

Early liver transplant for severe alcoholic hepatitis: establishing a new frontier by ignoring the rule?

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Alcoholic liver disease (ALD) has become one of the most common indications for liver transplant (LT) in the United States and Canada. In 2016, a total of 7,841 LTs were performed in the United States, and among them, 28% were given to persons with ALD (1). Organ allocation for ALD has been rising from 2005 to 2016, in contrast to hepatitis C viral (HCV) that is on the decline during the same period in the era of direct-acting anti-viral therapies. Despite this general trend, as of 2018, about half of transplant centers in America have not performed any LT on persons with severe alcoholic hepatitis (SAH) refractory to medical therapies (2). This may be a result of the general recommendation given by the American Society of Transplantation and AASLD in 1997, which outlined a minimal 6-month abstinence period before listing a person with ALD (3), effectively excluding early transplant for majority of SAH, most of whom do not survive to qualify the 6-month abstinence rule.

Patients with SAH have a poor prognosis, especially when refractory to medical therapy, and the 6-month mortality was estimated to be as high as 75% (4). A survival benefit was demonstrated by Mathurin *et al.* in 2011, where 26 carefully selected patients with SAH received an early LT (5). It is with this mind that we review the article published by Lee *et al.* in the recent issue of Gastroenterology (6). The new study is a retrospective chart review by design. Data from 2006 to 2017 were collected from 12 LT centers in the United States. One hundred and forty-seven transplant recipients were included, of whom all had SAH as an indication for LT. None had documented episodes of alcoholic hepatitis or known liver disease prior to their hospitalizations. The median MELD score was

39 and the median Lille score was 0.82; 54% of them received corticosteroids before LT. The median duration of abstinence before LT was 55 days. The primary outcomes were 1 and 3-year survival rates post transplant, which were 94% and 84% respectively. Another primary outcome was post-transplant alcohol use at 1 and 3-year, which was 25% and 34% respectively. Overall 72% were abstinent post LT, while only 11% demonstrated sustained alcohol use and 18% drank alcohol occasionally that was not sustained. The study found younger age at LT predicted alcohol relapse, and there was an increased mortality risk [hazard ratio (HR) 4.59] attributed to alcohol use post LT.

This study has several merits. It is a multi-centered study consisted of relatively large number of patients, in comparison to the previously published European study by Mathurin *et al.* (n=26) (5) and another American study published in 2015 that reported on 45 patients with SAH undergoing early LT (7). The larger patient number allows for more meaningful statistical analysis and subgroup analyses. It has a reasonable long post transplant follow-up period, allowing for the evaluation of short- and long-term recidivism rate, and the close examination of the impact of recidivism on patient outcomes. However, the design of the study being retrospective review in nature has numerous limitations compared to prospective controlled studies. Patient selection biases, the lack of a unified definition of SAH, the lack of standardized medical treatment of SAH before LT, and missing data are some of the examples. The high listing rate (35.9%) and transplant rate (29.1%) for severe AH reported by this study is discordant with other studies (2,5,8), which may stem from the afore mentioned

limitations seen in a retrospective study. The results of this study shed light on several important questions regarding early LT in severe AH.

Impact of early transplant on patient survival

The study reports a major survival advantage from early LT in patients with SAH who failed all conventional medical therapies, as only 20% would otherwise be alive at 6 months according to the propensity score from the study. By having a LT, 94% were still alive at 1 year. This is consistent with results from other studies (4,5).

Evaluation of post-transplant recidivism

Heterogeneity in the documentation and methodology in assessing alcohol relapse post LT across America was highlighted by the study. While 7 of the 12 transplant programs asked direct questions about alcohol intake at each clinical visit in conjunction to routine urinary/blood test for alcohol metabolites, at 2 centers, blood or urine tests were conducted in selected individuals only. The remaining 2 centers did not use any blood or urinary screening test to detect alcohol relapse. There seemed to be a general lack of standardization in assessing post transplant recidivism across the transplant programs.

Assessing factors associated with recidivism

An important consideration in early transplantation of alcohol hepatitis patients is attempting to predict the risk of recidivism post-transplant. Patients with SAH undergoing early LT have not been subjected to the 6-month abstinence rule. On the other hand, in the typical alcoholic cirrhosis situation, having met the 6-month abstinence rule is also no guarantee that the individual will remain abstinent and the degree of recidivism reported in this study is similar to what is experienced by transplant centers in real world clinical practice. Considering factors associated with alcohol relapse will help transplant programs allocate precious organs to the most suitable candidates.

The current study identified younger age as a factor associated with post-transplant recidivism. However, due to the retrospective design, and the fact that all transplant recipients in this study had strong social support as a prerequisite before LT, the more complex psycho-social aspects of alcoholism and recidivism remain unexplored. Patients transplanted for ALD in general are more likely

to drink alcohol than those transplanted for non-ALD indications consistent with ALD being a behavioral disorder, an addiction, as well as a liver disease. Many other predictors of post transplant recidivism were identified by other studies, and they were: younger age, driving under the influence (DUI), prior alcohol dependence, co-existing illicit substance use, having at least one sister with alcoholism, having no AA attendance (9,10). Prolonged sobriety (>19 months) was identified in a retrospective study to independently predict abstinence post-LT in general, and with each month of abstinence pre-transplant, the likelihood of post-transplant recidivism decreased by 5% (11).

Validity of the 6-month abstinence rule

Importantly, the validity of 6-month rule is questioned by this study and previously evaluated by several studies. Longer than 6-month abstinence predicted post-transplant sobriety with relative high specificity (>90%), however the lack of 6-month abstinence was associated with a poor sensitivity at 50% at predicting future behavior (9). In other words, due to its poor sensitivity, an arbitrary 6-month rule is a good inclusion criteria in those patients who could survive that long, however it is a bad exclusion criteria in LT for those who may not survive 6 months and could deny otherwise reasonable candidates a life-saving transplant. We note that another retrospective cohort study from US was published in 2018, where 46 carefully selected severe AH patients (SAH) were transplanted between 2012–2017, while no recipient had 6-month sobriety (12), recidivism rate was almost identical at 28% (SAH) versus 24% (alcohol cirrhosis). Similarly, the study found that 6-month abstinence rule was not a predictor of recidivism.

Impact of recidivism on allograft longevity and overall patient survival

Recidivism can reduce allograft longevity and overall patient survival as accumulative alcohol use is toxic to the allograft as it is to the native liver. Some even argue that fibrosis and cirrhosis develop much earlier in the transplanted liver than the native liver for the equivalent amount of alcohol consumed by an individual. One should also separate occasional drinking from problematic sustained drinking as it is appropriately done by this study. In this study, 25% were occasional users (slip only) and 75% were sustained users among the 40 patients who used any alcohol post LT. The study found patient survival was

reduced in alcohol users compared to the non-users post-transplant but did not differentiate between the slip only group and the sustained users. Similar to this study, other studies also reported worsen long-term outcomes at 5-year among any alcohol users, although early survival appeared to be similar amongst drinkers and non-drinkers post-LT. There is an increased risk of *de novo* malignancy in patients transplanted for ALD, with highest risk in patients who resumed drinking post-transplant (13).

In conclusion, the study reaffirms a substantial survival benefit by early LT in SAH. It also calls for well formed pre-transplant assessment and careful patient selection, in determining who is a candidate. Large prospective studies are needed to make a new management algorithm in SAH that incorporates early LT. Most importantly, the 6-month abstinence rule may be obsolete and arbitrary, given the evidence presented by this study and other studies. From a practical point of view, we note that this study as well as the other recent American study (9) were retrospective reviews of clinical practice indicating that some American centers are currently transplanting patients with severe AH and are ignoring the 6-month rule.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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