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Editorial

Early Liver Transplantation: The Last Chance Therapy for Patients With Alcohol-Associated Hepatitis and Acute on Chronic Liver Failure

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Alcohol-associated hepatitis (AH) is a syndrome of rapid-onset jaundice, elevated aminotransferases, and liver failure accompanied by signs of systemic inflammation that occurs in persons who have been drinking [1]. Severe AH carries a mortality of up to 40% at 6 months, whereas even milder forms (model for end-stage liver disease [MELD] score $\leq$20) are associated with mortality of 12% in the same timeframe [1,2]. Challenges to the management of patients with AH, such as the limited range of effective treatment options and the variable clinical course of AH-related liver failure, are confounded further by concomitant alcohol use disorder (AUD). Currently, corticosteroid therapy remains one of the only options in the treatment armamentarium for AH, with data pointing to a 28-day, though not a 90-day, survival benefit in selected patients. As we will discuss, patients with AH whose clinical trajectory deteriorates rather than recovers with medical support and abstinence from alcohol often develop multisystem organ failure and meet criteria for the diagnosis of acute on chronic liver failure (ACLF) [3].

ACLF refers to a clinical entity in which a patient with chronic liver disease experiences an acute decompensation involving one or more organ failures [3]. Definitions of ACLF vary, but one of the most widely used is that of the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium, which includes criteria for organ dysfunction, as well as an overall grading system for ACLF. ACLF is graded according to the number of organ systems in failure, ranging from ACLF-1 to ACLF-3, with a high short-term mortality of up to 70% at 28 days associated with higher grades. Factors precipitating ACLF include events causing increased inflammation, such as AH and bacterial infections, as well as gastrointestinal hemorrhage. There is no clear precipitating cause of ACLF in up to 40% of cases. Therapies for ACLF focus on treating the precipitating event, and providing supportive therapy, often in the intensive care unit (ICU). Liver transplantation is becoming an increasingly recognized option for ACLF, with recent prospective data showing acceptable post-transplant survival, with 28-day, 90-day, and 1-year survival at 93%, 86% and 77%. Faced with the prospect of death, early liver transplantation (eLT), which refers to access to liver transplantation without a required minimal interval of abstinence, is a therapeutic option for patients with AH and ACLF [4]. In this editorial, we discuss the nexus of AH, ACLF, and selection of patients for eLT.

Until relatively recently, AH was considered an absolute contraindication to liver transplantation. This was largely due to the prevailing belief that a minimum period of alcohol abstinence of six months was necessary prior to transplant, both to allow spontaneous recovery and thereby avoid unnecessary liver transplantation, along with concerns regarding clinical outcomes and the toll of a return to alcohol use after transplantation [5]. However, in 2011, the high short-term mortality in AH patients prompted the landmark study of Mathurin and colleagues that showed that patients with AH not responding to medical management had much better short-term survival after eLT than matched historical controls [6]. These findings were corroborated in a US multicenter retrospective cohort [7]. Initial studies showed that up to 34% of recipients returned to alcohol use after transplant. Furthermore, as care of patients with alcohol-associated liver disease (ALD) has progressed toward multidisciplinary teams integrating addiction medicine and hepatology, the prospects for better care for patients at risk of return to alcohol use after transplant have also evolved [8].

However, the decision to move forward with eLT in patients with AH is not straightforward, not least since some AH patients recover after receiving medical therapy alone. Parker et al. [9] have shown that the initial trajectory of serum bilirubin is a key prognostic indicator for these patients in that those whose total bilirubin falls in the first seven days of hospital care, the 'fast fallers' in Parker's parlance, tend to recover without recourse to corticosteroids or liver transplantation. In contrast, in a single center experience of ALD patients who had consumed alcohol in the prior 90 days, and who presented with MELD score >25, Musto and colleagues [10] found that only 40% survived for 90 days in the absence of a liver transplant. Similarly, a study of patients with MELD score >20 and recent alcohol use found that rates of recompensation among the group of patients who had been declined for transplant on the grounds of clinical improvement were just 28% [11].

Musto et al. [12] also reported that survival over the first 10 years of patients who received an eLT was similar or better than that for other diagnoses, despite a higher incidence of post-liver transplantation alcohol use in the eLT recipients. Thus, we contend that for patients with severe AH not responding to clinical care, eLT is a life-saving intervention.

AH that progresses to ACLF presents additional challenges for clinical management and in consideration for liver transplantation. The acuity of AH-ACLF is prognostic: for example, in one study, AH without ACLF was associated with a 28-day cumulative incidence of death of 10.4%, while in the presence of ACLF, this increased to 54% [13]. Furthermore, the 28-day mortality by AH-ACLF escalates with the ACLF grade. The presence of ACLF in association with AH impacts the potential effectiveness of high-dose corticosteroids so much so that corticosteroids should be avoided in patients with AH-ACLF-3. Moreover, ACLF is associated with a high risk of infection, which is increased by corticosteroids [3]. Taken together, these data suggest that when a recovery fails to materialize in AH-ACLF, eLT is the next best option. Unfortunately, multisystem organ failure, which is the hallmark of ACLF, acts as an impediment to selection for transplant, independent of the issues that characterize the selection process in patients with AH alone, such as AUD and the risk of return to drinking after transplant.

There are several proposed selection models for determining appropriateness of eLT, with the goal of selecting patients who would not otherwise recover and have a favorable profile for maintaining abstinence after transplant. In their 2011 study, Mathurin and colleagues [6] used a stringent set of selection criteria, including Maddrey's discriminant function $\geq$32, nonresponse to corticosteroids with a Lille score of $\geq$0.45 on day 7 or a continuous increase in MELD score, no prior decompensating event, presence of close and supportive family members, no coexisting severe or psychiatric disorders, and patient agreement to life-long abstinence from alcohol. More recently, citing the presence of a prior decompensating event as a contraindication to eLT has been called into question [14]. In like manner, the notion of life-long abstinence has come under scrutiny as being unrealistic for many patients with AUD, a disorder of remission and relapse, and has been replaced by the goals of timely recognition of episodes of drinking post-transplant and taking steps to restore sobriety. In a multicenter retrospective database, the patient and graft survival of persons who achieved 're-abstinence' was similar to those who did not drink after liver transplantation [15].

Both AH and ACLF encompass potential complications of alcohol-related liver disease that are associated with high mortality, and for which eLT is increasingly recognized as a valuable treatment option. AH and ACLF often co-exist, and we propose that the presence of ACLF in patients with AH should not preclude *ab initio* consideration for eLT. Indeed, in our view, identifying and grading ACLF in patients with AH can help to select those patients most likely to benefit from eLT; namely, the patients for whom treatment options are limited, who are unlikely to achieve spontaneous recovery, but who are likely to live for many years after eLT.

Key Points

- Alcohol-associated hepatitis (AH) carries a high mortality and can progress to acute on chronic liver failure (ACLF).
- Liver transplantation is an increasingly recognized therapeutic option for ACLF, with acceptable post-transplant mortality.
- Early liver transplantation, without a minimum period of alcohol abstinence, is also increasingly recognized as a therapeutic option for AH, but challenges in predicting which patients will recover with time and alcohol abstinence still exist.
- The development and grade of ACLF in AH are associated with increasing short-term mortality, and moreover, limit therapeutic options for treating AH with corticosteroids.
- The presence of ACLF in patients with AH should not preclude early liver transplantation, and indeed, can help identify those patients who would benefit most from early liver transplantation.

Availability of Data and Materials

Not applicable.

Author Contributions

MRL: conception, design and drafting of the manuscript. BRE: conception, design and drafting of the manuscript. Both authors contributed to revising the manuscript critically for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

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