WHAT IS THE OPTIMAL TIMING OF LIVER TRANSPLANTATION FOR CHILDREN WITH BILIARY ATRESIA? A MARKOV MODEL SIMULATION ANALYSIS

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What is the Optimal Timing of liver Transplantation for Children with Biliary Atresia? A Markov Model Simulation Analysis

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Introduction

Biliary atresia (BA) is a progressive obliterative disorder of intra- and extra-hepatic bile ducts leading to hepatic fibrosis and frequently end-stage liver disease. If untreated, this disease is uniformly fatal (1). Up to two thirds of children with BA will undergo liver transplantation (LT) at some stage in their lives, including children who had an initial successful Kasai operation (2,3).It is the single most common liver disease leading to LT during childhood with an annual transplant rate in the United States of 130 patients/year. Almost 50% of the patients with BA underwent LT before the first year of life (5).

Most children with a failed porto-enterostomy (PE) will undergo LT after the development of complications including failure to thrive, ascites, cholangitis and/or variceal hemorrhage but the optimal timing of listing and LT is not clear. Early transplantation has the advantage of performing a major surgical procedure before severe complications had occurred in a “healthier patient” with potentially a better outcome. On the other hand, the incidence of vascular complications such as hepatic artery thrombosis is higher in younger (and much smaller) infants (6, 7). Early LT and early use of immunosuppression in young EBV naïve infants might be also complicated with a higher incidence of post-transplant lymphoproliferative disease (PTLD).The clinical decision regarding the optimal time of LT is more complicated as it is difficult to predict the time of an available appropriate organ, unless there is a living donor option.

Markov chain models, named after a Russian mathematician provide a convenient means to account for the medical treatment options and risks that occur not only in the present but also over time. Markov models are used to describe random processes characterized by some indeterminacy in their future evolution described by probability distributions. Even if the initial condition is known, there are many possibilities of how this process may evolve, even if some paths are more probable than others. These models used to simulate diseases and analyze disease progression, when evaluating various medical interventions (8).

The natural history of a chronic disease can be viewed as a sequence of particular states of health. The Markov models assume that the patient is always in one of a finite number of states of health referred to as Markov states. All events of interest are modeled as transitions from one state to another. A Markov process is a state-transition diagram, where each state is represented by a circle and interest has been focused on estimating the transition rates between the stages, comparing them between subgroups of patients or between different periods and modeling in terms of covariates (9).

The goal of our study was to determine the optimal timing of LT for children with BA, using a Markov model simulation analysis.

METHODS

A Markov analytic model was constructed presenting the progression of the severity of liver status for patients with BA who had PE before 60 days old (Figure 1). By using Monte Carlo simulations we estimated life expectancy in years (LY) and survival curves for a virtual cohort of patients with BA who had PE before 60 days old. We compared three treatment strategies:

(1) Early liver transplant for moderate liver disease (early LT)
(2) Late liver transplant for severe liver disease (late LT)
(3) “No LT”.

We simulated 10,000 patients in each strategy. Definitions of mild, moderate and severe liver disease were based on the calculated PELD and the following complications:

(i) Failure to thrive with no response to NG feeds
(ii) Ascites
(iii) Variceal bleeding
(iv) Sepsis/cholangitis/spontaneous bacterial peritonitis.

Definitions of disease severity were:

- **Mild:** PELD<15 with no complications
- **Moderate:** PELD 15 -25 with/without one complication
- **Severe:** PELD>25 or PELD<25 with more than one complication or ”status 1”.

In addition the model includes the following health states:

- Liver transplantation (LT)
- Early Re-LT (<=30 days after LT)
- Late Re-LT (>30 days after LT)
- Status post LT (period after first liver transplantation)
- Death

Baseline estimates

The baseline estimates of the model variables were derived from a systematic review of published studies. MEDLINE was searched for publications in English from 2006 to 2012 using search strategies that included the keywords biliary atresia and liver transplantation. We included prospective and retrospective series that enrolled patients younger than 18 years of age with BA. The studies were analyzed if they included information on outcomes after LT. Studies including <20 patients were excluded.

Transition probabilities were based on the literature and we estimated the parameters of Weibull distributions by linear regression and the Nelder–Mead method. In the Monte

Carlo simulation we used Triangular distributions sampling of the parameters in the model where the minimum and the maximum of the Triangular distributions were the values of the 95% confidence intervals obtained by the linear regression. Time horizon was between 10 years to 20 years. Table 1 presents the base assumptions in the model. Analyses were performed using TreeAge and MATLAB software.

RESULTS

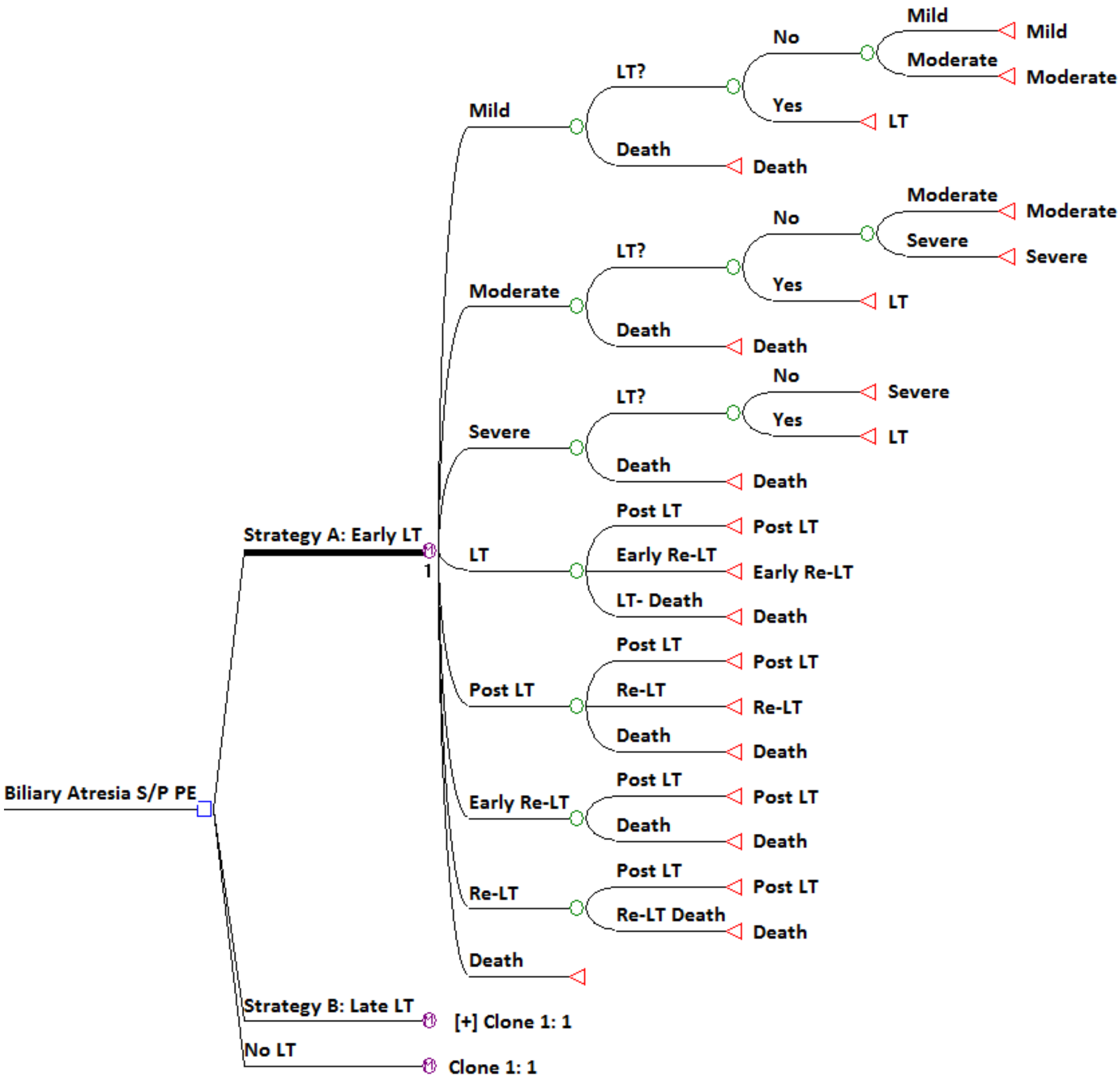
For cases with available liver for transplantation (living donors) early transplantation was associated with an increase of 10.6% additional expected LY as compared with late transplantation. For time horizon of 10 years (120 months), the LE were 87.38, 78.9 and 64.2 months with Early LT, Late LT and no-LT, respectively. Patient survival rates after 10 years were 60.1% and 49.4% in the Early LT and Late LT strategies respectively. For the patients with no-LT the survival rate after 10 years was 26.5%. Sensitivity analysis of the parameters revealed robust results.

Figure 2 depicts the Kaplan Meir survival curve obtained in 10,000 individuals Monte-Carlo simulation (with 95% CI of the curves). Cox regression analysis revealed that the HR of Late-LT vs. Early-LT is 1.38 (95% CI: 1.32-1.43).

In addition we sampled 100 trials of 10,000 patients and calculated the mean LE of the trials. The mean and standard deviation of the LE of the 100 trials were 88.12±0.43, 79.53±0.42 and 64.29±0.38 for Early-LT, Late-LT and No-LT strategies, respectively. Figure 3 presents a scatter plot of the LE of all the trials. The base value of time horizon is 120 months (10 years). Figure 4 presents a Monte-Carlo one-way sensitivity analysis of time horizon (120-240 months). As time horizon increases, the increased rate of LE in Early-LT strategy is greater than the increased rate of LE in Late-LT. Early-LT was associated with an increase of 10.6%, 14.0% and 15.9% additional expected LY as compared with Late-LT for time horizon of 120, 180 and 240 months, respectively.

For cases with deceased donor liver transplantation, the probability of transplantation from time of listing is essential and may have geographical differences even in the absence of available live donors. When the probability of transplantation was low (less than 40% from time of listing at 3 months), there was no increase in expected LY of Early-LT strategy. ”NO LT” resulted in about 50% reduction of expected LY compared to LT for patients with severe liver disease.

Table 1: Base assumptions in the model and the relevant sources.



<u>Figure 1:</u> Schematic presentation of the Markov model.

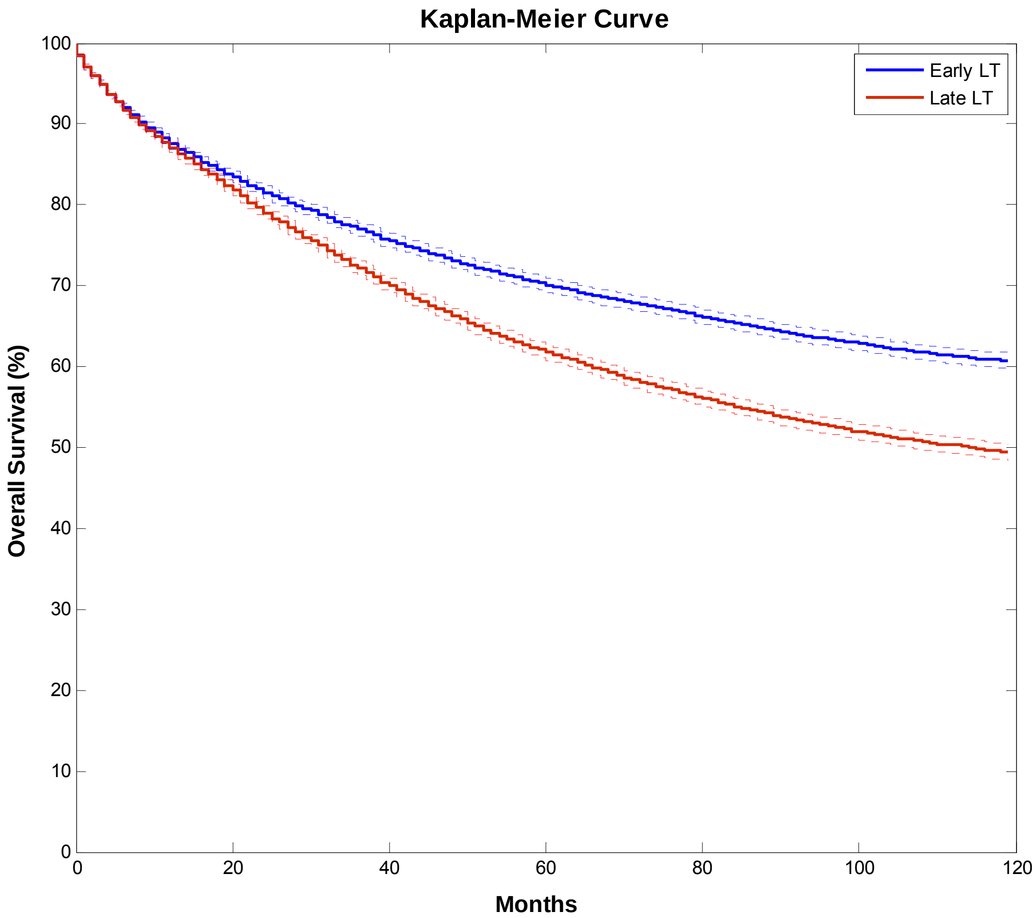


Figure 2: Kaplan-Meier Survival curve of 10,000 patients with BA who had PE before 60 days old. The Blue line is the overall survival (%) in the Early-LT strategy and the red line is overall survival (%) in the Late-LT strategy. The dotted lines are the 95% confidence interval of the curves.

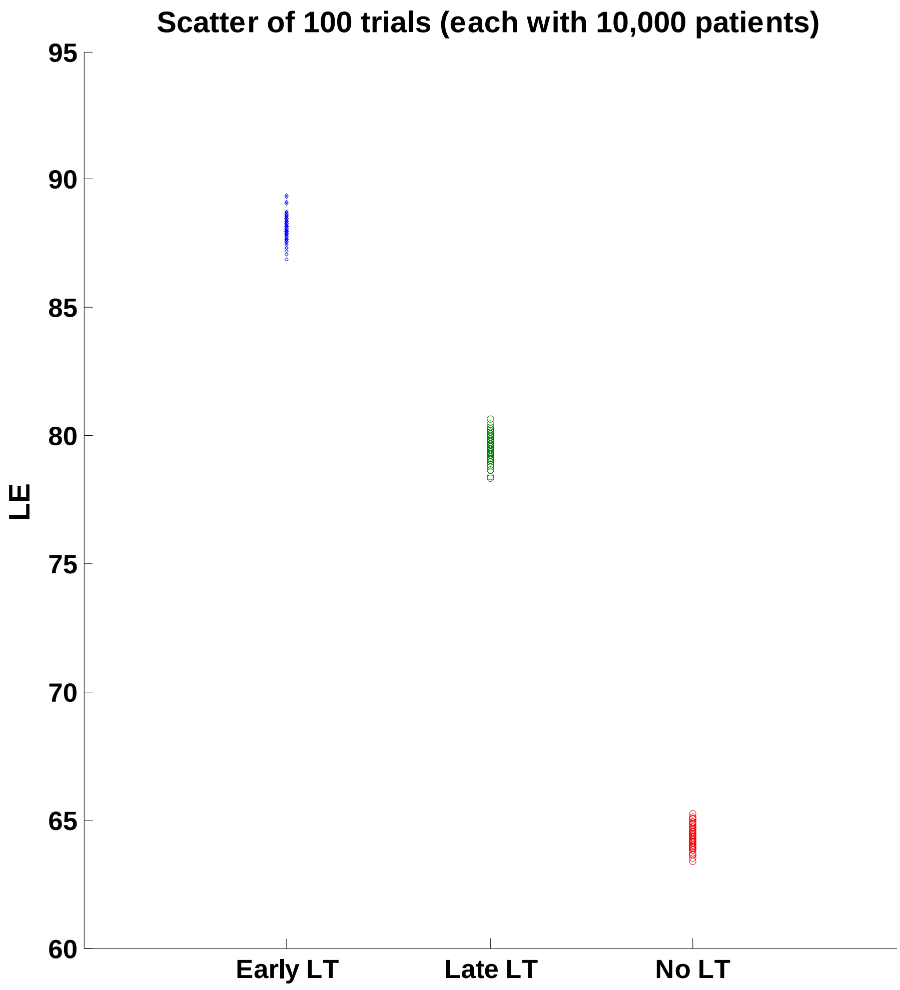


Figure 3: Scatter plot of the LE (months) of 100 trials sampled with 10,000 patients in each trial and Early-LT, Late-LT and No-LT strategies respectively.

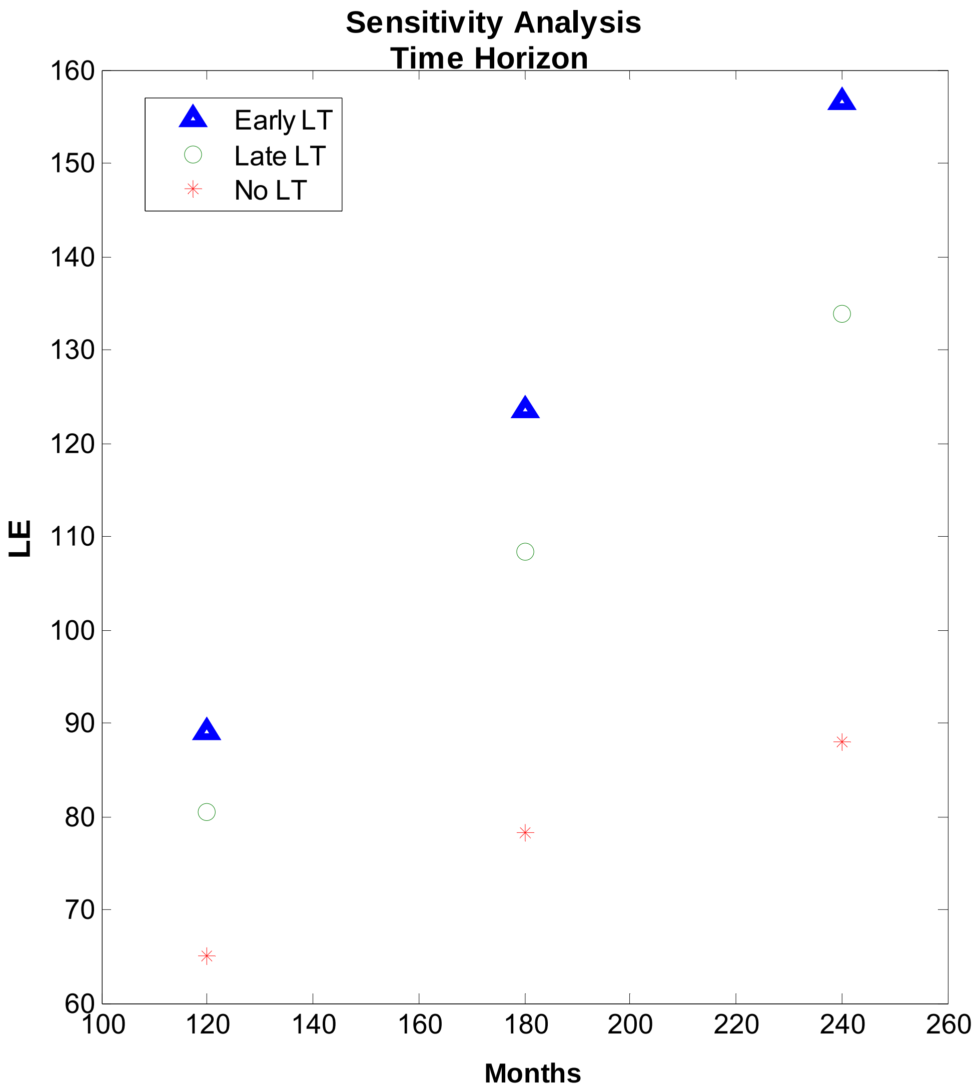


Figure 4: A Monte-Carlo one-way sensitivity analysis of time horizon (120-240 months).

Discussion

Markov process is a frequently used mathematical model to describe disease progression over time (9). Such models are best suited to analyze the final outcome of a disease process that varies between a limited numbers of distinct disease states.

The movements of patients among the various disease states are governed by chance. During each cycle of the Markov chain, the patients are newly distributed among the various states of the Markov chain according to a given set of predefined transition probabilities. After multiple cycles of fixed lengths of time, the Markov chain reaches a steady state that describes the long-term outcome of the disease and the expected distribution of patients among the various disease states (16). Markov processes have been used to analyze, for instance, the clinical outcomes of ascites and spontaneous bacterial peritonitis, esophageal varices, gallstone disease, and HBV and HCV infections (17, 18). The present Markov analysis serves as tool to determine the optimal timing of LT for children with BA.

Biliary atresia is not “homogenous disease”. There is an association between clinical and anatomic features of infants undergoing Kasai portoenterostomy (KPE) for biliary atresia (BA) and outcomes. Superina et al
(20) described a group of 244 infants who underwent Kasai operation for BA.
The risk of transplant/death was increased in patients with porta hepatis atresia (Ohi type II and III vs type I; HR: 2.03, P = 0.030), nonpatent common bile duct (Ohi subtype: b, c, and d vs a; HR: 4.31, P = 0.022), BA splenic malformation syndrome (HR: 1.92, P = 0.025), ascites > 20 mL (HR: = 1.90, P = 0.0230), nodular liver appearance compared to firm (HR: = 1.61, P = 0.008), and age at KPE ≥ 75 days (HR: 1.73, P < 0.002).

The only effective treatment for 'failing' Kasai portoenterostomy is LT.

Careful timing of LT is of critical importance, although recent trends include earlier consideration of LT in children with biliary atresia (19).

Barshes et al (5) identified pre-transplant variables that predict patient survival after primary LT for biliary atresia in a cohort of 1,976 pediatric patients undergoing primary liver transplantation for biliary atresia between 1/1988 to 12/2003 by using United Network Organ Sharing database (UNOS) . A multivariate analysis revealed that cadaveric partial/reduced liver grafts, a history of life support at the time of LT, and decreased age were independent predictors of increased post-LT mortality. Decreased patient age (and weight) was previously reported as a risk factor for an increase in post-OLT patient mortality in other studies (21) and is related to higher rate of vascular complications, PNF and infections in technically challenging cases. Older patients may have more complication of advance liver disease that can impact the post transplant outcome.

We believe that there is a need to develop a model to determine the optimal timing of LT for children with BA as a group. As previously mentioned ,we aware that an adjustment (“fine tuning”) for a specific case might be needed while using this model. Having a model may be valuable for the health care providers, like pediatric hepatologists to decide when to list and transplant ,to the decision makers in UNOS for a better allocation of limited resources of organs and for the patients and their parents.

We decided to use the definitions of mild, moderate and severe liver disease based on the calculated PELD and the evidence of complications. Calculated PELD is not an accurate tool to estimate the severity of patient with BA awaiting LT. In fact, the is a very high exemption rate and the actual PELD at transplant is higher due to multiple complications like failure to thrive in spite nasogastric feeding, ascites, variceal bleeding and recurrent cholangitis. Using actual PELD could have been not accurate as the decisions regarding the final score is being done by multiple local regional committees and might be different according to the different reviewers.

We decided to use 5 health states for our model: LT, Early Re-LT (<=30 days after LT), Late Re-LT (>30 days after LT), Status post LT (period after first liver transplantation) and death. The etiology for early Re-LT is different from that of late retransplantion.Early retransplantion in patients with BA is usually secondary to PNF or vascular complications as HAT. The most common indication for late retransplantion is chronic rejection.Patients with BA who need early retransplant are usually sicker than patients who require late transplant, for example secondary to chronic rejection.

We decided to use the model in two different scenarios, when there is a potential liver donor or when the is only a deceased donor option.

For cases with available liver for transplantation (living donors) early transplantation was associated with an increase of 10.6% additional expected LY as compared with late transplantation. We thinks that this findings that can be used in the decision making process. It is also important for the parents as potential living donors.

Of note, we did not include in our model data on the cost and our perspective was from the recipient angle only, ie we did not include the risk for morbidity and mortality of the donor.

For time horizon of 10 years (120 months), the LE were 87.38, 78.9 and 64.2 months with Early LT, Late LT and no-LT, respectively.

This findings reflects the advantage of early LT while there is still moderate liver disease (by our definition) in comparison to late LT for severe liver disease.

There is still a debate in the literature when is the best time to transplant children with BA. There are many aspects of this decision that relates to the recipient and to the availability of the graft. The availability of the graft in many cases reflect the “supply and demand” at the specific region. Another factor relates to the surgeons’ decisions which organ to approve to their patients. Waiting too long for the “perfect” organ might delay the transplant and might lead to worse outcome of a patient with more advanced liver disease. We found that When the probability of transplantation was low (less than 40% from time of listing at 3 months), there was no increase in expected LY of Early-LT strategy.

Sensitivity analysis of the parameters revealed robust results.

Figure 2 depicts the Kaplan Meir survival curve obtained in 10,000 individuals Monte-Carlo simulation (with 95% CI of the curves). Cox regression analysis revealed that the HR of Late-LT vs. Early-LT is 1.38 (95% CI: 1.32-1.43).

How this finding may help the care giver to decide how to approach the specific case, why not to list everyone ASAP?

Limitation of the study

As with all models, Markov models are simplifications of the real world. As for every model, its output needs validation. Still they could be of great importance, particularly when they are carefully designed to simulate the physiological disease process and its interactions and every differential equation included has been carefully validated by their use in predicting the results of an existing or an ongoing trial (8).

Other inherent limitations are related to the definitions of severity of this chronic liver disease. We defined the severity based on the calculated PELD and the common complications.

The definitions were based on the literature (Ben's article on complications, check ref 13) and our clinical experience. Different definitions could result in different prediction of outcome.

CONCLUSIONS

LT is a valuable procedure for patients with BA and failed PE. Early listing and transplantation is beneficial in cases with an available liver for transplantation. For cases where the probability for LT is low there is no advantage to early listing. A validation of this model in "real" cohort of patients with BA is needed .

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Name Description	Base-Case Value	Low	High	Source
		95% CI		
HR Moderate Health State vs. Mild Health State	2.8	1	3	1
HR Severe Health State vs. Mild Health State	8.81	2	10	1
Cycle length	1			assumed
Time horizon (months)	120	120	360	assumed
γ - (Weibull distribution parameter for calculating the transition probability of Mild State to Death)	0.2195	0.1995	0.258	2
γ_{Re_ErLT} (Weibull distribution parameter for calculating the transition probability of Early Re -LT to Death)	0.1199	0.0959	0.159	3
γ_{Graft} (Weibull distribution parameter for calculating the transition probability of Graft failure)	0.2227	0.159	0.2703	4
γ_{LT} (Weibull distribution parameter for calculating the transition probability of S/P LT to death)	0.4574	0.3012	0.5019	3
γ_{Re_LT} (Weibull distribution parameter for calculating the transition probability of Late Re -LT to Death)	0.298	0.2205	0.3253	3
λ (Weibull distribution parameter for calculating the transition probability of Mild State to Death)	0.0498	0.0438	0.0533	2
λ_{Graft} (Weibull distribution parameter for calculating the transition probability of Graft failure)	0.0691	0.1099	0.1349	4
λ_{LT} (Weibull distribution parameter for calculating the transition probability of S/P LT to death)	0.0131	0.0376	0.0543	3
λ_{Re_ErLT} (Weibull distribution parameter for calculating the transition probability of Early Re -LT to Death)	0.3809	0.3374	0.3721	3
λ_{Re_LT} (Weibull distribution parameter for calculating the transition probability of Late Re -LT to Death)	0.1418	0.1304	0.1806	3
Transition probability of LT to death	0.029	0.01	0.06	5
Transition probability of Mild health state to Moderate health state	0.045	0.02	0.06	6

Transition probability of Moderate health state to Severe health state	0.05	0	0.05	6