategy. Further data are needed to better define the selection of patients with ALD who have been abstinent for less than 6 months as suitable LT candidates and to improve the treatment of alcohol use disorder in those patients who have received a LT reducing the risk of alcohol abuse recurrence.

Keywords: alcohol-related liver disease (ALD), liver transplant (LT), early LT, alcohol abstinence, abuse recurrence

1. Introduction

Excessive alcohol use is the main cause of avoidable deaths in the USA with more than 95,000 deaths/y and 29 years lost per death [1].

Alcohol-associated liver disease (ALD) is the most frequent type of liver disease, existing on a spectrum that ranges from steatosis to steatohepatitis (with and/or without fibrosis), acute liver failure, severe alcoholic hepatitis (SAH) and cirrhosis [2].

Patients with severe ALD who do not respond to medical therapy have a poor prognosis and the only therapeutic option associated with a survival benefit is liver transplantation (LT).

To date, ALD is the most common defined cause for both LT (31%) and waiting-list diagnosis (31%) in the US [3]. As of 2019 in Europe, alcohol-related cirrhosis has become the most frequent LT indication, with graft survival rates of 78% at 3 years and 73% at 5 years post-transplantation [4].

The survival benefit of LT in patients with SAH and acute-on-chronic liver failure (ACLF) has been established [5–7]. Instead, survival benefit of transplantation versus no transplantation in patients with intermediate disease severity has not been proven [8, 9].

Nevertheless the consistent increase in the number of LT for AILD and its favorable outcome, less than 5–10% of potential candidates with this disease are listed for LT [10, 11].

Often alcoholics are held accountable for their disease. Moreover, these patients remain in situations of social and economic vulnerability that makes them susceptible to fall back into alcohol abuse. This has increased the disappointment towards their inclusion in transplant list.

Building on this, until some years ago, LT centers required a 6-month abstinence period to considerate patients for transplantation. However, data regarding the 6-month rule as a predictor of long-term sobriety are controversial [12].

Indeed, this period is arbitrary and has never been shown to affect survival after liver transplantation [13]. In addition, patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%.

Since 2011, an increasing number of papers suggests that transplantation without a specific period of abstinence (early LT) among patients with severe and nonmedical-therapy responder alcoholic hepatitis is an effective therapeutic strategy [14].

Based on these data, transplant centres have gradually changed their procedures for handling of early liver transplantation. The percentage of early LT has tripled in France and has doubled in the USA over a period of almost 20 years [15]. However, before early LT can be expanded, it is vital to understand the long term survival and the factors associated with poor transplant outcomes.

2. Evaluation of alcohol-related liver disease patients for LT

In general, all LT candidates for ALD underwent careful evaluation by a multidisciplinary transplant committee, which consisted of transplant surgeons, hepatologists and licensed social worker. The latest guidelines in Europe and the USA have endorsed the integration of experts in addiction medicine in the process of assessing and managing alcohol use disorder in ALD during evaluation of individual patients for a transplant [16, 17].

Team members requested stringent selection for at least two reasons. First, donor grafts are not enough, second, in the allocation system based on MELD scores, patients with SAH and nonmedical-therapy response are like reaching the top of the transplant waiting list.

Foster *et al.* have proven that the length of pre-LT abstinence from ethanol alone is a poor predictor of post-LT abstinence when analyzed as a categorical variable like $<$ or \geq 6-month abstinence and quantitative variable [18].

Furthermore, similar selection criteria are not applied to other LT candidates such as patients with nonalcoholic fatty liver disease (NAFLD) or intentional drug overdose, suffering from a similar addiction [19].

The transplant community must ensure that patient selection is fair and equitable and engenders continued faith and trust in the process. Appropriate safeguards are essential to excellent long-term outcomes comparable with other liver failure etiologies.

Wells *et al.* have proven that cirrhosis on explant pathology exceeded 95% in both early LT and standard LT groups, emphasizing that chronic liver disease is present in most patients despite an acute presentation. High rates of SAH on explant pathology was seen in 31% of patients in the standard LT group, despite patients reporting 6 months of abstinence [20].

This finding may reflect the heterogeneity in the duration of inflammation associated with alcohol or it may depend on ongoing alcohol abuse though patient-reported abstinence [20].

On the other hand, a meta-analysis of 92 studies involving ALD 8000 patients found that psychiatric comorbidities, abstinence for less than 6 months before transplantation, an unmarried status and smoking were predictive factors of alcohol relapse [21, 22].

Actually, transplantation community needs focus its interest from adherence to this arbitrary duration time of abstinence to identification of factors associated with poor post-transplant outcomes, post-transplant interventions that minimize relapse and strategies that treat relapse when it occurs. In addition, it's important to underline that the high prevalence of comorbidities in ALD candidates mandates a careful screening of extrahepatic comorbidities. Indeed, also other organs can be damaged by excessive drinking, for example alcohol-related acute pancreatitis is a relative contraindication to transplantation. A thorough cardiovascular and neurological assessment is required to exclude respectively cardiomyopathy and neuropathy alcohol-related.

All patients evaluated for liver transplantation should be screened also for malnourishment and sarcopenia. Sarcopenia is in fact a hallmark of frailty and functional decline and it has been recently identified as an independent predictor of waiting list mortality and worse post-transplant survival [23, 24].

Finally, alcohol-related cirrhosis is associated with an increased risk of hepatocellular carcinoma but also of other extrahepatic tumors, like cancer of the upper aerodigestive tract and, less often, colon and breast tumors [25].

3. Early vs. standard liver transplant

The treatment of patients with ALD has changed markedly over time. To ration organs, most programmes require a 6 month period of abstinence prior to evaluation of alcoholic patients, presumed to enable some patients to recover from their liver disease and identifying patients likely to maintain abstinence after LT [26].

However, data regarding the 6-month rule as a predictor of long-term sobriety are controversial [12]. Indeed, SAH is a life-threatening condition and corticosteroids for 1 month are the only approved medical treatment. Unfortunately, most alcoholic hepatitis deaths occur within 2 months and no pharmacological option has been proven efficient.

Starting from these data, 10 years ago Mathurin *et al.* selected 26 patients with severe alcoholic hepatitis at high risk of death (median Lille score, 0.88) and without severe coexisting or psychiatric disorders, with close family support and agreement for lifelong abstinence for early LT (median of 13 days after nonresponse to medical therapy). Mathurin *et al.* have shown that early transplantation was associated with higher cumulative 6-month survival rate compared with no early LT ($77 \pm 8\%$ vs. $23 \pm 8\%$, $P < 0.001$). Moreover, 2-years survival rates was higher in early-LT patients (hazard ratio, 6.08; $P = 0.004$). Finally, the assessment of alcohol relapse revealed that approximately 11% of patients remained daily alcohol drinker more than 3 years after LT [27]. Following this strategy, others Centers expanded access

Paper (authors and year)	Inclusion criteria	Exclusion criteria	Alcohol relapse rate (%)	1-year survival (%)
Mathurin P. [27] Dharancy S. (2020) [28]	<ul style="list-style-type: none"> • Medical therapy failure • First decompensating event due to severe AH • Close supportive family members and patient agreement to total abstinence • No psychiatric disorders 	<ul style="list-style-type: none"> • Recent infection • Recent gastrointestinal bleeding 	Clinical relevant: 10%	83%
Im G.Y. (2016) [29]	<ul style="list-style-type: none"> • Medical therapy failure • First decompensating event due to severe AH • Close supportive family members and patient agreement to total abstinence 	<ul style="list-style-type: none"> • Concomitant chronic liver diseases • Concomitant hepatocellular carcinoma • Concomitant HIV • Severe comorbid conditions or psychiatric disorders 	Any use: 22% Clinical relevant: 11%	89%
Weeks S.R. (2018) [30]	<ul style="list-style-type: none"> • Medical therapy failure • Close supportive family members and patient agreement to total abstinence • No coexisting psychiatric disorders • Patients with history of psychiatric symptoms included if psychiatric assessment demonstrated stably managed disease 	<ul style="list-style-type: none"> • Concomitant liver disease • Concomitant hepatocellular carcinoma • Patients who received transplants previously 	Any use: 28% Clinical relevant: 17%	97%
Lee B.P. (2018) [31]	<ul style="list-style-type: none"> • Age older than 18 years • First liver decompensating event due to severe AH • No prior diagnosis of chronic liver disease or episodes of AH • Strong social support by family and friends • Absence of severe comorbid medical disorders • Patient agreement to total abstinence 	<ul style="list-style-type: none"> • Concomitant presence of other liver disease • HIV • Other contraindications to LT 		
Germani G. (2021) [32]	<ul style="list-style-type: none"> • Age older than 18 years • Clinically diagnosed severe acute AH • Severe AH as the first liver decompensating event • Strong social support -Absence of severe comorbid medical disorders • Patient agreement to total abstinence 	<ul style="list-style-type: none"> • Patient <18 years old • Concomitant presence of other liver disease • HIV 	Any: 13%	100%

Paper (authors and year)	Inclusion criteria	Exclusion criteria	Alcohol relapse rate (%)	1-year survival (%)
Louvet A. (2022) [33]	<ul style="list-style-type: none"> • Aged 18 years or older. • High alcohol intake, clinical diagnosis of alcohol related hepatitis, hospitalized for less than 1 month • Maddrey score of 32 or higher at admission and poor response to medical management¹ (Lille model score ≥ 0.45) or early • worsening of liver function despite an initial good therapeutic response (Lille model score < 0.45) 	<ul style="list-style-type: none"> • HBsAg, hepatitis C virus, HIV antibodies, pregnancy, breastfeeding, evolving neoplasia likely to threaten 1-year outcome, and uncontrolled bacterial, fungal, parasitic, or viral infection 	Any: 23%	89%

Table 1.
 Selection criteria and outcomes in studies published on eLT for sAH.

to transplantation without 6-months rule among well-selected patients after careful assessment of their addiction profile **Table 1** [29, 31, 34].

Only 18 of 233 evaluated patients (7.7%) underwent transplant in the French cohort. In the initial US multicenter experience, the Accelerate trial, 36% of evaluated patients underwent transplant [31].

Recently, Herrick-Reynolds *et al* retrospectively analyzed data from largest single-center cohort of early LT for ALD to date to define patient, allograft, and relapse-free survival. Using standard LT as a comparison group, they also investigated the association of early LT with these survival outcomes [35].

In addition, a multicenter Italian study has shown that early LT significantly improves survival in SAH non-responding to medical therapy, when a strict selection process is applied. Overall, 6-, 12-, and 24-month survival rates were indeed 100% significantly higher in SAH candidates to early LT compared with non-responders to medical therapy who were denied LT (45%, 45%, and 36%, $p < 0.001$) [32].

Recently, Louvet *et al.* have conducted a multicentre, non-randomized, non-inferiority, controlled study in 19 French and Belgian hospitals. They cannot conclude non-inferiority in terms of rate of alcohol relapse post-transplant between early and standard LT proving that high alcohol intake is more frequent after early LT. On the other hand this prospective controlled study have confirmed the important survival benefit related to early LT for severe alcohol-related hepatitis [33].

Based on these data, despite the frequent use of the six-month rule, the United Network for Organ Sharing (UNOS), the International Liver Transplantation Society (ILTS) and the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on ALD and on LT did not endorse this measure as a formal recommendation [36].

4. Post-transplantation assessment

The proportion of patients returning to drinking any amount of alcohol range from 8 to 20% at 1 year post-transplantation and then gradually increase to 30–40% at 5 years post-transplantation [37].

DiMartini *et al.* have investigated patterns of alcohol use prospectively in long-term follow-up studies of LT patients and they observed no or minimal alcohol use over the follow-up period in 80% of patients [38].

Unfortunately, the reported rates of alcohol consumption after liver transplantation vary between studies because of the heterogeneous definitions used to classify recurrent drinking [26].

Available data indicate that, regardless of abstinence, a reduction in alcohol consumption is associated with a decrease in overall morbidity, mortality and health costs and an improvement in psychosocial status [39, 40].

Moreover, different studies have showed that only heavy or persistent drinking appear to be deleterious to the graft and long-term liver disease-related deaths in transplant recipients for ALD [41, 42].

Proceeding from this, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have defined drinking decreases a goal to assess efficacy in clinical trials. Accordingly, the EMA endorsed drinking risk levels reduction as outcome in alcohol pharmacotherapy trials in line with the WHO 4-category classification **Table 2** [39, 43].

Most trials focused in fact on abstinence goal until now, otherwise ongoing trials recognize alcohol level reductions as indicators of treatment outcome. This marks a revolution in the management of alcohol use defining drinking risk level reductions as a more worthwhile endpoint for ALD patients [44].

In a review of community-based epidemiology studies, alcohol dependence had the highest median untreated rate (78%) of the eight psychiatric disorders examined [45].

Reasons for these poor treatment rates may include the stigmatization of being labeled an alcoholic and individuals' resistance to stop drinking when treatment programs have traditionally focused on abstinence.

The link between alcohol abuse and poverty, discrimination, disadvantage and increased rates of psychological distress and are well known [46]. Alcohol related issues are best supported by a specialist team and the literature suggests specialized professionals embedded within the transplant team are the most effective in reducing post-transplant alcohol relapse and mortality [47, 48].

Psychosocial assessment is fundamental to establish predictive factors of unfavorable outcomes and associated possible intervention measures. Not adequate social assistance, ethanol/substance addiction and psychiatric problems may need heterogeneous strategies. Moreover, several patients can have multiple psychosocial problems that necessitate a coordinated pluridisciplinary approach [46].

Further research in this field is required to improve preoperative and postoperative patient-centred liver transplant outcomes.

Risk levels	Men	Women
Abstinence	0	0
Low risk	1–40	1–20
Medium risk	41–60	21–40
High risk	61–100	41–60
Very high risk	>101	>61

Table 2.
WHO risk levels of alcohol consumption, (g/day).

5. Conclusions and future directions

An increasing incidence of hospitalization for AH has been seen both in the United States and Europe, with a parallel increase in mortality rates in recent years.

Early LT for SAH is an emerging treatment option, although heterogeneities persist in national transplantation guidelines across countries.

We believe that a change in the approach to treating alcohol dependence is underway.

The core of the debate in the world of transplants is an ethical end cultural nature.

Is it right to donate a precious organ to patients who could resume post-LT alcohol addiction potentially resulting in the organ loss? The idea that patients without a proven period of alcohol withdrawal could damage to other patients on the waiting list has a potential detrimental effect on the willingness to donate organs.

Nevertheless, several studies have proven the important survival benefit related to early LT for SAH and these data have led to a gradual change in transplant centre practices.

Further progress is required to enhance the role of preoperative psychosocial counseling on the improvement of the recipient compliance and the addiction management after liver transplantation.

Moreover, the liver transplant candidate selection process needs to be standardized. The patient assessment need to focus on alcohol use disorder, coping skills and awareness and agreement to adhere to lifelong alcohol abstinence. Quality of affective relationship, presence or absence of caregiver support, good social and occupational functioning must be considered as critical factors.

Finally, we need prospective studies of interventions to treat alcohol dependence after transplantation focused on reduction in consumption of alcohol as opposed to abstinence.

Conflict of interest

The authors declare no conflict of interest.

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