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The optimal timing of hepatitis C therapy in transplant eligible patients with Child B and C Cirrhosis: A Cost-Effectiveness Analysis

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Abbreviations: expected value of perfect information (EVPI), hepatitis C (HCV), Ledipasvir-Sofosbuvir (LDV/SOF), model for Endstage Liver Disease (MELD), quality adjusted life-years (QALY), willingness-to-pay (WTP)

Abstract

Background: Ledipasvir/sofosbuvir (LDV/SOF) has demonstrated high efficacy, safety and tolerability in HCV-infected patients. There is limited data, however, regarding the optimal timing of therapy in the context of possible liver transplantation (LT).

Methods: We compared the cost-effectiveness of 12 weeks of HCV therapy before or after LT or nontreatment using a decision analytical microsimulation state-transition model for a simulated cohort of 10 000 patients with HCV Genotype 1 or 4 with Child B or C cirrhosis. All model parameters regarding the efficacy of therapy, adverse events and the effect of therapy on changes in model for endstage liver disease (MELD) scores were derived from the SOLAR-1 and 2 trials. The simulations were repeated with 10 000 samples from the parameter distributions. The primary outcome was cost (2014 US dollars) per quality adjusted life year (QALY).

Results: Treatment before LT yielded more QALY for less money than treatment after LT or nontreatment. Treatment before LT was cost-effective in 100% of samples at a willingness-to-pay threshold of $100 000 in the base-case and when the analysis was restricted to Child B alone, Child C, or MELD > 15. Treatment before transplant was not cost-effective when MELD was 6-10. In sensitivity analyses, the MELD after which treatment before transplant was cost-effective was 13 and the maximum cost of LDV/SOF therapy at which treatment before LT is cost-effective is $177,381.

Conclusion: From a societal perspective, HCV therapy using LDV/SOF with ribavirin prior to LT is the most cost-effective strategy for patients with decompensated cirrhosis and MELD > 13.

Introduction

Efficacious, safe and well tolerated direct-acting antiviral therapies have transformed the care of patients with hepatitis C (HCV) in a few short years.[1-6] The standard of care has progressed from frequent treatment failures to readily available cures with rare adverse events.[7,8] While many important questions remain, 2 of the greatest relate to the cost-effectiveness and coverage of treatment[9] and the timing of therapy for those undergoing evaluation for liver transplantation. Given the cost of novel therapies, cures for chronic HCV require a significant upfront investment. However, in view of the morbidity of HCV infection, viral eradication has been proven reproducibly to be cost-effective from the societal perspective by reducing the need for liver transplants, the rate of hepatocellular carcinoma and leading to longer more productive lives.[10-12]

There is limited data, however, to guide clinicians and payers regarding whether to initiate anti-HCV therapy before or after transplantation for patients presenting with decompensated cirrhosis (Child Class B or C). On one hand, eradication of HCV prior to transplant has clear benefits. These include the prevention of recurrent HCV posttransplant, which is a major cause of graft-loss.[4,5] Further, for patients with advanced fibrosis, successful HCV treatment prevents the development of liver failure.[13] As for patients with decompensated cirrhosis, there is evidence from the SOLAR-1 and 2 trials of ledipasvir/sofosbuvir (LDV-SOF) with ribavirin that viral eradication often leads to a reduction in the patient's MELD score (Model for Endstage Liver Disease) and which could, in some patients, obviate the need for liver transplantation.[3] On the other hand, patients with decompensated cirrhosis are at increased risk

of death both before and in the perioperative period. The stage of cirrhotic decompensation, or Child Class, may therefore impact the risk-benefit assessment for costly HCV therapy in the setting of an uncertain future. For this reason, it is unclear whether pretransplant treatment of patients with decompensated cirrhosis will prove cost-effective from the societal perspective.

Herein, we compared the cost-effectiveness of HCV treatment before or after liver transplantation in patients with Child B or C cirrhosis using a secondary analysis of the SOLAR-1 and 2[3] of LDV-SOF with ribavirin.

Methods

Model Overview

We developed a probabilistic decision analytical microsimulation state-transition model[14] using dedicated software (DATA 3.5, TreeAge, Williamstown, MA). The analysis was performed according to published guidelines.[15,16] We simulated a cohort of 10 000 patients with decompensated cirrhosis (all Child B or C) who reflected the patients enrolled in the SOLAR-1 and 2 trials of LDV/SOF and ribavirin.[3] Study subjects were ≥ 18 years of age with HCV genotypes 1 or 4 HCV and were enrolled at 29 US clinical sites. Patients were excluded from enrollment if they had human immunodeficiency virus, hepatitis B virus, prior exposure to an NS5a inhibitor, hemoglobin ≤ 10 g/dL, platelets ≤ 30 000/mm3, alanine aminotransferase or aspartate aminotransferase or alkaline phosphatase ≥ 10 times the upper limit of normal, total bilirubin ≥ 10 mg/dL, or creatinine clearance <40 mL/min. All patients received LDV/SOF and ribavirin and while they were randomized to receive 12 or 24 weeks of therapy, there were no differences in outcome based on duration.[3] During the SOLAR trials, MELD scores were

calculated before, during and after HCV therapy. The pre-post treatment difference in MELD was calculated for all patients attaining sustained virologic response (SVR).

Three treatment strategies were modelled: usual care without HCV therapy, treatment before transplant and treatment after transplant. (Figure 1) All patients are Child B or C and progress through the model receiving transplants or dying at probabilities based on their MELD score. Each patient enters the model with a randomly generated MELD between 6 and 40.The odds of transplant are based on a patient's MELD score at the beginning of a 12 week cycle and modelled based on pooled national data (irrespective of transplant region).[17] While the odds of transplant are low for patients with low MELD, as they are Child B and C, there remains a statistical probability of transplant during the cycle in view of the risk of further decompensation. (Table 1, Figure 2) All patients are eligible for transplant irrespective of the success of treatment before transplant.

The modelled treatment duration is 12 weeks, provided either at the outset of the model (treat before transplant) or after transplant. Though it is possible that SVR can be achieved if therapy is abbreviated by the transplant while the patient's viral load is negative,[4] the model was tested both with the simplifying assumption that patients are not transplanted during the course of therapy and that patients could be transplanted during therapy. As observed during the SOLAR study, pretransplant patients can experience improvements or worsening in their MELD scores after therapy. These data were calculated for patients with MELD > and $\leq$ 15 as well as Child B alone or Child C. (Figure 3) Once a patient's MELD has changed following HCV

clearance, it does not progress. Conversely, for patients without SVR and for those who are not treated prior to transplant, their MELD advances each cycle based on published estimates. (Table 1) All patients are assumed to be transplant eligible. The modelled patients do not have hepatocellular carcinoma and do not develop cancer during observation as a simplifying assumption. Treatment after transplantation is assumed to be provided 3 months postoperatively. After transplantation, graft and patient survival is derived from published estimates and is affected in part by the presence of active HCV infection. The probability of graft loss is increased in patients who have not achieved SVR or for whom treatment was deferred. It is assumed that graft loss can be treated with retransplantation only once during this model.

Model Parameters

Table 1 details the model parameters as well as their sources. Transition probabilities are modelled as beta distributions, costs as gamma distributions (save for the cost of therapy[18]), and utilities as triangular distributions. All utilities reflect published estimates derived exclusively from patient reported metrics. There is evidence that successful treatment leads to increases patient-reported quality of life (QOL).[6] We used a conservative estimate that 57% of subjects obtaining SVR would experience an 0.026 increase in their reported annual utilities.[19] For the probabilistic sensitivity analyses, the proportion of patients attaining a QOL benefit was modelled as a beta distribution and the magnitude of QOL benefit was modelled as a triangular distribution 0.026 (0.00 – 0.026).

Given that the probability of SVR is conditional on survival during treatment and we modelled the risk of death before the chance of SVR, we performed a secondary analysis of the SOLAR data to derive the SVR statistics based on survivors for both pre and posttransplant treatment strategies. Similarly, for the sensitivity analyses of outcomes by Child class, we determined the changes in MELD after therapy for Child B or Child C patients separately.

Model Procedures

The goal of this analysis was to model 2 outcomes simultaneously based on the generation of discounted costs (2014 US dollars) and discounted quality adjusted life years (QALY) that accrue to our cohort over time. There is uncertainty related to any input parameter (ie confidence intervals or ranges of values). Each time a patient enters the decision model, they experience a unique set of model parameters derived from distributions reflecting the input confidence intervals. Therefore, this model is a microsimulation, following the stochastic movements of individual subjects through the chances of developing clinical outcomes. It is also a probabilistic analytic model which analyzes 10 000 random samples within each parameter's distribution for each simulated patient. The end result is the probability of cost-effectiveness for a given strategy in the overall set of simulations. The primary outcome – cost per QALY – is derived from probabilistic sensitivity analyses which were performed using Monte Carlo microsimulation of 10 000 patients with 10 000 samples taken from the input parameter distributions.

Once the relative cost-effectiveness of the strategies is calculated, the results are interpreted in the context of society's willingness-to-pay (WTP) threshold. The WTP threshold is the amount of money per person that society is willing to pay to adopt a new clinical strategy for an additional QALY over the current acceptable strategy. It is generally considered to be 2-3 times the individual share of gross domestic product.[20] We discuss most results in terms of a WTP of $100 000 but also assess the probability of cost-effectiveness for each strategy across a range of WTP up to $200 000 in 'cost-acceptability curves'. Finally, we calculated a metric called the population 'expected value of perfect information' (EVPI). The population EVPI is a reflection of the benefit derived from further research and is therefore a measure of the uncertainty in this analysis.

Subgroup and Sensitivity Analysis

We performed 5 subgroup analyses. We reran the model with transition probabilities (MELD changes after therapy and SVR rates) specific to 4 subgroups with 1,000 samples from the parameter distributions: Child B alone, Child C alone, MELD 6-10, MELD 11-15, and MELD > 15 (Table 1, Figure 3). We also re-ran the model with variable transplantation rates in order to simulate hypothetical transplant regions with low (MELD 20-25) and high (MELD > 30) average MELD at the time of transplant. To do so, we modelled the former scenario by setting the rate of transplantation at MELD 20-25 and 25-30 equal to the rate at MELD > 30 (Table 1); high MELD regions were simulated by setting the rate of transplant at MELD $\leq$ 30 equal to zero. Each subgroup was re-analyzed in the same fashion as the primary outcome. Specific 1-way sensitivity analyses of the base-case included MELD at entry, the cost of therapy

and overall SVR, and cost of transplantation. We also assessed the impact of withholding allografts from patients with SVR based on the proportion of HCV-positive allografts by performing a sensitivity analysis of the reduction in the available donors.

Data Analysis

The model assumed a 12-week cycle length and terminated after 5 years. We repeated the analyses for a 10-year time horizon which did not affect the strategy rankings but focused on 5 years given that only short-term data is available for the novel therapeutics, particularly in the peritransplant setting. All costs, life-years and utilities were discounted at a rate of 3% per annum. Half-cycle correction was performed. All costs were inflated to 2014 values and converted to American dollars. Sensitivity analyses were performed for all variables.

The population EVPI is calculated according to previously published procedures.[21] The population with decompensated cirrhosis attributable to hepatitis C is unknown but probably falls between 50 000 and 100 000 so we assumed a 10-year lifespan for the modelled therapy and 75,000 applicable patients per year.

Results

The results derived from base-case as well as the 4 disease-state substrata are detailed in Table 2. In the base-case, the treat before transplant strategy yields more QALYs at a lower cost compared to the other strategies and is therefore a dominant strategy. Both treatment strategies

yield more QALYs than the nontreatment arm. Nontreatment is less costly in 4 substrata: patients with MELD 6-10, MELD 11-15, patients who are Child B alone or patients who are Child C alone. Treatment before transplant offers more QALYs in each of the disease-state strata save for patients with MELD > 15 where treatment after transplant provides higher QALYs. Treatment before transplant is the most cost effective strategy within a WTP threshold of $100 000 per additional QALY in all cases save for patients with initial MELD 6-10. For patients with a MELD of 6-10 at study entry, treatment before transplant is associated with an incremental cost > $100 000/QALY over nontreatment and is therefore not cost-effective.

The effect of a given region's average MELD at the time of transplant was explored with 2 subgroup analyses. (Table 3) First, we simulated a hypothetical region where the rate of transplantation with MELD > 20 was set as the same for MELD > 30 (ie 0.88, range 0.70-1). [22] In this context, treatment before transplantation is the dominant strategy, cost-effective in 100% of simulations, by producing more QALY for lower cost than treatment after transplant or no treatment at all. Second, we simulated a hypothetical region where transplantation only occurred with MELD > 30. Here, no treatment was cost-effective at the lowest WTP thresholds. However, because treatment before transplant produced the most QALY for a marginal incremental cost ($27,878 per additional QALY), it was the most cost-effective strategy overall at contemporary WTP thresholds.

Cost-acceptability curves were generated to capture the results of each probabilistic sensitivity analysis (Figure 4). The proportion of simulations where a given strategy is cost-

effective was assessed for the range WTP thresholds from $0 to $200 000 for the base-case and each disease-state sub-strata. In the base-case, treatment before transplantation was cost-effective in the majority of simulations with non-treatment being the most cost-effective in a minority (<1%) of simulations up to a WTP threshold of $100 000. After at WTP threshold of $100 000, treatment before transplantation is the most cost-effective strategy in the vast majority of simulations for the base-case and each Child Class, B or C. Treatment before transplant is cost-effective at all WTP for patients with MELD > 15. It is cost-effective in the majority of simulations for patients with MELD 11-15 beginning at a WTP of $70 000. For patients with MELD 6-10, however, treatment before transplant is the most cost-effective strategy in the majority of simulations at WTP of $130 000. Finally, treatment before transplantation was the most cost-effective strategy at all WTP > $30 000 irrespective effect of a region's average MELD at transplantation.

There were 5 notable results from additional 1-way sensitivity analyses in the base-case. First, the MELD score at which treatment before transplant becomes the most cost-effective strategy is 13. Second, the pretransplant SVR at which treatment before transplant becomes more cost-effective than nontreatment is 49.2%. Third, the maximum cost of therapy for which treatment before and after transplantation becomes more cost-saving than nontreatment are $177,381 and $57,850, respectively. Conversely, when the population is restricted to patients with MELD 6-10, treatment before transplant is only cost-saving up to a treatment cost of $24,685 and treatment after transplant is only cost-saving up to $6,150. Fourth, there is no cost of transplantation that alters the results. Even if liver transplantation were to cost $0, treatment before transplant remains cost-effective. Fifth, there is no proportion of HCV-positive donors

that alters the results. Treatment before transplant prevents a sufficient number of transplants and deaths such that its cost-effectiveness is robust to a shrinking donor pool when excluding HCV-positive allografts. Strictly from a perspective of total costs (irrespective of QALY), the no treatment becomes a cost-saving strategy when the proportion of HCV-positive donors exceeds 17%.

The population EVPI was calculated to determine the value of further research on this question as a measure of uncertainty for these results. The population EVPI was calculated for the base-case, Child B and Child C patients, all at a WTP threshold of $100 000. The value of further research for the base-case is $185,806 and $556,808 and $12 million for Child B and C patients, respectively.

Discussion

Evidence increasingly supports the widespread uptake of highly effective, safe treatments for chronic hepatitis C therapy.[1-4,10,23,24] For clinicians and payers alike, a significant gap in the available data regards the timing of therapy for patients with Child B or C cirrhosis who are simultaneously at increased risk for death and liver transplantation. Prior decision analyses have established the cost-effectiveness of novel direct acting antiviral therapies for simulated cohorts of treatment naïve patients with HCV (with a range of generally early stage disease),[10,12] patients with exclusively early fibrosis,[25,26] noncirrhotic patients with genotype 2 or 3 HCV,[11] and patients with recurrent HCV after liver transplantation.[27] In this study of patients with decompensated liver disease utilizing clinical trial data, these findings demonstrate that treatment

with LDV-SOF and ribavrin is cost-effective from the societal perspective for patients with Child B or C cirrhosis related to genotype 1 or 4 HCV, particularly those with MELD > 13.

Microsimulations allow us recreate and test the outcomes of clinical trials in the context of uncertainty about the results by varying the input parameters – be it SVR, MELD score before therapy and quality of life – over a wide range of values. Specifically, our microsimulation generalizes the outcomes of from the SOLAR study by re-running the trial for 10 000 simulated patients with 10 000 separate trials for each patient using different permutations of the values of the clinical variables listed in Table 1. These data are therefore robust and extend the findings of prior literature in 4 main ways. First, we quantify the benefits of therapy for patients with decompensated cirrhosis across MELD scores and Child classes. No prior cost-effectiveness study has analyzed the impact of therapy on MELD scores and the risk of death or transplantation on the waiting list. It is likely that the key to our observed treatment cost-effectiveness is the often significant reduction in MELD score after therapy which simultaneously leads to reductions in death as well as the need for liver transplantation. For these reasons, the baseline MELD among patients with decompensated cirrhosis after which treatment before transplant is the most cost-effective strategy is 13. An improvement in the MELD is inherently valuable for patients with MELD > 13 because MELD drives transplant (cost) at the same time as mortality. Accordingly, treatment before transplant is a dominant strategy when transplant occurs at early MELD (> 20) and sensitivity analyses show these findings to be robust at SVR roughly half of that observed (49.2%) and a cost of therapy roughly twice of that currently charged ($177,381). Similarly, there is no cost of transplantation at which another strategy becomes cost-effective because treatment before transplant provides substantial

incremental increases in most patients' QALYs. Cost-effectiveness is determined by the cost for each additional QALY. In the case of treatment before transplant, it is both saves money (by reducing transplants) and improves and prolongs life (ie QALYs), making it a superior strategy largely independent of the costs of care.

Second, in contrast to the prior decision analyses which rely entirely on published estimates for modelling, this study's core strength is that major determinants of clinical decision making are derived from a clinical trial. For this reason, conditional variables such as SVR both before and after transplant, as well as the clinical impact of therapy (measured in changes in MELD score) reflect clinical experiences. Crucially, we model SVR from the 'intention to treat,' accounting for deaths on treatment. For this reason and others, we capture the fact that patients with Child C have lower SVR before or after transplant than Child B. Third, the EVPI analysis shows that given the magnitude of benefit as well as its robustness in a probabilistic sensitivity analysis, the value of further research on this topic is extremely limited. Fourth, we test the possibility that by treating patients with HCV prior to transplant, we contract the donor pool by foregoing transplantation with HCV+ donors. In a sensitivity analysis, we demonstrate that owing to the reduced risk of death or transplant as a function of generally lower MELD after therapy, there is no proportion of HCV+ donors at which the optimal treatment strategy changes from treatment before transplant.

These data must be understood in the context of the study design. First, these data model outputs from SOLAR study which had notable exclusions, including patients with coinfections,

total bilirubin $\geq$ 10 mg/dL and creatinine clearance <40 mL/min. These data cannot be generalized to those Child B and C subpopulations, likely including patients with MELD > 35. Second, the modelled benefits of SVR on QOL were modest and restricted to a 57% of the population which may underestimate the benefits of therapy.[6] Similarly, the natural history of decompensated cirrhosis following SVR is not fully understood. We assigned the same MELD-based risk of death and transplant to patients with and without SVR. Third, while a strength of this model is the use of input parameters from a clinical trial, it should be noted that some of the observed estimates are likely conservative relative to those from subsequent cohort studies (eg posttransplant SVR rates for Child C patients). [28] Fourth, we did not model the risk and impact of hepatocellular carcinoma (HCC) diagnoses and treatment in order to specifically answer questions specific to treatment for patients with decompensated cirrhosis. However, given that for patients with HCC time on the waitlist is the primary driver of transplantation, treatment therefore does not reduce the need for transplant.

Finally, we modelled cost-effectiveness from the societal perspective. For the individual patient, however, a reduced risk of transplantation may or may not be preferable. Treatment of HCV may forestall MELD progression and the risk of decompensation. Accordingly, for patients with sufficiently poor waitlist QOL, stable reductions in MELD in the post-MELD era of transplant allocation could lead to the so-called 'MELD Purgatory.'[29] While we modelled changes in MELD following SVR, we could not model the probability of improved Child score after therapy, which could potentially impact QOL, independent of effects on MELD. The main results of SOLAR trial as well as ASTRAL-4 do suggest, however, that many patients experience improvements in Child-Pugh score.[3,30] Therefore, treatment after transplant may be

desirable from the perspective of patients unwilling to accept the possibility of stable MELD in the setting of decompensated cirrhosis. Cost-effectiveness from the societal perspective relates entirely to the prolonged lives with higher QOL and lower costs (ie transplant). However, the individualized benefits of treatment may clash with this perspective and can only be reconciled in the context of the patient-doctor relationship. Some patients may benefit from transplant over treatment (avoid MELD purgatory) and some may benefit from early treatment.

In conclusion, these data support the cost-effectiveness of LDV/SOF and ribavirin in patients with Child B or C cirrhosis prior to transplantation from a societal perspective.

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FIGURE LEGENDS

Figure 1: Flowchart of Patient Evaluation By Strategy

MELD = model for endstage liver disease. SVR = sustained virologic response

Figure 2: A Simplified Depiction of the Microsimulation State-Transition Model

Each station reflects the 'health states' for any given patient as the model progresses with each cycle. Multiple factors help determine whether a patient 'transitions' between states including their model for endstage liver disease score and whether they achieved a sustained virologic response.

Figure 3: Change in MELD Scores after Treatment

The changes in Model for Endstage Liver Disease (MELD) score after treatment are depicted, stratified by MELD score (> 15 or $\leq$ 15) and Child Class (B or C).

Figure 4: Cost-Acceptability Curves: Strategy Cost-Effectiveness by Willingness-to-Pay Threshold (WTP)

Each microsimulation has been repeated with many samples from the input parameter distributions (10 000 for the base-case and 1,000 for each subgroup). For each strategy, at each WTP threshold, there is a variable probability (proportion of samples) that it is the most cost-effective. This figure details how the 'Treat Before Transplant' strategy is the dominant strategy at all WTP thresholds > $100 000 for each disease strata (MELD 11-15, > 15, Child B or C) save for MELD 6-10. As treatment before transplant can reduce a given patient's MELD score, it can reduce the risk of death (which increases the average QALYs) and transplantation (which reduces the average cost).

MELD = Model for Endstage Liver Disease, QALY = quality adjusted life year

Figure 1

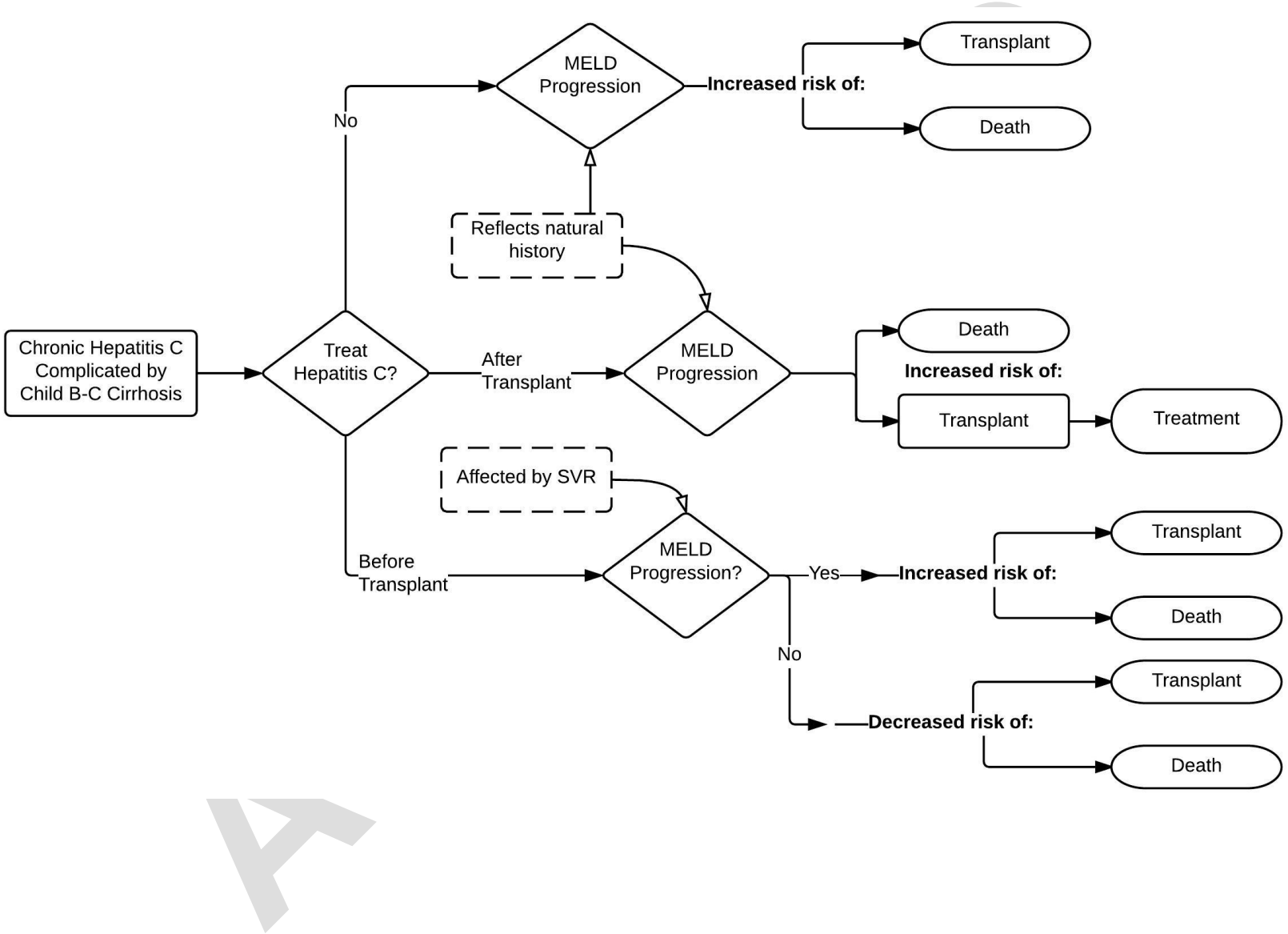


Figure 2

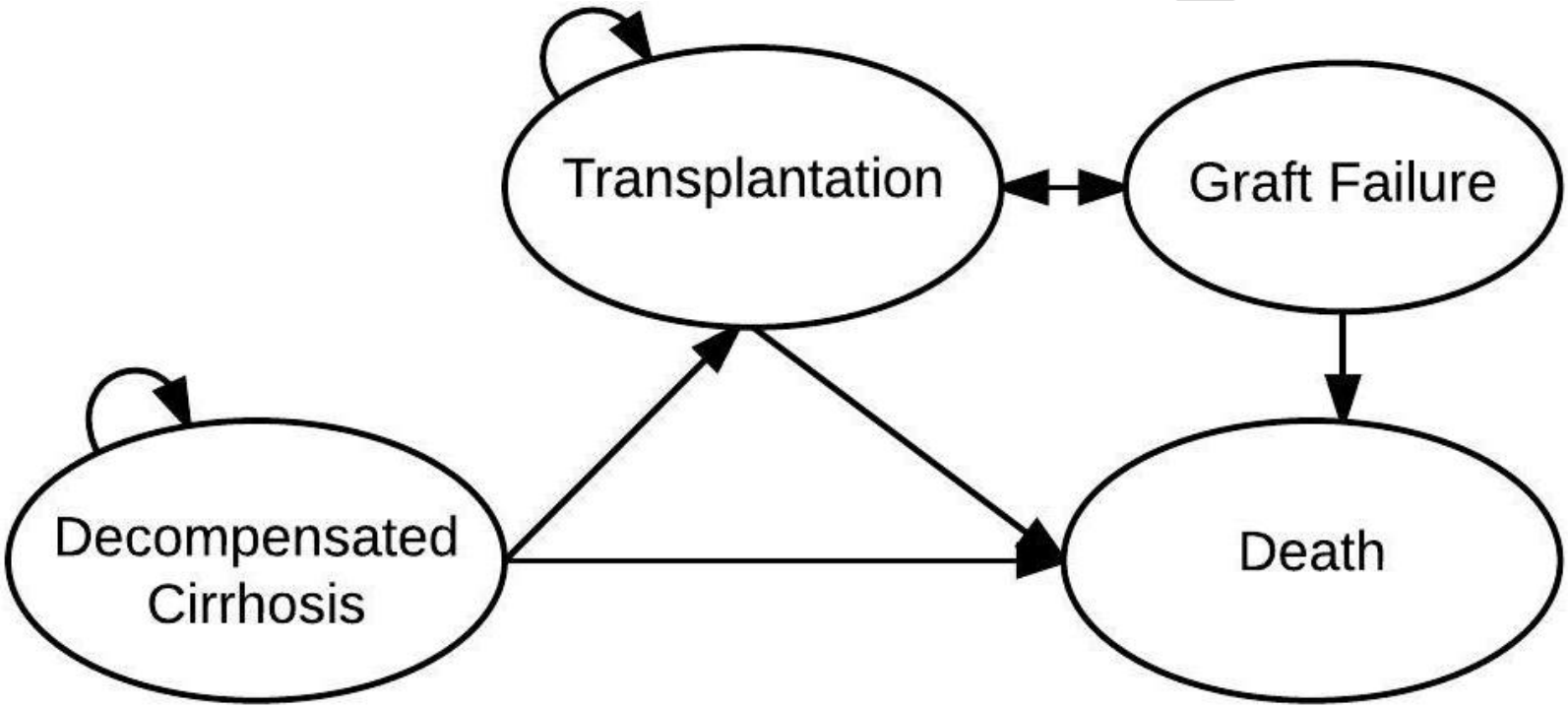
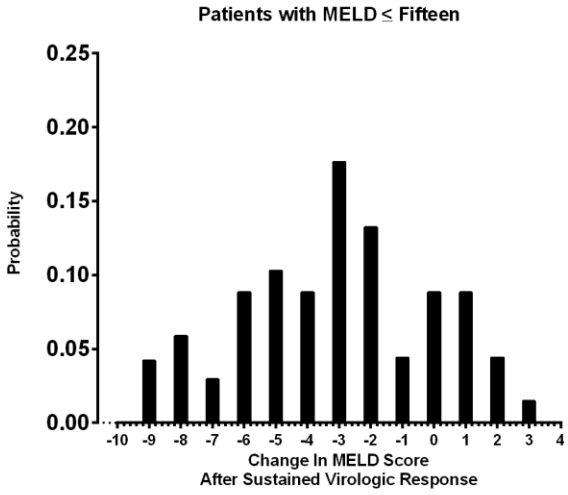
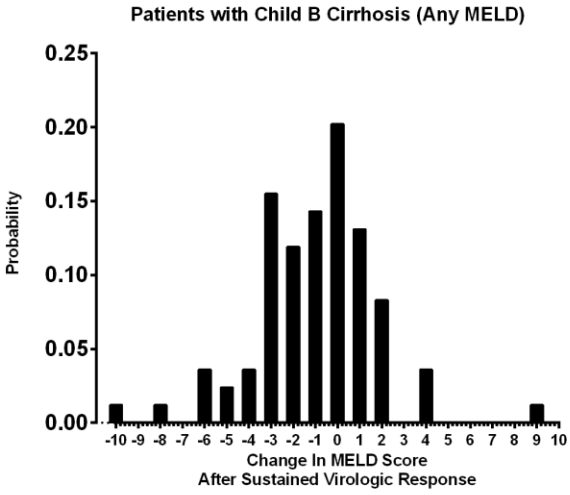
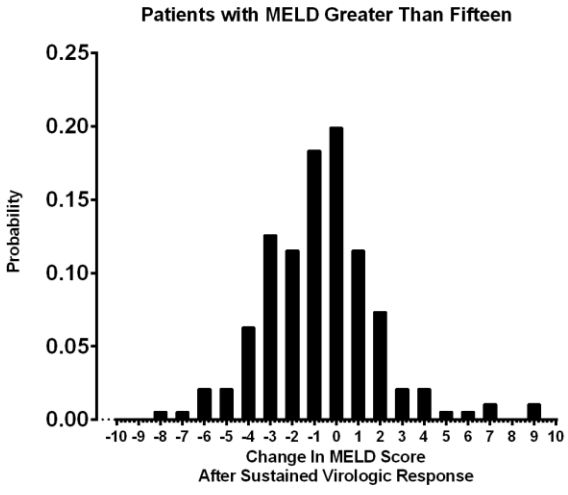


Figure 3







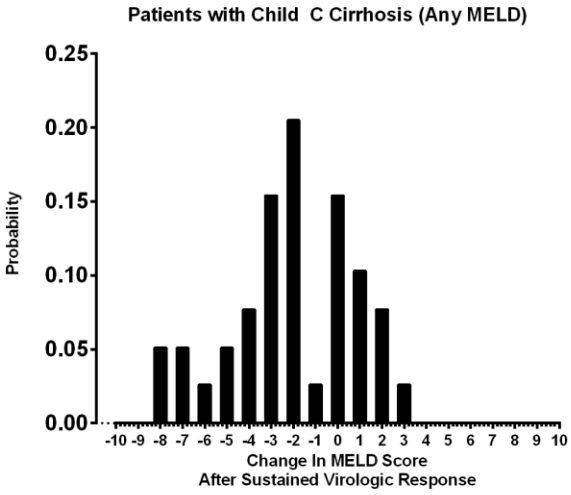


Figure 4

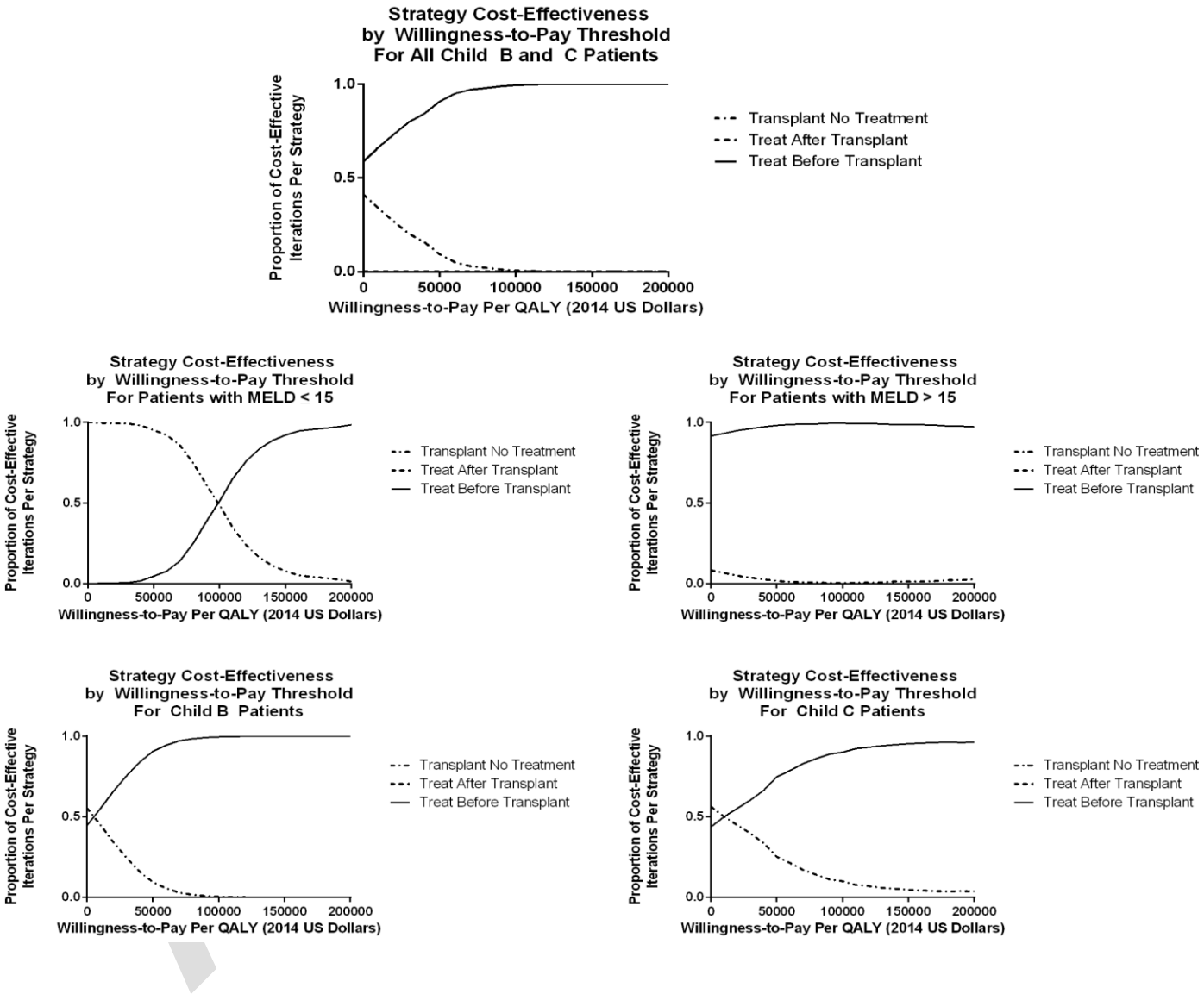


Table 1: Estimates of Test Performance and Disease Prevalence for the Model

Transition Probabilities	Probability(event)/other modifiers	Estimate (distribution)	Source
Probability of Waitlist Death within 90 days	MELD 6-10	0.019 (0.016-0.022)	17
	MELD 11-19	0.06 (0.05-0.07)	
	MELD 20-29	0.20 (0.16-0.23)	
	MELD $\geq$ 30	0.54 (0.44-0.62)	
Probability of Transplantation within 90 days	MELD 6-15	0.024 (0.019-0.029)	22
	MELD 16-30	0.39 (0.31-0.46)	
	MELD >30	0.88 (0.70-1)	
Treatment	Major Adverse Event	0.063 (0.050-0.076)	3
	SVR – Pre-Transplant Child B and C	90.9% (80/88 subjects)	Secondary analysis of SOLAR trial
	SVR – Child B (Pre)	88.2% (45/51 subjects)	
	SVR – Child C (Post)	94.6% (35/37 subjects)	
	SVR – Post-Transplant Child B and C	91.8% (45/49 subjects)	
	SVR – Child B (pre)	95.3% (41/43 subjects)	
	SVR – Child C (post)	66.7% (4/6 subjects)	
Disease Progression	Annual MELD progression without treatment	1.23 $\pm$ 0.42	31
Posttransplant	Survival, year 1	0.86 (0.86-0.87)	22
	Annual mortality, $\geq$ Year 2	0.066 (0.053-0.79)	32
	Graft Failure with HCV	0.08 (0.04 – 0.16)	33
	Graft Failure without HCV	0.06 (0.03 – 0.12)	
	Death in year after graft failure	0.21 (0.21-0.23)	34
	Retransplantation after graft failure	0.52 (0.50 – 0.52)	
Costs (2014 US Dollars)	**Details**	**Estimate (Distribution)**	**Source**
ledipasvir/sofosbuvir and ribavirin	12 week course	95,523	18
Decompensated Cirrhosis	Annual costs of care	16,263 (13, 011 – 40,198)	35,36
Transplant	Annual costs of care (year 1)	344,030 (267,493 –344,030)*	37,38
	Annual costs of care (> year 1)	47,081 (42,277 – 51,365)	
Death	Minimum annual costs	61,655 (38,866 – 65,975)	39,40
Utilities	**Details**	**Estimate (Distribution)**	**Source**
Child B/C Cirrhosis	Utility per annum	0.60 (0.46 – 0.71)	37,41-44
Posttransplant	Utility per annum (Year 1)	0.69 (0.55 – 0.78)	42
	Utility per annum (> Year 1)	0.79 (0.62 – 0.79)	37,42,45

MELD = Model for endstage liver disease, SVR = sustained virologic response. * Sensitivity analyses assessed transplant costs from $0-344,030

Table 2: Main Results

	Average Overall Cost (USD)	Incremental Cost (USD)	Average Overall QALYs	Incremental QALYs	Cost per incremental QALY
Base Case: Patients with Child B or C Cirrhosis Representative of the SOLAR Study					
Treat before transplant	354,560		2.31		
No treatment	356,824	2,264	2.15	-0.16	N/A
Treat After Transplant	409,445	54,885	2.26	-0.04	N/A
Patients with a MELD score 6-10					
No treatment	197,088		2.20		
Treat After Transplant	218,567	21,479	2.23	0.03	715,967
Treat before transplant	245,724	48.636	2.57	0.38	127,989
Patients with a MELD score 11-15					
No treatment	224,404		1.85		
Treat before Transplant	252,667	28,263	2.25	0.39	71,568
Treat after transplant	254,323	29,920	1.91	0.06	541,705
Patients with a MELD score > 15					
Treat before transplant	396,248		2.27		
No treatment	414,220	17,971	2.2	-0.07	N/A
Treat After Transplant	477,720	81,471	2.35	0.08	1,047,623
Patients with Child B Cirrhosis Alone					
No treatment	276,674		2.12		
Treat before transplant	278,194	1,519	2.4	0.28	5,470
Treat After Transplant	314,412	37,738	2.19	0.07	521,568
Patients with Child C Cirrhosis Alone					
No treatment	412,059		2.17		
Treat before transplant	412,914	854	2.28	0.11	8,103
Treat After Transplant	474,986	62,927	2.26	0.08	749,225

All incremental data reference a common baseline. Prices are in 2014 US dollars. Negative cost-effectiveness ratios are not presented (hence n/a). MELD = model for endstage liver disease, QALY = quality adjusted life years, USD = US Dollars

Table 3: The MELD Score At the Time of Transplant Affects Treatment Cost-Effectiveness

	Average Overall Cost (USD)	Incremental Cost (USD)	Average Overall QALYs	Incremental QALYs	Cost per incremental QALY
Hypothetical Region with High Transplant Rate at MELD > 20					
Treat before transplant	351,714		2.43		
No treatment	361,700	9,986	2.26	-0.16	N/A
Treat After Transplant	414,010	62,295	2.38	-0.04	N/A
Hypothetical Region with High Transplant Rate only at MELD > 30					
No treatment	177,943		1.63		
Treat Before Transplant	199,450	5,018	1.81	0.18	27,878
Treat After transplant	182,961	21,507	1.68	0.05	430,140

All incremental data reference a common baseline. Prices are in 2014 US dollars. Negative cost-effectiveness ratios are not presented (hence n/a). MELD = model for endstage liver disease, QALY = quality adjusted life years, USD = US Dollars