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Model to Calculate Harms and Benefits of Early vs Delayed Liver Transplantation for Patients with Alcohol-Associated Hepatitis

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Abstract

Background & Aims: Early liver transplantation (without requiring a minimum period of sobriety) for severe alcohol-associated hepatitis (AH) is controversial—many centers delay eligibility until a specific period of sobriety (such as 6 months) has been achieved. To inform ongoing debate and policy, we modeled long-term outcomes of early vs delayed liver transplantation for patients with AH.

Methods: We developed a mathematical model to simulate early vs delayed liver transplantation for patients with severe AH and different amounts of alcohol use after transplantation: abstinence, slip (alcohol use followed by sobriety), or sustained use. Mortality of patients before transplantation was determined by joint-effect model (based on model for end-stage liver disease

[MELD] and Lille scores). We estimated life expectancies of patients receiving early vs delayed transplantation (6-month wait before placement on the waitlist) and life-years lost attributable to alcohol use after receiving the liver transplant.

Results: Patients offered early liver transplantation were estimated to have an average life expectancy of 6.55 life-years, compared to an average life expectancy of 1.46 life-years for patients offered delayed liver transplants (4.49-fold increase). Net survival benefit from early transplantation was highest for patients with Lille scores of 0.50–0.82 and MELD scores of 32 or more. Patients who were offered early transplantation and had no alcohol use afterward were predicted to survive 10.85 years compared to 3.62 years for patients with sustained alcohol use after transplantation (7.23 life-years lost). Compared with delayed transplantation, early liver transplantation increased survival times in all simulated scenarios and combinations of Lille and MELD scores.

Conclusions: In a modeling study of assumed carefully selected patients with AH, early vs delayed liver transplantation (6 months of abstinence from alcohol before transplantation) increased survival times of patients, regardless of estimated risk of sustained alcohol use following transplant. These findings support early liver transplantation for patients with severe AH. The survival benefit was maintained in all simulated extreme scenarios, but should be confirmed in prospective studies. Sustained alcohol use following transplantation significantly reduced but did not eliminate the benefits of early transplantation—strategies are needed to prevent and treat post-transplantation use of alcohol.

Keywords

6-month rule; accelerate-ah; Markov model; drinking

INTRODUCTION

Alcohol-associated liver disease has recently become the most common indication for liver transplantation (LT) in the United States and accounts for 40–50% of liver-related deaths in the U.S.[1,2] Alcohol-associated hepatitis (AH) represents a subset of alcohol-associated liver disease, in which patients present with acute jaundice in the setting of chronic heavy alcohol use, and is implicated in 10% of alcohol-associated liver deaths.[3] Indeed, in severe medically-refractory AH, 6-month mortality can approach 70%.[4] Deaths in the first 90 days of presenting with severe AH are associated with the severity of systemic inflammatory response, while survival beyond this acute phase of liver injury is dependent on abstinence from alcohol.[5,6] At present, there are no medical therapies that improve long-term survival.[4,7]

Early LT for severe AH, defined as LT without a minimum period of sobriety prior to surgery, is a relatively new, and controversial indication for LT.[8,9] Although early LT for highly select patients with AH is increasing in application across the United States, many centers have not adopted an early LT policy and still require a minimum period of abstinence before LT listing. In most programs, the minimum period of abstinence is 6 months, but there is some variability across programs.[10] Overall, intermediate post-LT survival rates after

early LT for AH are acceptable (~85% at 2-3 years), but a proportion of those transplanted may return to alcohol use post-LT and be at risk for poorer outcomes.[9]

The negative consequences of alcohol use post-LT are more likely to influence long-term, not short-term outcomes;[11,12] yet, long-term survival outcomes after early LT for AH, and how outcomes are influenced by rates of post-LT alcohol use are unknown.

Further, to meaningfully evaluate the risks and benefits of early LT for severe AH, one must consider mortality prior to listing and while on the waitlist as well as post-LT outcomes. Given high short-term mortality in persons presenting with severe AH, where 75–90% of deaths occur within 90 days of presentation, wait-list mortality may indeed have a significant impact on overall outcomes when programs decide to offer early LT for AH, and this likely varies in United Network for Organ Sharing (UNOS) regions with short versus long waitlist times.[4,8,13]

To inform policy regarding this controversial indication for LT,[14-16] we sought to 1) evaluate the comparative effectiveness of early LT versus delayed LT (6-month wait) for severe AH by different rates of post-LT alcohol use, and 2) quantify the harm of post-LT alcohol use on graft and patient survival.

METHODS

Model Overview

A previously validated Markov-based mathematical model, SIM-LT (*Simulation of Liver Transplant Candidates*), was adapted to perform our analysis.[17] The SIM-LT model was revised for this study to simulate a virtual trial comparing patients with AH who were offered early LT (i.e. listing after determining medically-refractory disease by Lille Score, in addition to time allotted for psychosocial and financial evaluation for early LT eligibility) versus delayed LT (i.e. listing after 6 months of abstinence). Data from published studies[6,18], the UNOS database and ACCELERATE-AH trial[9], were utilized for the model inputs. Patients' likelihood of receiving an organ was dependent on their MELD score. In the MELD-allocation system, patients enter the waitlist, and their position on the waitlist is decided based on their MELD score (those with higher MELD are higher on the list), not based on how long they have been on the list. To best approximate the probability of LT among the severe AH population (i.e. high MELD, disease from alcohol use) in the Share-35 era (implemented June 2013), national and regional transplant probabilities were estimated using median wait-times from the UNOS database among adult LT recipients with a primary listing diagnosis of alcohol-associated liver disease, and excluding human immunodeficiency virus, hepatitis C virus (HCV), hepatocellular carcinoma, prior LT, and MELD exceptions, from June 2013 to December 2017 (Appendix Table 1). Sensitivity analysis of transplant probabilities was performed by including those with a listing or transplant diagnosis of HCV. We also simulated natural fluctuations in pre-transplant MELD scores based upon UNOS waitlist data.[17,19,20] Pretransplant mortality was estimated by joint-effect model using MELD and Lille scores using weekly MELD score and the Lille score of a patient (Appendix Table 2).[21] The Lille score was calculated once for each patient during the simulation, as a Day 7 from initial hospitalization score.

Model outcomes were validated with ACCELERATE-AH and a Franco-Belgian study of early LT for AH.[8,9] The Franco-Belgian[8] study was not used to inform model inputs. SIM-LT was developed in the Java programming language.

Base Case Population

We simulated a cohort of severe alcohol-associated hepatitis patients, similar to the ACCELERATE-AH[9] cohort. Specifically, the ACCELERATE-AH cohort only included those with clinician-diagnosed AH as first presentation of liver disease (i.e. patients with prior episodes of AH, or previously diagnosed chronic liver disease, were excluded). All analyses were performed by conducting a virtual trial simulating 10,000 hypothetical patients. In our base case analysis, mean age was 43, 70% were male, and listing MELD and Day 7 Lille scores reflected the distributions of the ACCELERATE-AH cohort: median 38 (IQR, 34-40) and 0.82 (IQR, 0.56-0.97), respectively. Full baseline characteristics of the original ACCELERATE-AH cohort are summarized in Appendix Table 3. To account for possible survivor bias in our model, the distribution of MELD at initial hospitalization was calibrated such that the MELD at listing predicted by the model matched the distribution of listing MELD in the ACCELERATE-AH cohort. All patients who received liver transplant were categorized into one of the following three alcohol-use categories post-transplant: abstinent (defined as no evidence of any alcohol use), slip (defined as alcohol use followed by sobriety), sustained (defined as ongoing alcohol use). All post-LT transition probabilities post-LT (alcohol use, graft failure, and survival) are summarized in Table 1.

Interventions

For each patient, we simulated long-term outcomes under two LT policy scenarios: 1) offering delayed LT listing and 2) offering early LT listing (Figure 1). Patients in both scenarios had the same baseline characteristics.

In the delayed LT scenario, patients were listed for liver transplant only if they achieved 6-months of abstinence prior to LT. If they slipped and used alcohol during the pre-LT period, then they re-initiated a new 6-month sobriety period. To estimate the likelihood of alcohol use in the 6-month sobriety period, we used data from a French study that estimated 22% of AH patients used alcohol within a 6-month period after hospitalization for AH, given that there is no U.S. data specific to the AH population regarding post-hospitalization alcohol use.[6] This rate is similar to a U.S. prospective study that recorded that 25% of patients with alcohol-associated liver disease with recent alcohol use under consideration for LT had evidence of alcohol use after study randomization but before transplant.[18] In the sensitivity analysis, we tested this rate of alcohol use (22%) with an extreme case (favoring the delayed LT scenario), assuming that 0% of patients used alcohol during the 6-month follow-up. After a patient achieved 6-month sobriety, they were listed for liver transplant.

In the early LT scenario, patients were listed after determining medically refractory disease by Day 7 Lille score, and allotting time for psychosocial and financial evaluation for LT listing, which was based on the median time from initial hospitalization to date of LT listing in the ACCELERATE-AH cohort (13 days).[9] After a successful transplant, patients moved

to the post-LT health state. At any time, patients could die from liver-related mortality as well as background mortality (Figure 1).

At any time in the post-LT state, patients could return to alcohol use. The likelihood of using alcohol, either sustained or slip, was informed from ACCELERATE-AH data.[9] In the base case, we assumed that patients who achieved 6-month sobriety pre-LT had the same likelihood of relapsing as those in the early liver transplant arm. We then performed sensitivity analyses with varying rates and patterns of alcohol use in either arm, to assess the impact of alcohol use on survival, as measured by life-years.

Patients could also experience graft failure post-transplant. Post-transplant mortality was defined as graft failure without re-transplantation. Given the limited published data on graft survival in LT for AH recipients, we used post-LT patient survival data as a surrogate. The likelihood of a graft failure was dependent on patients' alcohol-use category; those who used alcohol had a higher probability of developing graft failure. Specifically, we increased the graft failure probability with hazard ratios of 4.59 and 2.31 if the patients were sustained users and slip users, respectively (Table 1).[9] Graft failure with re-transplantation was not modeled as a possible scenario for patients with alcohol use after LT, as patients with relapse after LT would be unlikely to be offered re-transplantation. Graft failure with re-transplantation was modeled as a possibility for patients with no alcohol use after LT, modeled based on probabilities from the UNOS database. We conducted sensitivity analyses using a wide range of hazard ratios.

We validated our model's predicted 6-month patient survival in the delayed LT arm with those from the Franco-Belgian trial, and separately with prior U.S. data.[8,22] We also validated our model's predicted post-transplant survival with ACCELERATE-AH data (Appendix Figure 1).[9]

Model Outcomes

Our primary model outcome was life expectancy, measured in life years. We estimated the life expectancy for a patient presenting with severe AH in both early and delayed LT simulation scenarios, defined as the interval between date of hospitalization for AH and date of predicted death.

We also estimated life expectancy separately for each of the 11 UNOS regions. For this regional analysis, we adjusted the likelihood of receiving LT for each UNOS region using region-specific transplantation rates (Appendix Table 3).

We performed one-way sensitivity and probabilistic sensitivity analyses to estimate the effects of uncertainty in all model parameters (Table 1) on the improvement in life years with early versus delayed LT.

We also performed extreme scenario analyses where we evaluated cases where 1) all patients who undergo early LT have sustained alcohol use post-LT and 2) all patients who undergo delayed LT refrain from any alcohol use post-LT.

Further, some LT centers have recently adopted policies that shorten the period of mandated sobriety for LT eligibility among AH patients.[10] To model the impact of such policies, we estimated life expectancy in scenarios in which the sobriety period in the delayed LT arm was shortened to i) 3-months; ii) 1-month.

RESULTS

Early LT versus Delayed LT:

Outcomes by Varying Rates of Alcohol Use Life expectancy was estimated for a patient presenting with severe AH in both simulation scenarios, defined as the interval between date of hospitalization for AH and date of predicted death. In our base case analysis, which assumed equivalent incidence of sustained alcohol use and slips post-LT in both scenarios, life expectancy was 6.55 years by offering early LT versus 1.46 years with delayed LT, with a net gain of 5.09 years (Table 2; Figure 2a). The proportion of deaths among early versus delayed LT during initial hospitalization, pre-LT probation period (for delayed LT), LT waitlist, and post-LT are summarized in Appendix Table 5.

In the most extreme scenario analysis in which all patients after early LT had sustained alcohol use and no patient after delayed LT had any alcohol use, life expectancy was 3.62 years by offering early LT versus 2.30 years with delayed LT, with a net gain of 1.32 years (Table 2; Figure 2a). In a second extreme scenario analysis in which no patient in the delayed LT arm had any alcohol use in the 6-month pre-LT period, but maintained the same risk of post-transplant alcohol use as in the base case analysis, life expectancy with delayed LT was 1.81 years compared to 6.55 years in patients offered early LT (Table 2; Figure 2a). In a third extreme scenario analysis in which no patient who underwent early LT had any alcohol use after transplant, life expectancy was 10.85 years, as compared to 3.62 years in a scenario where all LT recipients have sustained alcohol use after transplant. Thus, sustained alcohol use after early LT was associated with 7.23 life-years lost, or approximately 67% of life years gained from early LT (Table 2; Figure 2a).

Early Versus Delayed LT by Varying Durations of Pre-LT Abstinence

When shortening the period of required sobriety in the delayed LT arm to 3-months, life expectancy with delayed LT increased to 2.32 years (Figure 2b). With a 1-month delay, life expectancy increased further to 3.92 years. In both scenarios, the life expectancy remained lower than 6.55 years, observed in early LT arm.

Early versus Delayed LT by UNOS Region

We performed scenario analysis by UNOS region (Appendix Table 5; Figure 3). The absolute survival benefit was highest in Region 3 (i.e. the region with the shortest waitlist time), and least in Region 9 (i.e. the region with the longest waitlist time). In Region 3, life expectancy was 6.96 years with early LT versus 1.55 years with delayed LT, with a net gain of 5.42 life-years. In Region 9, life expectancy was 6.25 years with early LT versus 1.42 with delayed LT, with a net gain of 4.83 life years.

Early versus Delayed LT by Varying Lille and MELD Scores

Early LT (versus delayed LT) provided survival benefit across all simulated Lille and MELD scores of patients with medically-refractory severe AH (i.e. Day 7 Lille score ≥0.45). However, the magnitude of net survival benefit was dependent on both initial MELD and Day 7 Lille scores (Figure 4; Appendix Figure 2a; Appendix Figure 2b). Figure 4 shows the net benefit of early LT at any combination of Lille and MELD score. For example, with an initial MELD of 35 and Day 7 Lille score of 0.87, the net survival benefit of early LT was 5.0 life-years. With an initial MELD of 16 and Day 7 Lille score of 0.48, the net survival benefit of early LT was 2.0 life-years. Net benefit of early LT was highest in patients with Lille score 0.5-0.82, and MELD≥32.

One-way Sensitivity Analysis

We conducted a one-way sensitivity analysis to identify model inputs in Table 1 that most strongly influenced the difference in life expectancy of early versus delayed LT. Net survival benefit was most strongly abrogated by increased probability of liver-related death post-transplant, alcohol use after transplant, and increasing age. However, early LT offered a net survival benefit exceeding 3 years versus delayed LT across all sensitivity analyses (Appendix Figure 3).

Probabilistic Sensitivity Analysis—In the probabilistic sensitivity analysis, the mean life-expectancy in early versus delayed LT were 6.84 life-years (95% CI, 2.77-11.5) versus 1.51 life-years (95% CI, 0.74-2.45), respectively. The mean net survival of early LT (vs. delayed LT) was 5.33 life-years (95% CI, 2.14-9.26). Early (versus delayed) LT resulted in the gain of at least 2 life-years in 99.3% of the simulation runs and at least 5 years in 49.6% of the simulation runs (Appendix Figure 4).

DISCUSSION

Early liver transplantation for AH is increasing across the United States.[10,16] Long-term outcomes are needed to inform ongoing debate and policy-making for this relatively new LT indication. Using a mathematical model that simulated a virtual trial of early versus delayed LT, we found that offering early LT to a patient with medically-refractory severe AH provided a 4-fold survival benefit over delayed LT. The survival benefit was present across all UNOS regions and persisted irrespective of any estimated risk of sustained alcohol use post-LT. These findings support the clinical use of early LT as definitive therapy for severe AH.

Our results highlight the potential harm in delaying LT in appropriate candidates for early LT. Even in the most extreme scenario — where 100% of early LT recipients return to sustained alcohol use post-LT, and 100% of delayed LT recipients have complete abstinence post-LT — life expectancy by offering early LT was still 2-fold superior to delayed LT. These findings reflect the high short-term mortality in severe AH.[7,21] In fact, our model estimated that successful early LT recipients would have post-LT life expectancy exceeding 10 years, which is far higher than the average life-expectancy of 6.55 years in the group offered early LT; this difference reflects the high pre-LT mortality while determining

medically-refractory disease, LT eligibility, and waitlist time – with the median MELD and Lille scores of the ACCELERATE-AH cohort, our model estimated mortality of 14% within a week of initial presentation. We found that the survival benefit of an early LT policy was dependent on both MELD and Lille score, maximized among patients with Day 7 Lille score between 0.50-0.82. These findings suggest potential value in considering Lille score in early LT policy for AH to maximize survival benefit, which is consistent with the current UNOS allocation system, which prioritizes both the urgency of the candidate recipient and the avoidance of futile or unnecessary transplants.

While many centers apply restrictions regarding abstinence prior to LT, UNOS has never adopted a universal policy, and U.S. LT centers are allowed to determine their own abstinence policies for LT eligibility.[10] For example, some U.S. centers have recently adopted a 3-month abstinence policy,[10] our model suggests that such policies are unlikely to benefit most AH patients, with an estimated 64% relative loss in benefit with a 3-month delay policy as compared to a pure early LT policy.[7,21] A recent study concluded that Lille score at Day 4 was as accurate as Day 7 to predict short-term mortality.[23] Indeed, more efficient tools to identify candidates most appropriate for early LT, namely those with medically-refractory disease and at low-risk for return to harmful alcohol use after early LT, could further improve the utility of offering early LT for AH. It should be emphasized that model estimates were based on cohort studies that offered early LT to a highly select patient population with AH.

Importantly, we found that life expectancy was significantly decreased for early LT recipients who return to sustained alcohol use after transplant, with the early LT recipient with sustained alcohol use post-LT having a 67% lower life expectancy than recipients with post-LT abstinence. These results provide quantification to prior clinical studies, which have shown that return to sustained harmful drinking after LT is associated with accelerated graft failure and death.[11,12] Uniquely, this study has been able to provide a novel perspective by quantifying the harm of post-LT alcohol use – a patient undergoing early LT with sustained alcohol use post-LT has a 3.6-year life expectancy as compared to 10.8 years for a patient without any post-LT alcohol use. The ACCELERATE-AH cohort of highly selected patients undergoing early LT showed that return to sustained alcohol use was relatively infrequent, occurring in 17% after 3 years follow-up.[9,24] Clearly, given the poor outcome of those returning to harmful alcohol use, reducing the proportion that do so is critical -- highlighting the acute need for improved selection of candidates for early AH, as well as strategies to prevent and treat post-LT alcohol use.

Early LT was beneficial across all UNOS regions, with a net survival benefit consistently above 4 life-years in all regions. High wait-time regions (e.g. regions 5 and 9) had the least net survival benefit, as compared to low wait-time regions (e.g. regions 3 and 11). The contour lines in our joint-effect model were significantly different in early versus delayed LT; this difference illustrates how life expectancy with delayed LT is most significantly affected by pre-LT mortality, whereas life expectancy with early LT is most significantly affected by probability of LT. Thus, in regions where probability of LT is reduced due to high wait-time, survival benefit of early LT is reduced. Given that the allocation of liver organs is based upon MELD score, the relative lack of variability in early LT survival benefit

among regions is a reflection of the high probability of rapid LT once listed in this high-MELD cohort. Indeed, as early LT for AH continues to increase in application,[16] inherent prioritization by high MELD may affect waitlist outcomes for other LT indications; whether this will result in increased waitlist mortality for non-alcohol associated conditions could not be addressed by this model, and will require further study. Interestingly, a recent UNOS analysis reported that 40% of LT for AH has been performed in region 2 and 7;[25] these regions are below the net survival benefit of the national average in our model. These findings suggest that the uneven application of LT for AH amongst different UNOS regions may have largely been driven by shifting attitudes of local transplant providers, rather than differences in magnitude of clinical benefit – national policy may help to abrogate the inequity of disparate geographic access to this new LT indication.

Our study had some limitations. First, data on survival and alcohol use outcomes in early LT recipients for AH are very limited, and thus our model estimates are at risk for uncertainty. However, we used best available evidence in severe AH to inform inputs and degrees of uncertainty[6,7,9,21,22,26] and our conclusions were unchanged across a number of sensitivity analyses and extreme simulation scenarios: our main finding that offering early LT provides significantly higher life-expectancy than delayed LT is likely robust. Second, although we did account for natural fluctuations in MELD scores, simulated fluctuations were based on UNOS waitlist data, as neither the natural trajectory of MELD in medically-refractory severe AH nor the likelihood of receiving LT once listed have been described. Hypothetically, a patient surviving an episode of severe AH may have more significant improvement in MELD than a patient with long-established chronicity of liver disease, and even be less likely to require LT. This would differentially decrease the likelihood of receiving LT in the delayed LT group, and if present, would in fact strengthen our primary conclusions. Further, a recent prospective study in severe AH estimated that 85% of medical non-responders have an indication for LT at 6 months.[6] Third, our model assumes listing of early LT patients based upon the time from initial hospitalization to listing date among patients from the ACCELERATE-AH cohort, and the probation period in the delayed LT arm to begin at initial hospitalization. Given high pre-LT mortality, the generalizability of our results are thus sensitive to the LT center's evaluation process, which includes psychosocial or financial assessments, and requires time.[9] Some patients may present with a short period of sobriety prior to hospitalization, which may reduce their probation period with delayed LT policies. The implications of an early LT policy for patients who are ultimately deemed eligible versus ineligible, and the complexity of selection practices for early LT, could not be addressed by this study.

Despite these limitations, this study has several strengths. This study provides a comprehensive analysis of the possible outcomes for patients presenting with life-threatening AH of early LT policy across the United States. Although the results may vary across different populations, particularly acute on chronic liver failure from recent alcohol use, or non-U.S. populations, as a relatively new indication for liver transplantation, modeling with the inclusion of sensitivity analyses to aid in accounting for overall uncertainty, provides a more quantitative method of considering the benefits and harms of early LT for AH. Furthermore, our model provides a platform to conduct a virtual trial before a new strategy (e.g. early LT) is implemented widely.

In conclusion, a policy offering early liver transplant for severe alcohol-associated hepatitis provides a 4-fold long-term survival benefit compared to delayed LT (6-month wait), and is beneficial irrespective of any estimated risk of harmful alcohol use post-LT, supporting the use of early LT as definitive therapy for severe AH in carefully selected patients. Sustained alcohol use post-LT reduced but did not eliminate this benefit, resulting in 67% loss of the life-years gained by early LT followed by complete abstinence, highlighting the need for effective prevention and treatment for post-LT alcohol use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACCELERATE-AH	The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis
AH	alcohol-associated hepatitis
HR	Hazard ratio
LT	Liver transplant
MELD	Model for End-Stage Liver Disease
SIM-LT	simulation of liver transplant candidates
UNOS	United Network of Organ Sharing

References

1. Cholankeril G, Ahmed A. Alcoholic Liver Disease replaces Hepatitis C Virus Infection as the Leading Indication for Liver Transplantation in the United States. Clin Gastroenterol Hepatol 2018;16(8):1356–8. [PubMed: 29199144]
2. Liangpunsakul S, Haber P, McCaughan GW. Alcoholic Liver Disease in Asia, Europe, and North America. Gastroenterology 2016;150(8):1786–97. [PubMed: 26924091]
3. Lucey MR. Liver transplantation for alcoholic liver disease. Nat Rev Gastroenterol Hepatol 2014;11(5):300–7. [PubMed: 24393837]
4. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: A new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45(6):1348–54. [PubMed: 17518367]

5. Altamirano J, López-Pelayo H, Michelena J, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: Prediction and impact on long-term survival. Hepatology 2017;66(6): 1842–53. [PubMed: 28646515]
6. Louvet A, Labreuche J, Artru F, et al. Main drivers of outcome differ between short term and long term in severe alcoholic hepatitis: A prospective study. Hepatology 2017;66(5):1464–73. [PubMed: 28459138]
7. Thursz MR, Richardson P, Allison M, et al. Prednisolone or Pentoxifylline for Alcoholic Hepatitis. N Engl J Med 2015;372(17):1619–28. [PubMed: 25901427]
8. Mathurin P, Moreno C, Samuel D, et al. Early Liver Transplantation for Severe Alcoholic Hepatitis. N Engl J Med 2011;(365):1790–800.
9. Lee BP, Mehta N, Platt L, et al. Outcomes of Early Liver Transplantation for Patients With Severe Alcoholic Hepatitis. Gastroenterology 2018;155(2):422–430.e1. [PubMed: 29655837]
10. Zhu J, Chen PY, Frankel M, Selby RR, Fong TL. Contemporary Policies Regarding Alcohol and Marijuana Use among Liver Transplant Programs in the United States. Transplantation 2018;102(3):433–9. [PubMed: 29019813]
11. Dumortier J, Dharancy S, Cannesson A, et al. Recurrent Alcoholic Cirrhosis In Severe Alcoholic Relapse After Liver Transplantation : A Frequent and Serious Complication. Am J Gastro 2015;110(5):1160–6.
12. Rice JP, Eickhoff J, Agni R, Ghufran A, Brahmbhatt R, Lucey MR. Abusive Drinking After Liver Transplantation Is Associated With Allograft Loss and Advanced Allograft Fibrosis. Liver Transplant 2013;19:1377–86.
13. Donckier V, Lucidi V, Gustot T, Moreno C. Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy. J Hepatol 2014;60(4):866–71. [PubMed: 24291238]
14. Lucey MR. Liver transplantation for severe alcoholic hepatitis– The PRO view. Liver Int 2017;37(3):343–4. [PubMed: 28240837]
15. Fung JYY. Liver transplantation for severe alcoholic hepatitis–The CON view. Liver Int 2017;37(3):340–2. [PubMed: 28240836]
16. Mathurin P, Lucey MR. Alcohol, liver disease, and transplantation. Curr Opin Organ T ransplant 2018; 1.
17. Chhatwal J, Samur S, Kues B, et al. Optimal timing of hepatitis C treatment for patients on the liver transplant waiting list. Hepatology 2017;65(3):777–88. [PubMed: 27906468]
18. Weinrieb RM, Van Horn DHA, Lynch KG, Lucey MR. A Randomized, Controlled Study of Treatment for Alcohol Dependence in Patients Awaiting Liver Transplantation. Liver Transplant 2007;13(3):465–6.
19. Alagoz O, Maillart LM, Schaefer AJ, Roberts MS. The optimal timing of living-donor liver transplantation. Manage Sci 2004;50(10):1420–30.
20. Shechter SM, Bryce CL, Alagoz O, et al. A clinically based discrete-event simulation of end-stage liver disease and the organ allocation process. Med Decis Mak 2005;25(2):199–209.
21. Louvet A, Labreuche J, Artru F, et al. Combining data from liver disease scoring systems better predicts outcomes of patients with alcoholic hepatitis. Gastroenterology 2015;149(2):398–406.e8. [PubMed: 25935634]
22. Im GY, Kim-Schluger L, Shenoy A, et al. Early Liver Transplantation for Severe Alcoholic Hepatitis in the United States - A Single-Center Experience. Am J Transplant 2016;16(3):841–9. [PubMed: 26710309]
23. Garcia-Saenz-De-Sicilia M, Duvoor C, Altamirano J, et al. A Day-4 Lille Model Predicts Response to Corticosteroids and Mortality in Severe Alcoholic Hepatitis. Am J Gastroenterol 2017;112(2): 306–15. [PubMed: 27922027]
24. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2015 Annual Data Report: Liver. Am J Transplant 2017;17 Suppl 1:174–251. [PubMed: 28052604]
25. Cholankeril G, Liu A, Sandhu J, et al. Increasing Acceptance of Severe Acute Alcoholic Hepatitis as an Indication for Liver Transplantation with Outcomes comparable to Fulminant Hepatic Failure. Hepatology 2017;66(1):17A.

26. Lee BP, Chen P-H, Haugen C, et al. Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis. Ann Surg 2017;265(1):20–9. [PubMed: 27280501]

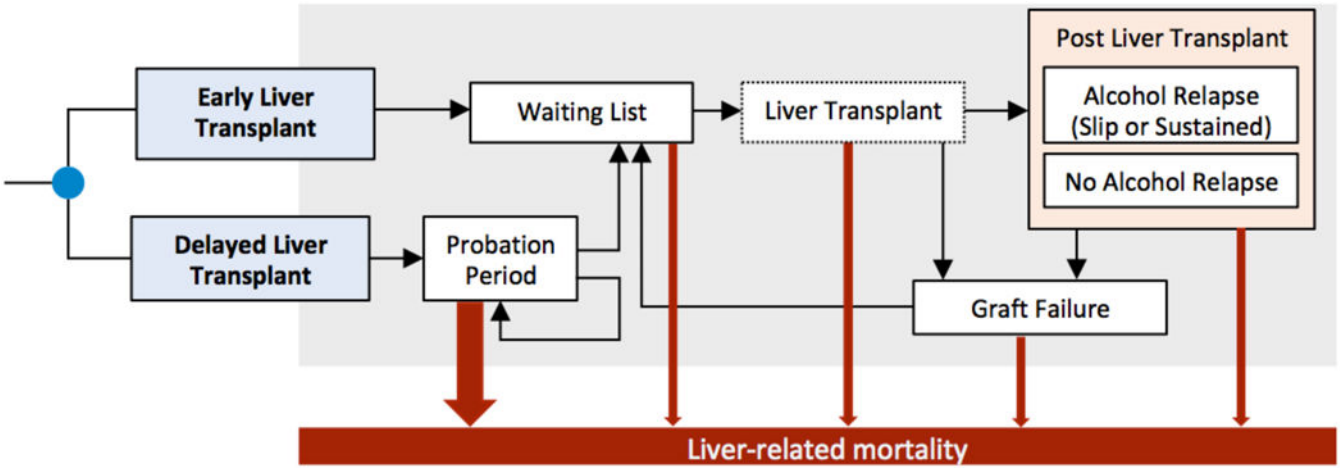
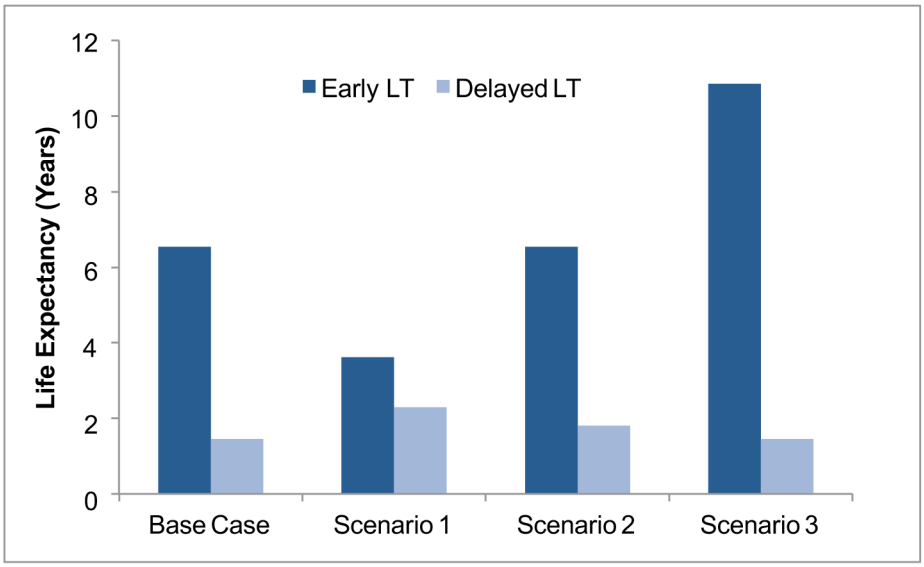


Figure 1. State-transition diagram for a microsimulation model comparing an early versus delayed liver transplant strategy in patients with severe alcohol-associated hepatitis.

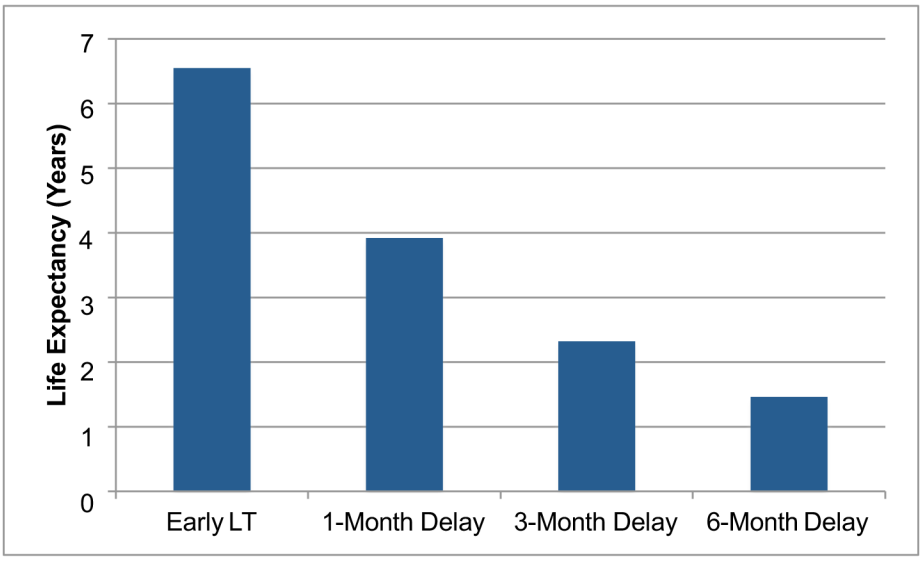
At any given time a patient occupies one of the health states represented by rectangles in the model schematic. Arrows between states depict possible transitions based on probabilities. At any given time, a patient can transition to a death state from any of the above health states (these transitions arrows are not shown in the figure for clarity).



Abbreviations: LT, liver transplantation

Figure 2A. Overall life expectancy by offering early LT (dark blue) versus delayed LT (light blue): base case and by varying rates of alcohol use.

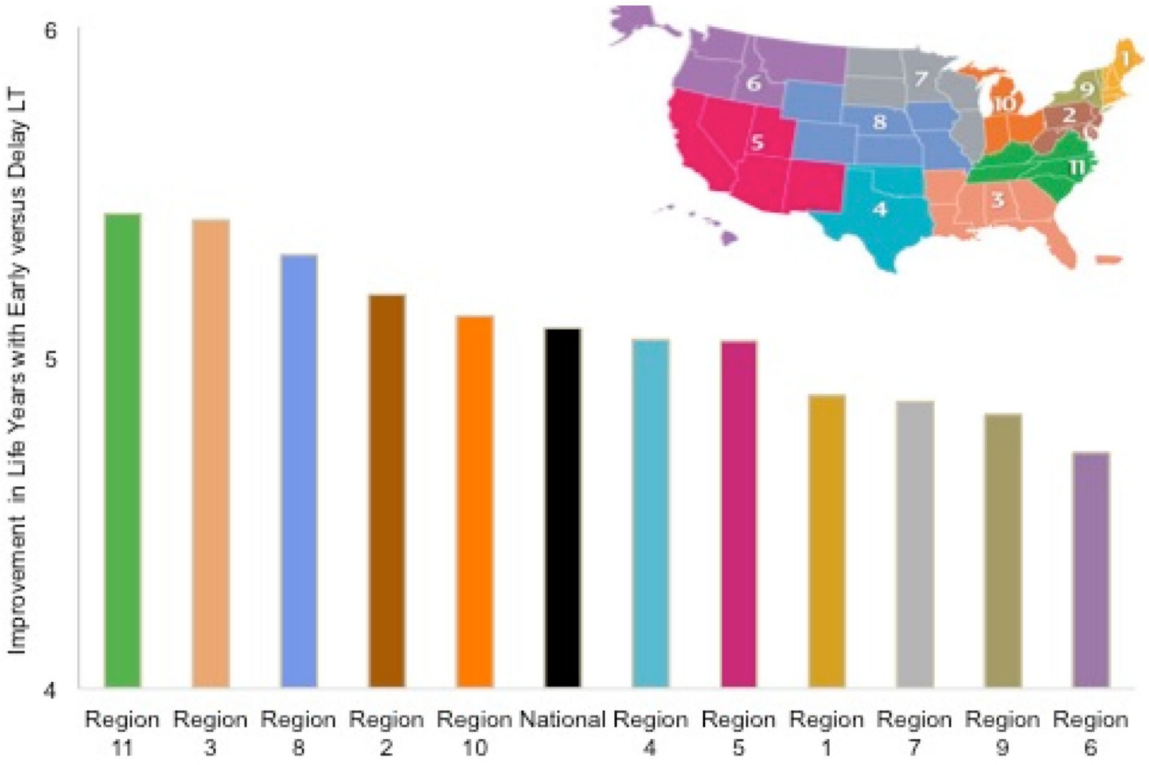
Base case analysis assumes equivalent incidence of sustained alcohol use and slips after liver transplant (LT) in both early and delayed LT scenarios. Scenario 1 assumes all patients after early LT have sustained alcohol use and no patient after delayed LT has any alcohol use. Scenario 2 assumes no patient offered delayed has any alcohol use in the 6-month pre-LT period. Scenario 3 assumes no patient offered early LT has any alcohol use after LT.



Abbreviations: LT, liver transplantation

Figure 2B. Life-Expectancy with Early, 1-Month, 3-Month, and 6-Month Delayed LT

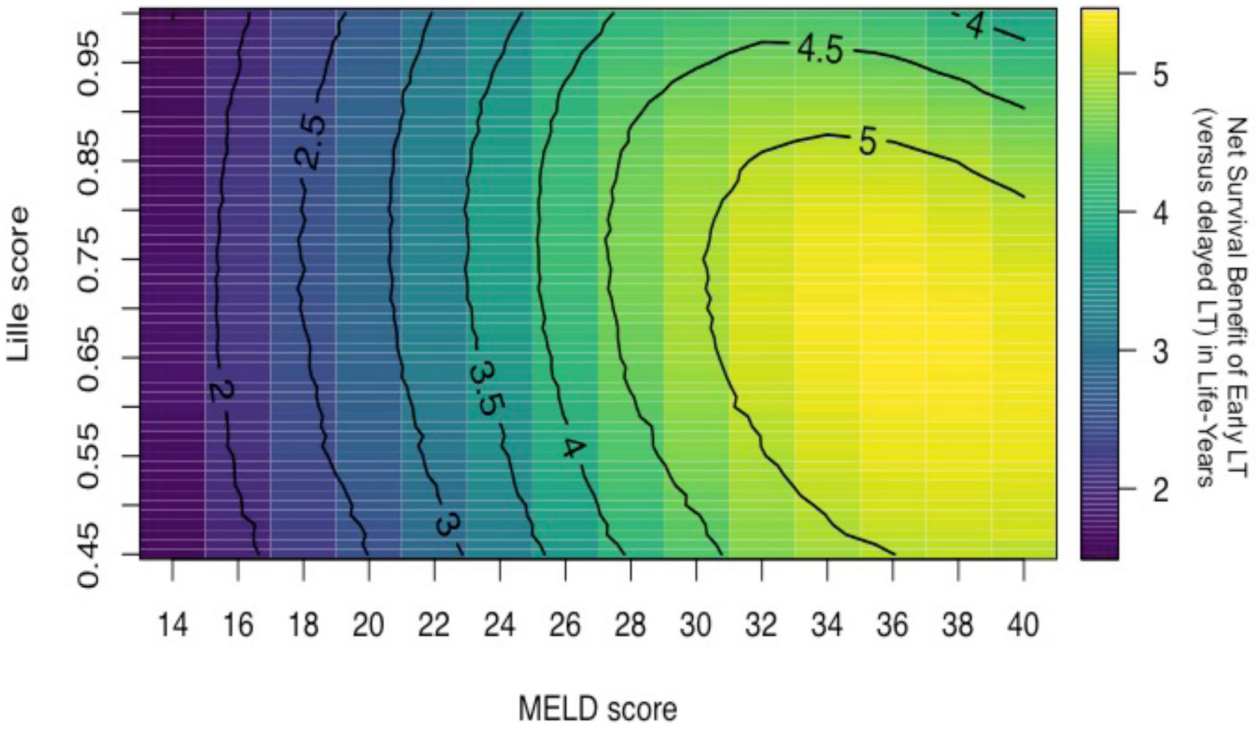
In our base case analysis, early LT vs. 6-month delay, life expectancy was 6.55 vs. 1.46 years, respectively. When shortening the period of mandated sobriety in the delayed LT arm to 3-months, life expectancy was 2.32 years. With a 1-month delay, life expectancy in the delayed LT arm was 3.92 years.



Abbreviations: LT, liver transplantation; UNOS, United Network of Organ Sharing

Figure 3. Net difference in life years, comparing early versus delayed liver transplant, stratified by UNOS region.

The national (black bar) net survival benefit of offering early versus delayed liver transplant was 5.09 years. In Region 3 (highest net survival benefit) life expectancy was 6.96 years with early LT versus 1.55 years with delayed LT, with a net gain of 5.42 life-years. In Region 9 (lowest net survival benefit), life expectancy was 6.25 years with early LT versus 1.42 with delayed LT, with a net gain of 4.83 life years.



Abbreviations: LT, liver transplantation; MELD, Model for End-Stage Liver Disease

Figure 4. Net survival benefit of early LT (versus delayed LT) by Lille and MELD scores.

This figure shows the net survival benefit of early LT at any combination of Lille and MELD score. For example, with an initial MELD of 35 and Day 7 Lille score of 0.87, the net survival benefit of early LT was 5.0 life-years. With an initial MELD of 16 and Day 7 Lille score of 0.48, the net survival benefit of early LT was 2.0 life-years.

Table 1.

Model Variables Used in Microsimulation

Parameter	Base Case[a]	Min[b]	Max[b]	Reference
Baseline age	43	34	51	9
Male proportion	0.70	0.60	0.80	9
Transition probabilities (time frame)				
Probability of alcohol use before delayed LT (6 months)	0.22	0.10	0.34	6
Probability of alcohol slip after LT (1.6 years *)	0.177	0.05	0.40	9
Probability of sustained alcohol use after LT (1.6 years *)	0.106	0.05	0.16	9
Annual graft failure after LT for abstinent patients **	0.03	0.01	0.05	9
Annual graft failure to repeat transplant **	0.805	0.60	1.00	UNOS
Hazard ratio for patients with sustained alcohol use after LT	4.59	1.45	14.5	9
Hazard ratio for patients with alcohol slips after LT	2.31	1.00	10.4	9
Annual graft failure after LT for patients with sustained alcohol use after LT ***	0.130	0.045	0.210	9
Annual graft failure after LT for patients with alcohol slips after LT ***	0.068	0.023	0.112	9

*1.6 years as median post-LT follow-up in ACCELERATE-AH cohort[9]

**Patients with graft failure who do not receive re-transplantation had death. Only patients with no alcohol use after LT were eligible for re-transplantation – probability of re-transplantation was modeled by UNOS probabilities.

***Annual graft failure among patients with alcohol use, calculated by 1-(1-probability of death among abstinent patients)$^{\text{hazard ratio}}$, Patients with sustained alcohol use after LT were assigned a 4.59-fold higher risk of graft failure compared to patients without alcohol use after LT. Patients with slips after LT were assigned a 2.31-fold higher risk of graft failure compared to patients without alcohol use after LT. Graft failure with re-transplantation was not modeled as a possible scenario for patients with alcohol use after LT, as patients with relapse after LT would be unlikely to be offered re-transplantation.

[a]Base Case refers to model inputs for primary analysis

[b]Min and Max refer to minimum and maximum values for inputs used in this study's sensitivity analyses. These values are based on the interquartile range of the reported papers for baseline demographics, and the 95% confidence intervals for transition probabilities.

Abbreviations: SIM-LT, simulation of liver transplant candidates; LT, Liver transplant; HR, Hazard ratio; UNOS, United Network of Organ Sharing

Table 2.

Overall Life Expectancy by Offering Early LT versus Delayed LT: Base Case and by Varying Rates of Alcohol Use

	Life Expectancy (Life Years)		
	Early LT	**Delayed LT**	**Net Difference (Early versus Delayed LT)**
Base Case[a]	6.55	1.46	5.09
Scenario 1[b]	3.62	2.30	1.32
Scenario 2[c]	6.55	1.81	4.74
Scenario 3[d]	10.85	1.46	9.39

[a]Base case analysis assumes equivalent incidence of sustained alcohol use and slips after liver transplant (LT) in both early and delayed LT scenarios.

[b]Scenario 1 assumes all patients after early LT have sustained alcohol use and no patient after delayed LT has any alcohol use.

[c]Scenario 2 assumes no patient offered delayed has any alcohol use in the 6-month pre-LT period (i.e. all patients in delayed LT arm are abstinent during 6 month pre-LT probation period).

[d]Scenario 3 assumes no patient offered early LT has any alcohol use after LT.