Liver Transplantation in Patients with Severe Alcoholic Hepatitis

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MINI REVIEW

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Severe alcoholic hepatitis (AH) presents as decompensated liver disease in persons who drink excessive amounts of alcohol. There is a wide dose-response to the toxic effects of alcohol. Approximately 20% of individuals who consume 60 grams of alcohol or more on a regular daily basis for 20 or more years have been observed to develop clinical liver disease, although many women who drink less also will exhibit signs and symptoms of the disorder. Severe AH should be thought of as a form of acute-on-chronic liver failure, because of the latent presence of variable amounts of fibrosis and inflammation in affected individuals. The clinical presentation, therefore, may be any combination of liver-decompensation syndromes including, but not limited to, hepatitis with jaundice and coagulopathy, portal-hypertensive bleeding, hepatic encephalopathy, hepatorenal syndrome, and ultimately progression to multi-organ failure. Mortality depends on the stage of underlying fibrosis and the degree of inflammation, and may be as high as 70%. Thus, it is understandable that affected patients have been treated with varying degrees of success, mainly with steroids; nonresponse to medical therapy is associated with a six-month survival of approximately 30%. [1] Severe AH has been considered a contraindication to liver transplantation (LT), although Shakil, et al. demonstrated long-term survival after LT comparable to that of controls in nine patients with severe AH, defined as persons with a Maddrey discriminant function greater than 32. [2] It otherwise has been customary to demand that patients with end-stage liver disease from alcohol be abstinent for at least six months before they can be considered as LT candidates.

In a landmark study published in 2011, Mathurin et al. challenged the requirement of a prescribed abstinence period for transplant eligibility.3 Authors randomized patients with severe AH to treatment with LT or medical management. Study candidates were required to exhibit a lack of response to standard medical therapy, which was defined as a failure of the Lille score [1, 3] to decline to 0.45 or less, or as an increase in the MELD score [3] after seven days of treatment with a daily dose of 40 mgs of prednisolone and routine supportive care. The presence of AH was documented by trans-venous liver biopsy in 23 of 26 transplanted patients and confirmed by histologic examination of the explanted livers. Six-month survival of transplanted patients was superior to that of un-transplanted non-responders to medical therapy (77±8% vs. 30±6%, P<0.001) but not significantly different from that of treatment responders (77±8% vs. 85±4%, P=0.33). Three of 26 transplanted patients resumed drinking: one at 720 days, one at 740 days and one at 1,140 days after LT. Despite

counseling by an addiction specialist, one patient continued to consume more than 50 gm of alcohol daily, one 30 gram of alcohol daily and one approximately 15 gram of alcohol weekly. Subsequently, many other studies addressing survival, recidivism and public opinion regarding transplantation as a treatment option for patients with severe AH have been published. [4-15]

In 2017, Lee presented a retrospective review of the results of liver transplantation in patients with severe AH. [4] This research was conducted at 12 centers in multiple American transplant jurisdictions. Patients with no prior diagnosis of liver disease had undergone LT in the years 2006 through 2017 before they could demonstrate six months of alcohol abstinence. Among 147 transplanted patients, the median duration of abstinence before surgery was 55 days, during which 54% had been treated with corticosteroids. The median Lille score of transplanted patients was 0.82 and the median MELD score 39. Cumulative survival one year after LT was 94% (95% CI, 89-97%) and, at three years, 84% (95% CI, 75-90%). Following hospital discharge, 72% of LT patients were abstinent, 18% had slips, and 11% had sustained alcohol use; the cumulative incidence of any alcohol use was 25% at one year (95% CI, 18%-34%) and 34% at three years (95% CI, 25%-44%). Only younger age at LT predicted alcohol relapse (P = .01). Sustained alcohol use after LT was associated with an increased risk of death (hazard ratio, 4.59; P = .01). The investigators concluded that one- and three-year patient survival after LT for severe AH was similar to survival after LT for other indications. Sustained alcohol use after LT was infrequent but associated with increased mortality. It was the opinion of the investigators that these findings support the selective use of LT as a treatment for severe AH. [4 - 6]

Singal et al. compared outcomes of LT for AH using UNOS data from the years 2004 through 2010.10 Adults undergoing liver transplantation for AH were each matched by age, gender, ethnicity, MELD score, donor-risk index, and year of transplantation with three patients transplanted for alcoholic cirrhosis. Post-OLT patient and graft survival was similar in study and control groups. They concluded that liver transplantation may be considered for a select group of patients with AH who fail to improve with medical therapy. [10]

Because the ethical propriety of allocating a scarce resource to persons with end-stage liver disease due to alcohol who may resume drinking after LT is an important concern, Lee at al. compared the incidence of any alcohol consumption in patients transplanted for AH (23.5%) to the incidence of alcohol relapse with alcoholic cirrhosis patients who had six or more months of abstinence prior to LT (29.2%; p>0.99); binge and frequent drinking were more common in the AH group, although this finding was not statistically significant. [7] Indeed, the duration of abstinence before transplantation is a poor predictor of alcohol relapse. [11, 12] LT may be lifesaving in cases of AH and inflexible sobriety rules may exclude patients with a low risk of relapse. Current data suggest that alcohol relapse rates are similar among patients with AH and alcoholic cirrhosis patients. An ongoing alcohol use assessment, both pre- and post-transplant, is critical to achieving good long-term outcomes. [12]

Lee et al. also created a scoring system to predict alcohol relapse. [13] Among 134 LT recipients for AH with a median alcohol abstinence pre-LT of 54 days, 74% were abstinent, 16% had slips only, and 10% had sustained alcohol use after a median of 1.6 years post-LT (IQR: 0.7-2.8). Using complex statistical analysis, they found four variables associated with sustained drinking post-LT and used them to formulate a score with a range of 0 to 11 predictive of alcohol relapse after LT (Table 1). A SALT score of greater than or equal to 5 had a 25% positive predictive value (95% CI: 10%-47%), and a SALT score of less than 5 had a 95% negative predictive value (95% CI: 89%-98%) for sustained alcohol use post-LT. [13] This work led them to conclude that the SALT score may assist in the selection of patients with AH who are likely to remain abstinent after early LT, and guide in risk-based interventions post-LT.

LT is associated with a clear survival benefit when compared to standard medical care in patients with severe AH. Opponents of making AH patients eligible for LT, however, emphasize the correlation between alcohol relapse and poor LT outcomes, and also public resistance to

transplantation for AH that may create distrust among potential donors. They argue that transplant centers need to establish improved models to predict relapse and standardize candidate selection criteria before LT for severe AH becomes accepted practice. [12, 14, 15] Ultimately, it is undeniable that we must have more uniform pre- and post-LT guidelines for evaluation and management of patients with "behavioral disease" that has created a need for LT.

Variable	Points
>10 drinks/day at presentation	+4
≥2 prior failed rehabilitation attempts	+4
Any history of prior alcohol-related legal issues	+2
History of non-THC illicit substance abuse	+1

TABLE 1. SALT Score to Predict Sustained Alcohol Use Post-LT. [13] The SALT score was generated from a full LASSO (the least absolute shrinkage and selection operator) logistic point-score model to predict sustained alcohol use post-LT. The score assigns points to variables that were associated with sustained alcohol use post-LT, and ranges were 0-11. Using a cutoff of 5, the SALT score had a C statistic estimate of 0.76 to predict sustained alcohol use post-LT (Lee et al. Hepatology, Vol. 69, No. 4, 2019).

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