A Cost-Effectiveness Decision Analysis of Living Donor Liver Transplantation

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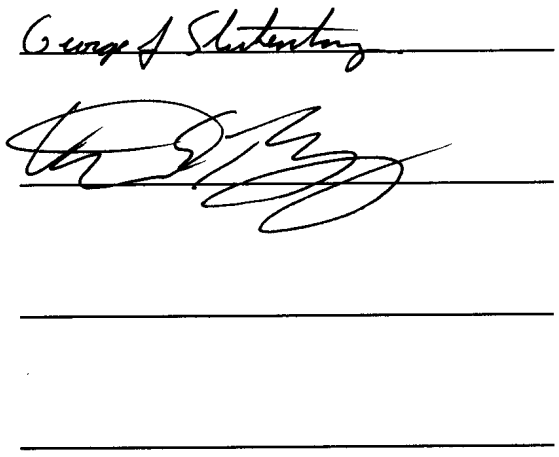

Abstract

Background: Liver transplantation is considered the standard of care treatment for end stage liver disease and cirrhosis. Because of the sizable waiting list and relatively long waiting times over the past few years in the U.S., donation of a portion of liver from a living donor has arisen as an alternative to deceased donor organ allocation. The LDLT shortens recipient time on the waiting list but has significant risks to the living donor. This study is a cost-effectiveness analysis designed to explore the costs and benefits of adding LDLT to the treatment of end stage liver disease.

Methods: A complex Markov decision analysis model was developed to simulate all of the important events in the course of cirrhosis. Treatment strategies including no transplantation, DDLT-only, LDLT-only, or combined DDLT/LDLT were investigated using a Monte Carlo cohort analysis and expected value calculations to determine cost effectiveness. A sensitivity analysis was performed to determine variables important to the model.

Results: Demonstrating good external validity, using the base-case values, the model produced raw survival rates and event occurrence rates similar to those published in the literature. Baseline cirrhosis offered 2.0 QALY survival while costing $17,000, DDLT-only offered 4.1 QALY survival and cost $121,000, LDLT-only offered 3.8 QALY survival and cost $143,000, and combined DDLT/LDLT offered 4.4 QALY survival and cost $162,000. The LDLT-only strategy was dominated. The DDLT-only strategy had an ICER of $49,920 over no transplant

while combined DDLT/LDLT had an ICER of $129,474 over DDLT-only. The sensitivity analysis showed the model to be sensitive to the rate of donor death, the cost of the actual transplant procedures, and the rate of post-transplant recurrent disease causing graft failure.

Conclusions: DDLT is a cost-effective treatment strategy for end-stage liver disease. The addition of LDLT to the treatment paradigm offers slightly longer quality adjusted survival at much greater cost. Society, third party payers, and government agencies will eventually be forced to determine the willingness to pay for the various treatment strategies for end-stage liver disease. More studies are needed to clearly define the risks and benefits of this controversial procedure.

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Introduction and Background

This study is an evaluation of the cost-effectiveness of adult-to-adult Living Donor Liver Transplantation (LDLT) compared to Deceased Donor orthotopic Liver Transplantation (DDLT). Cost-effectiveness is evaluated using a Markov process-based medical decision analysis model that includes key event probabilities, outcomes, and the costs of these alternatives. The model incorporates comprehensive current data on variables such as donor morbidity and mortality probability, complication events probabilities, and quality-of-life estimates derived from the latest published literature. Costs for modeled events are derived through detailed micro-costing algorithms using cost data for transplant patients from a large regional hospital. This study is designed to provide a comprehensive decision analysis model of chronic liver disease and liver transplantation that can be used to aid transplant teams, third party payers, and policymakers, in funding and policy decisions related to this important and expanding field of medicine.

DDLT has been the definitive treatment for end-stage liver disease in the United States since the advent of effective immunosuppression. Steadily increasing demand for liver transplants has resulted in longer waiting lists for organs donated from deceased donors. At the end of December 2003, there were over 17,500 patients on the national waiting list for liver transplants. In the year 2000 there were only about 5000 liver transplants performed in the U.S., a number that has remained relatively stable in recent years. In 1999 about 15%

of patients awaiting transplantation died (1). The median waiting time for liver transplant in 1999, for all listed adult recipients, was between 222 and 612 days, depending on recipient blood type (2).

LDLT is an alternative to traditional deceased donated transplants. In 1989, the first successful living donor liver transplant was performed in Australia from an adult donor to a child recipient (3). With refinement of the procedure in children, the LDLT has become a well-established treatment for many forms of end-stage liver disease in the pediatric population. More than 3000 of these pediatric transplants have been performed worldwide and there is adequate evidence that risk to the donors and recipients are within the range of accepted medical interventions (4, 5).

Technical aspects of the adult-to-adult LDLT, including larger required graft size, have led to a more difficult surgical procedure and more variable clinical outcomes in the adult recipients. This has made extrapolation of pediatric outcomes data to the adult population difficult. As such, there is little reliable outcomes data for adult LDLT on which to base clinical decisions, patient counseling, or health policy.

Although the number of centers that are now performing LDLT is rapidly increasing, much of the LDLT process is not standardized and varies greatly between centers. For example, requirements for donor liver biopsy, biliary imaging, and mesenteric angiogram vary widely (6, 7). This exposure to potential donor morbidity and mortality has not been evaluated systematically

and case series reported in the literature vary in claims of donor morbidity in the immediate perioperative period from minimal (8) to 18% (9). There have been three reported deaths in healthy living donors in the United States but some have challenged that underreporting of donor deaths is likely (10). There are no systematic long-term follow-up studies for U.S. living donors reported in the literature. Some authors (11, 12) have called for stronger internal regulation and better informed consent in order to protect involved patients and donors until definitive research has shown the proper indications, workup, and contraindications for LDLT in adults.

Several centers have reported costs related to deceased and living donor liver transplantation (13, 14). These costs vary widely but it is generally acknowledged that when all costs are considered, LDLT is more expensive than deceased donor liver transplantation. The expectation that LDLT recipients have shorter times spent on the waiting list leads to the implication that LDLT may be more cost effective because of improved quality-of-life and less chance of death while awaiting transplant.

Counterbalancing this potential benefit of shorter waiting times for the recipient is the risk to the healthy donor and the cost of his or her care. Significant long-term injury to the donor, who is by definition in a good state of health, would detract from the effectiveness of LDLT from a societal point of view. Published data on LDLT tend to focus on recipients or, less commonly,

donors, but usually fail to address both recipient and donor and the relationship between their respective outcomes.

Although analyses of costs (14-19), outcomes (6, 8, 9, 20, 21), and quality of life (5, 22-30) in relation to LDLT, have been published, few have evaluated the true cost-effectiveness of LDLT using a formal medical decision analysis (31-34). Sagmeister, et al (33), evaluated the cost-utility of LDLT in combination with DDLT compared to DDLT alone, in Switzerland with a formal Markov decision analysis. However, the model used in this study was greatly simplified and no accounting for living donor morbidity or mortality was included. Cost data specific to Switzerland also limited external validity. Sarasin, et al (34), used a more complete model but assessed the narrow case of LDLT for hepatocellular carcinoma. This study was also hindered by a lack of accurate outcomes data in regard to donor outcomes. A definitive decision analysis incorporating accurate donor outcomes and U.S. based costs is needed to expand this important literature. This type of decision analysis involving appropriate costs and quality-adjusted survival can be used to compare the effectiveness of LDLT to other medical interventions commonly accepted as cost-effective, such as ambulatory hemodialysis for end-stage renal disease in the U.S. Information derived from cost-effectiveness models can be used by policymakers and third party payers to form reimbursement patterns and governmental regulations.

Methods

Decision Analysis Model

The Markov process decision model developed for the study considers six health states that can occur for patients with end-stage liver disease any time over a ten year time horizon while they await transplantation and after transplantation, as summarized in Figure 1. The model was developed in consultation with a panel of clinicians who have extensive experience caring for transplant patients at a single large academic medical center. The model provides a conceptual framework for organizing the relationship of events, costs, and the utility of different outcomes for DDLT only compared with DDLT/LDLT.

For validation purposes, the model was extended to include treatment arms for both “no transplant available” and for “LDLT-only”. The four treatment arms simulate situations where patients with cirrhosis have no access to transplantation, have access to only a wait-listed standard DDLT approach, have access to only an LDLT approach, or have access to combined DDLT/LDLT. The “no transplant available” and the “LDLT-only” arms do not represent realistic situations in the U.S., but instead are used as reference conditions to evaluate the decision model’s performance and to assess the model’s ability to simulate valid expected survival distributions for each situation.

A Monte Carlo simulation of the Markov process decision model was used to estimate the distribution of events that would occur for 1,000 patients (cohort members) over ten years. All event probabilities in the model were calculated

using a one-month cycle length, which was selected as the most clinically pertinent time increment to simulate chronic liver disease and transplantation events. Half-cycle corrections were included (except for the first and last cycle) to account for mid-cycle cost and utility accumulation (35).

In the model, members cycle through one of six basic health states. Pre-transplant members can cycle on the waiting list without active complications ("waiting compensated") or with an active complication of end-stage liver disease ("waiting with complications"). Members selected for transplantation traverse either the "LDLT" or "DDLT" event, after which they move to the post-transplant state. After transplantation the DDLT/LDLT members enter separate post-transplant states depending on the type of transplant received. Members of the DDLT-only cohort cannot receive LDLT as a treatment option. Complications for some members may result in death, and these patients are assigned for all remaining cycles to the absorbing state of "death". Members with hepatocellular carcinoma as complication of end-stage liver disease can also pass to the "develops contraindication to transplant" state where they continue to accumulate some quality of life and costs until they progress to death. Because of the high short-term mortality of end-stage liver disease, pre-transplantation all-cause mortality was not modeled. In contrast, post-transplant all-cause mortality was included in the general survival model.

Pre-Transplant Complications

All members awaiting transplantation cycle through the pre-transplant health events that simulate the costs and complications associated with chronic liver disease. Significant events experienced by members awaiting transplantation with active complications included complicated ascites, frequent encephalopathy, hepatocellular carcinoma, and acute variceal bleeding. Significant disease events not depicted as specific health states in the model were either too rare in the U.S. population to significantly affect the model (familial amyloidosis) or the morbidity and costs of the process (severe pruritis or hepatopulmonary syndrome) were incorporated into the "waiting with complications" health state using estimated utility decrements and costs. Figure 2 presents the complete series of sequelae of chronic liver disease considered for these patients.

Members suffering from complicated ascites could respond to therapy, contract spontaneous bacterial peritonitis (SBP), or receive a transjuglar intrahepatic portosystemic shunt (TIPS). Both SBP and TIPS have defined mortality rates in the model. Members with frequent encephalopathy could respond to therapy or die from encephalopathy. Hepatocellular carcinoma (HCC) could result in getting interventional treatment for the tumor, developing a contraindication to transplantation, or dying from the tumor. Acute variceal bleeding could result in TIPS, survival of the bleeding episode, or death.

Each of the health events in the pre-transplant model has the possibility of resulting in death. Every cycle of the model can also possibly result in a complication resolving (simulating a patient responding to therapy) with the member cycled back to the “waiting compensated” health state. Significant adverse health events in the model all resulted in additional costs and decrements in utility for the members passing through those events. Since members undergoing LDLT and DDLT suffer the same pre-transplant complications, these DDLT/LDLT and DDLT-only branches of the model were exactly the same. Differences between LDLT and DDLT branches in time spent on the waiting list were significant and were modeled using separate values for the probabilities of transitioning to these health states.

Transplantation

A transplantation event occurred only once for each member in the cohort, unless the member developed an indication for re-transplantation. The potential for donor complications was included in the DDLT/LDLT branch, and were categorized as “minor or none”, “severe”, or “death”. While death and severe complications are rare events for living donors, single occurrences of these events can produce huge costs and decrements in total quality of life and utility over the time period considered. Donor utility losses were included in the model as a direct decrement from the recipient utilities for the remainder of the recipient’s lifespan. Immediate post-transplant events for the recipient included

graft primary non-function (PNF), defined as graft failure within 30 days of transplantation, early recipient death within 30 days of transplantation, or 30-day survival of the recipient and graft. The model allowed for a variable proportion of members with PNF to undergo either retransplantation or death. Figure 3 presents the series of events modeled for members with transplantation.

Post-Transplant Complications

After receiving transplantation (or retransplantation) and surviving for more than 30 days, members transitioned to the post-LDLT or post-DDLT health state and could remain in the "no major complications" state or experience one of five different post-transplant complications. Members could have disease recurrence causing chronic graft failure that resulted in either retransplantation or death. If retransplantation occurred, the member transitioned to the "waiting with complications" health state to simulate a return to the transplant waiting list.

Opportunistic or aggressive systemic infections resulting from immunosuppression were included in the model and members could either respond to therapy or die from the infection. Direct surgical complications such as bleeding, intra-abdominal abscess, or anastamotic stricture could result in re-operation or death. Biliary complications were separately modeled and could result in death, surgical treatments, non-surgical treatments (ERCP), retransplantation, or death. Finally, significant acute rejection episodes resulted in retransplantation, response to therapy, or death. Except for donor events,

specific post-transplant events were the same for LDLT and DDLT patients although the rates and probabilities of those events differed between the groups. Figure 4 presents the series of events modeled for members with post-transplant complications.

Event Probabilities

Table 1 lists the baseline estimate for each event probabilities used in the model the range of values used for sensitivity analysis, and the sources of the data. Specific probabilities for events in the Markov model were calculated using these baseline estimates and non-linear functions that allow the values for these probabilities to change over the ten-year time horizon considered by the model.

Many of the event probabilities were drawn from data supplied by the United Network for Organ Sharing (UNOS) transplant registry (36) The UNOS supplied database, the Standard Transplant Analysis and Research (STAR) dataset, was queried to calculate actual event rates and distributions that occurred during all adult (recipient age 18 or older) liver transplants between January 1, 1999 and November 16, 2003. The STAR dataset is the most complete registry of U.S. transplantation events available to date and is reported by UNOS to capture greater than 99% of all liver transplants occurring in the U.S. Probabilities for events in the model that were not available from the STAR dataset were extracted from a review of the scientific literature, or were estimated based on local expert opinion. Broad ranges of minimum and maximum values

were used in subsequent sensitivity analysis of event probabilities not obtained the STAR dataset.

In the Markov process, all members begin the cohort simulation in the pre-transplant health states. Based on estimates from the STAR dataset and published literature, 25% of the initial cohort was placed in the “waiting compensated” health state and the remainder was placed in the “waiting with complications” health state. By definition, this would indicate that 75% of the cohort experienced at least one of the major complications of end-stage liver disease within the month prior to transplant registration. The monthly probability rates of transplantation, rates of graft PNF, and early recipient deaths (within 30 days of transplant) were calculated using the STAR dataset for DDLT and the literature for LDLT. The calculated average monthly rate of transplantation for DDLT was estimated using the STAR dataset. The LDLT transplantation rates per month are shown graphically in Figure 5 and were used in the model to accurately simulate the non-linear monthly transplantation rates for the LDLT cohort. This data is derived from preliminary data from national LDLT databases and from expert local opinion.

Financial Costs

All costs represented in the model are based on the third-party payer point of view. Accurate, easily generalized liver transplantation cost data was not available from either the literature or from the STAR dataset. Cost data for this

analysis was obtained from liver transplant patient hospitalization and physician administrative data abstracted from the University of Virginia Health System Clinical Data Depository (37) (CDR). The CDR is a secure comprehensive clinical database that captures all inpatient and outpatient clinical contacts in the UVA Health System. The database stores not only demographic and clinical information but, using micro-costing algorithms, captures extensive cost data in an actual utilization (non-DRG) framework. Financial transactions are recorded in the CDR as both third-party charges and real costs and are calculated using real-time discharge utilization algorithms. The development, accuracy, and validity of the UVA CDR have been published elsewhere (38-40). Because of the relative geographic isolation of the University of Virginia and lack of local competition in hepatology and transplant care, inpatient and outpatient costs related to transplantation are well represented in the CDR database. Cost data from the CDR have been used successfully in other decision analysis models and publications and costs calculated using the CDR have been shown to be comparable to adjusted national costs (41).

Table 2 shows the estimated cost data components for the LDLT model. Because of the cycle length of one month used in this model, health state costs were represented as the mean monthly cost for a given medical condition. The reported costs consider inpatient and outpatient direct costs related to medical care, equipment, and pharmacy. Societal costs were not considered in this model. Each cycle that a member spent in a specific health state incurred an

additional cost related to that specific health state. As a patient experienced a complication, an additional cost was exerted for that cycle in which the patient experienced that complication. This additional cost is a “toll” and is additive with other costs experienced during the cycle. When specific procedures, such as endoscopic retrograde cholangiopancreaticography (ERCP), TIPS, or surgical exploration were associated with complications in the model, the costs for the procedures were extracted from the CDR and a mean cost (using adjusted dollars) over the years 2000 through 2002 were used as an estimated cost. This was done to account for the rapidly changing procedure techniques and costs over the recent years in hepatology and transplantation.

The costs of organ allocation from deceased donors and living donors were included in the cost of transplantation incurred by the recipient. The costs of living donor complications or death were accounted for separately from the recipient costs and varied according to the donor complication rate. There was no ongoing cost for existing in the “death” health state although complications resulting in death had cost tolls associated with the death event. It was assumed that recipient event costs were the same for DDLT/LDLT events although these events may have happened at different rates.

Health Related Utility Measures

Accurate assessment of outcomes and endpoints is critical in assessing the effectiveness and true cost of medical interventions. Simple survival rates

and coarse outcomes such as length of stay in hospital are poor estimates of the quality of life associated with a particular health state (42, 43). Health outcomes research and health decision analysis depend on analyzing not only the length of time spent in a health state but the quality of life, or utility, associated with that state. This implies that time spent in a "sick" state is worth less than time spent in a perfect health state. Quantification of this level of sickness and the prorating of years of life spent in illness (compared to perfect health) enables a decision analysis to best quantify survival and standardize quality of life in order to more accurately compare medical interventions (44).

The quality adjusted life year (QALY) is the most commonly used standard measure of quality of life and is immediately scalable for use in decision analysis models. One QALY is equal to one year of life spent in perfect health. A year of life spent in less than perfect health is worth less than one QALY with zero generally being the minimum associated with death. Several techniques have been validated for measuring quality of life and utility but it is generally accepted that a patient's self-rating of his/her current health state is the most accurate way to assess the true quality of life of a health state (45). It has also been demonstrated that caretakers and health care providers substantially underrate the quality of life associated with a specific health state compared to patients who have experienced that health state (46). Several authors have reported health state utilities associated with chronic liver disease and liver transplantation derived by standardized and validated methods (47-54). Table 3 lists the utility

values for the health states in the model and specific event related utility tolls, or penalties, for adverse events in the model.

Donor Complications and Costs

Previously published models of LDLT have not adequately accounted for donor morbidity, mortality, or costs (33, 34). Evidence from the literature indicates that prospective donors are frequently disqualified from the donation process following discovery of pre-existing medical conditions, tissue incompatibilities, or by their eventual unwillingness to participate (55, 56). Donor death or serious morbidity could significantly affect the overall utility and costs of the LDLT process. The probability of these events is uncertain, but is becoming clearer as the published literature on donor complications expands (57-61).

In consideration of these issues the model in this study meticulously accounts for donor complications. The model assumes that all donors enter the simulation in a state of perfect health. For each recipient of an LDLT, 1.5 prospective donors are evaluated. This accounts for the extra cost of evaluating donors that are eventually deemed ineligible (55, 56). Variables were introduced into the model in order to account for differential rates of major complications between LDLT and DDLT and the various costs associated with these complications. The death rates and major complication rates for donors were extracted from the literature. Donor deaths incur a penalty of 1.0 utility points per month for the remainder of the simulation. Donor severe complications incur a

penalty of 0.30 utility points per month for the remainder of the simulation. This is based upon the documented health utility after complications from major surgery (62). Donor utility penalties continue to accrue for the remainder of the simulation in order to account for the loss of life for the donor who has died or of the quality of life for donors who suffer a major complication.

Sensitivity Analysis

The cost-effectiveness analysis results were assessed for sensitivity to each of the individual estimated probabilities, costs, and utilities in the model. Tables 1-3 list the range of minimum and maximum values considered for each estimated component in the model. Components of the model that were potentially related to each other and/or that were found to individually influence the cost-effectiveness analysis results were subsequently used in a two-way sensitivity analysis, where both factors were allowed to simultaneously vary to determine the joint influence on the model outcomes.

Additional Model Assumptions

To account for inflation, all costs are represented in year 2002 U.S. dollars. All utilities and costs are discounted by 3% yearly in order to account for the decreased present value of future costs and benefits (63). Risk aversion was not modeled because of the high likelihood of recipient death without intervention and the resulting theoretical minimal effect of risk aversion on transplant utilities.

Most specific assumptions involved in the model design are noted in Tables 1-3. Other general assumptions are as follows:

- All members enter the model eligible for transplantation and members in the LDLT branch have a willing donor ready to be evaluated.
- Approximately 75% or LDLT and 25% of DDLT recipients will undergo ERCP after transplantation (64).
- In recipients that undergo ERCP for biliary complications, the median number of procedures required is 2 (64).
- All recipients undergoing retransplantation for PNF within the first 30 days after initial transplantation receive a DDLT as the retransplant. All members with PNF not receiving retransplant die.
- Aside from specific event tolls, retransplantation costs are equivalent to initial transplantation costs.
- Members can receive more than one TIPS procedure. This helps account for revisions and TIPS while awaiting retransplantation.
- Members in the compensated state are 50% less likely to receive transplantation than those in decompensated states.
- The baseline health utility value of all post-transplant complications is equal, prior to tolls taken for specific events.
- Acute hepatic artery thrombosis (HAT) is accounted for in the “PNF” bracket. HAT occurring after 30 days is accounted for in the “disease recurrence” bracket.

Software

Data for Healthcare©, version 3.5 (TreeAge Software, Williamstown, MA) was used for computer assisted calculations and modeling and SAS©, version 8.0 (Cary, NC) was used for advanced statistical analysis and dataset manipulation.

Institutional Review Board Approval

The University of Virginia Human Investigations Committee reviewed and approved the use of the existing data obtained and original data collected for this study.

Results

Model Validation and Unadjusted Recipient Survival

Table 4 lists results from the Monte Carlo simulation of the Markov process decision model, with mean cost per patients, mean lifespan, number of transplants, and number of deaths estimated for each treatment strategy. Recipient deaths within 10 years were estimated to occur for 95.0% of patients with no transplant available, and for 50.8% of patients with access to the combined DDLT or LDLT. The main factor influencing the increasing survival was fewer deaths in the pre-transplant phase secondary to complications of cirrhosis. Post-transplant survival rates for DDLT (442 of 670, 66.0%) and LDLT (345 or 726, 47.5%) were comparable to reported 10-year survival rates in the literature. The lower rate of 10-year survival among the LDLT members occurred because the majority of LDLT patients were transplanted early in the course of the simulation, most within the first year, and therefore were susceptible to post-transplant complications for longer time periods than the DDLT members. This differential survival was most related to the chance of recurrent disease in the LDLT-only versus DDLT-only strategy (see Sensitivity Analysis). The 10-year survival rate for patients with no access to transplantation (5.0%) was comparable to that reported in the literature for end-stage liver disease. The LDLT-only simulation yielded 6 donor deaths (0.8%) and 84 major complications in donors (11.6%). The maximum survival was attained in the combined DDLT/LDLT treatment branch. In this branch there were 527 LDLT and 305

DDLT procedures with 138 patients (13.8%) dying prior to transplant and 370 patients (44.4%) dying after transplantation. This treatment branch terminated at 10 years with 30 patients still awaiting transplantation.

Figures 6 and 7 plot the monthly distribution of members in each of the six health states for each month during the 10-year simulation cycle. Figure 6 shows that the number of members waiting for transplantation in the DDLT-only treatment arm steadily decreases, with the most rapid drop in the first three years. In this treatment arm, after 26 months, 56% of the cohort has received DDLT, 11% continues on the waiting list, and 33% has died or developed a contraindication to transplantation. In contrast, in the combined DDLT/LDLT treatment arm shown in Figure 7, the number of members waiting for transplantation drops precipitously within the first year. At 26 months in this treatment arm, 46% has received LDLT, 26% has received DDLT, 3% remains on the waiting list, and 25% has died or developed a contraindication to transplantation. The major contributor to the increased five-year survival rate in the combined DDLT/LDLT treatment arm when compared to the DDLT-only treatment arm is the increased survival in the pre-transplant phase attributable to the decreased number of patients dying on the waiting list. The DDLT-only treatment arm had a 30.6% mortality rate on waiting list while the combined DDLT/LDLT treatment arm had 13.8% waitlist mortality. This yielded a relative risk of mortality of 2.22 in the DDLT-only group compared to the combined

DDLT/LDLT group and a number needed to treat of 6.0 to prevent one waitlist death.

Costs, Utility, and Cost-Effectiveness Analysis

Cost-effectiveness analysis results for the baseline case are summarized in Table 5 for each treatment strategy. Per person costs for the DDLT-only member cohort were $104,000 more than non-transplant care. Costs for LDLT-only were $23,000 higher than for DDLT-only, and the combined DDLT/LDLT approach was $41,000 more expensive than DDLT-only. Paradoxically, the increased cost of the combined DDLT/LDLT strategy was due to fewer waitlist deaths and thus more ongoing expenses in the survivors.

Effectiveness is reported as quality-adjusted life years. The “no transplant” strategy offered a quality-adjusted expected survival of 2.0 QALY’s, DDLT-only 4.1 QALY’s, and the LDLT-only strategy 3.8 QALY survival. This decreased adjusted survival in the LDLT group was directly related to donor death and morbidity. The combined DDLT/LDLT strategy resulted in 4.4 QALY expected survival, which was only 0.3 QALY more than the DDLT-only strategy.

Cost-effectiveness ratios are reported in dollars per QALY. The reference condition treatment arm of LDLT-only was dominated by the other treatment strategies, as it was both more expensive and less efficacious than the other treatments, because this alternative had both increased cost and decreased effectiveness due to the cost and morbidity of donor complications. The

combined DDLT/LDLT strategy yielded the highest cost per QALY. The incremental cost (ICER) of moving from the DDLT-only strategy to the combined DDLT/LDLT strategy was approximately $129,000 per QALY.

Sensitivity Analysis

Sensitivity analysis was performed on all variables in the model. However, only the most pertinent U.S. treatment strategies were included in the final calculation of cost-effectiveness: DDLT-only and combined DDLT/LDLT. The overall model was sensitive to the pre-transplant complications of liver disease, especially the probabilities of acute variceal bleeding, hepatocellular carcinoma, and hepatic encephalopathy, and their corresponding death rates. Repeated analysis using extreme estimates for each of these variables did not change the preferred treatment strategy with respect to cost-effectiveness. Quality-adjusted survival was highly sensitive to the post transplant probability of recurrent disease causing graft failure in LDLT recipients.

Figure 8 plots the relationship between the monthly probability of disease recurrence and adjusted survival for DDLT-only and for combined DDLT/LDLT. Combined DDLT/LDLT treatment is the preferred strategy until the post-LDLT recurrence rates exceeds 0.0088 per month, or approximately 11% per year. After this point, the DDLT-only strategy offers longer expected adjusted survival. The probability of donor death after LDLT was another important influence on adjusted survival in the model. This reflects the penalty on overall utility in the

model accrued after the death of a living donor. Figure 9 shows that the combined DDLT/LDLT strategy was preferred until the donor death rate exceeded 6.7%, after which DDLT-only became preferred. Donor morbidity had little effect on overall adjusted survival and quality of life.

Because of the very high costs associated with the DDLT and LDLT procedures, both of these variables were important in the sensitivity analysis with cost-effectiveness as the outcome. Figure 10 shows the one-way sensitivity analysis on the cost of the DDLT procedure compared to the LDLT procedure with cost-effectiveness as the outcome. This figure shows that when the cost of the DDLT procedure exceeds $152,000 dollars, LDLT becomes the most cost effective procedure. As stated in Table 1, these costs include the average costs associated with DDLT organ acquisition as well as the DDLT procedure and associated hospital stay. LDLT procedure costs include the costs of uncomplicated partial organ allocation from the living donor as well as the recipient procedure and both recipient and donor hospital stays. Two-way sensitivity analysis results comparing cost of the DDLT procedure versus the cost of the LDLT procedure are presented in Figure 11. This analysis indicates that comparably low LDLT costs are required to make combined DDLT/LDLT more cost effective than DDLT-only over all ranges of DDLT costs.

Waiting time determined whether cohort members received DDLT or LDLT. A mean DDLT waiting time of approximately four months was required to make adjusted survival and quality of life equal between those waiting for DDLT

and those waiting for LDLT. In a repeated cost-effectiveness analysis with a mean waiting time for DDLT of four months, the combined DDLT/LDLT strategy became dominated by the DDLT-only strategy with an ICER for the DDLT-only treatment arm of approximately $47,000.

Discussion

This study measures the cost-effectiveness of LDLT combined with the existing standard of care DDLT strategy for the treatment of end-stage liver disease using a Markov process decision model to simulate the major events that occur before, during, and after both living and deceased donor liver transplantation. To the author's knowledge, this is the first decision analysis model involving living liver donors that accounts specifically for the costs related to workup of potential donors that are eventually deemed ineligible for donation, the real impact of donor mortality and morbidity on costs, and the effect on quality adjusted survival and quality of life related to donor complications. The course of chronic liver disease and liver transplantation simulated by the model closely approximates to the course of events reported in the literature. Event probabilities, cost, and utility data were collected from UNOS transplant registry when possible, from the literature, or from estimates based on expert opinion, and from unpublished data from upcoming clinical trials. Because of its completeness and competing risks design, we feel that this model offers the closest possibility of an "intention to treat analysis" using liver transplantation as the medical intervention. The model was designed to be flexible enough to account for theoretical treatments such as "no transplant available" and "LDLT-only". With continuous updates based on the latest literature and results from clinical trials, we believe that this model can be used to simulate and analyze

many different interventions in the treatment of chronic liver disease and liver transplantation that cannot be analyzed through the use of randomized, controlled trials.

We found that liver transplantation is an expensive but effective treatment for end-stage liver disease and cirrhosis. The ICER for the standard-of-care DDLT-only approach was nearly $50,000. While more effective, mostly due to less time spent waiting for transplantation, addition of LDLT to the DDLT approach was an expensive alternative. The ICER of the DDLT/LDLT combined strategy was nearly $130,000. Interpretation of an ICER based on a simulation is by definition a subjective matter and is influenced by societal willingness to pay and by the validity of the model and its assumptions (65). Previously reported ICER for routinely performed medical interventions in the U.S. include $86,362 for screening for colorectal cancer in people over age 65 (66), between $8,000 and $900,000 (depending on age and type of drug used) for treatment of hypertension (67, 68), and $112,000 for screening for HCC in cirrhosis patients with ultrasound and alpha fetoprotein (69). In contrast, the traditional willingness to pay benchmark in the U.S. is based on the cost of chronic ambulatory hemodialysis (70-72). While an ICER of less than $50,000 has been traditionally accepted as a cost-effective addition to the medical system in the U.S., some authors have argued that based on the different economic calculations and assumptions used, a cost-effective medical intervention could range from as low as $24,000 to as high as $428,000 per QALY (73). In fact, if cost-effectiveness

values associated with hemodialysis derived from studies in the late 1980's are adjusted for year 2004 USD, an ICER of $75,000 may be a more proper benchmark for modern cost-effectiveness analyses.

All clinicians have empirically learned that benefits and costs attributed to society often do not directly apply to individual patient care. Therefore, it is clear that society, third party payers, and the governments involved must decide how much cost is acceptable for a medical intervention today considering the growing opportunity costs for high price medical services. While this study showed the range of costs and benefits available through the use of LDLT and DDLT, it is also clear that society has a low threshold for complications related to healthy donor death. This was vividly demonstrated in the decreasing numbers of LDLT procedures performed in the U.S. in the years subsequent to a single highly publicized donor death at a busy and prestigious transplant center in 2001 (74). While the model in this study showed that the effectiveness of LDLT was preserved until donor death rates exceeded 6.7%, this model assumed only a third party payer point of view and cannot account for legal, political, indirect, and intangible costs associated with donor death. Clearly, these societal costs could dwarf any system-wide medical benefits achieved in the proper setting.

In this and all previously published models of LDLT, the time spent on the waiting list was critical in the determination of the most cost-effective treatment. In this simulation, we used DDLT transplant rates based upon the actual transplant waiting lists in the U.S. as defined by the UNOS STAR dataset and

LDLT rates based upon the latest information from recently presented clinical cohort studies (75). Despite recent organ allocation changes in the U.S., average waiting times on the transplant list have changed only small amounts over past few years. With more than three people on the waiting list for each transplantation, it is unlikely in the near future that waiting times for the average cirrhosis patient will decrease. However, our model demonstrated a distinct dependence on the complications of chronic liver disease and their corresponding death rates. In fact, decreasing the rates, severities, and costs of the complications of cirrhosis uniformly increased the cost-effectiveness of both LDLT and DDLT. Continued research focus should be maintained to advance the treatment of disabling complications such as acute variceal bleeding, refractory ascites, and hepatic encephalopathy. Even moderate improvements in the treatment of chronic liver disease could have vast impacts on the future of liver transplantation. Increased prevention efforts including universal access to viral hepatitis vaccines, alcohol education and dependence counseling, and chemoprophylaxis could change the prevalence of chronic liver disease and prevent more real-world patients from the need for liver transplantation.

Aside from the actual costs of the transplantation procedures, the main recipient post-transplant event that hindered cost-effectiveness was the recurrence of disease in the transplanted graft. As most liver transplants in the world are performed for hepatitis C, disease recurrence is a frequent and difficult problem. Costs in quality of life and survival are high with disease recurrence

causing graft failure because often the only treatment outcomes are retransplantation or death from recurrent chronic liver disease. Even more concerning for LDLT is the recent data suggesting an increase in rates of post-transplant disease recurrence over that expected for DDLT (76-80). This increased recurrence rate in LDLT is represented in the model and had a significant effect on decreasing the cost effectiveness of LDLT compared to DDLT. While criticism of the literature claiming increased disease recurrence rates in LDLT has focused on selection bias for hepatitis C and HCC in the early LDLT cohorts, if this finding proves to be true it could greatly hinder the clinical effectiveness of LDLT when used for these diseases. Further research in the area of graft disease recurrence and prevention in all disease processes is clearly needed. It is also of interest that the well documented increased rate of recipient biliary complications did not strongly influence the overall cost effectiveness of LDLT.

All cost-effectiveness studies based on modeling have some inherent weaknesses. Ultimately, the quality of the model output and its resulting analysis is dependent on the quality of the model, its approximation of reality, and its probabilities, utilities, and costs used for the calculations. In the design of the current model, we have taken extreme care in designing a model that is flexible yet adequately represents most of the major events in chronic liver disease and liver transplantation. While quite complex, the model is an approximation of reality and cannot truly represent all the possible outcomes in this complicated

disease process. We have based the probabilities and health state utilities on the best available data from the literature or, when available, directly on large sample size estimations based on actual transplant data from the UNOS STAR dataset. We agree that much of the reported literature may be biased in one way or another but we have attempted to represent average reported values and used wide ranges in the sensitivity analysis when the literature was insufficient or weak. Cost data was center specific and this inherent weakness was unavoidable in this study. Using strong micro-costing algorithms and averaging several years' adjusted costs minimized this inherent weakness. The wide range of all costs (50-200%) used in the sensitivity analysis also helped guard against inaccurate cost data. In the analysis, the costs yielded from this model are consistent with other published cost data in the literature. Finally, when no published data was available, expert opinion and unpublished data was used but these occurrences were few and the following sensitivity analyses were conducted over a broad range.

Critics of cost-effectiveness modeling have traditionally scoffed at placing a monetary value on a year of life. Despite the relatively recent utilization of this principle in medical research, economists have for years used mathematics and subjective measurements in attempts to simulate reality and investigate the impact of policy change on quality of life and economic survival. The reader of medical cost-effectiveness analyses should accept them as another tool in health services research that can be used to guide policy analysis and illuminate areas

where further research is needed. Costs per quality adjusted life year should not be interpreted as a bounty or payoff for a year of life, but should only be understood as a standardized tool useful in comparing medical interventions and diseases with significantly different outcomes and impacts on the quality of survival. Future medical research will only encompass more decision analysis and cost accounting techniques and the savvy reader of the medical research literature will need to be familiar with the strengths and weaknesses of these health service research techniques.

In summary, this study presents a complex cost-effectiveness model simulating chronic liver disease and cirrhosis with treatment options including the standard of care DDLT-only and the DDLT/LDLT combination. Considering living donor costs, morbidity, mortality, and quality of life, this is the first model to accurately account for the true consequences to the donor in the LDLT treatment strategy. When using traditionally defined standards of cost-effectiveness, DDLT-only proved to be a cost-effective treatment for cirrhosis with an ICER of approximately $50,000 per QALY. However, LDLT in combination with DDLT, proved to be more effective but much more expensive than the DDLT-only strategy per QALY saved with an ICER of approximately $149,000. The sensitivity analysis showed that much of the increased cost of LDLT was due to donor complications and deaths as well as post transplant recipient disease recurrence. This study, along with the decision analysis model, should be a

useful tool for policymakers and transplant centers in allocating resources and guiding further investigation into the field of cirrhosis and liver transplantation.

Acknowledgements

The author would like to thank everyone responsible for making this project the successful endeavor that it became. Carl L. Berg, my clinical mentor, was incredibly helpful in his early insight into the need for a cost-effectiveness analysis in this field and his guidance in the formative stages was invaluable. Similarly, Kristen O. Arseneau was extremely helpful and patient in her early help and coaching in model design and debugging. I would also like to thank George J. Stukenborg, my HES mentor, who was always available and ready with important advice on designing the model, performing the complex analysis, and answering difficult questions with ease. Without his guidance this project would not have been possible. I also want to give much appreciation also to Vanessa D. Lee who labored tirelessly during her internship with the primary data collection. Sara Taranto at UNOS was critical in helping me obtain the data I needed from UNOS and was always willing to work with me. I am indebted to all the above and many more for helping make this work a reality.

Table 1: Event probabilities, ranges, and sources.

	Base Case Probability	Probability Range	Sources
Pretransplantation			
Monthly probability of symptomatic ascites	0.058	0.028-0.079	(36, 81, 82)
Probability of receiving TIPS for ascites or bleeding	0.048	0.02-0.097	(36, 81, 83)
Probability of death related to TIPS procedure or complication	0.03	0.026-0.053	(81, 83)
Probability of contracting SBP in patients with symptomatic ascites	0.204	0.080-0.300	(81, 84-87)
Probability of death from an episode of SBP	0.100	0.080-0.180	(81, 84, 86-88)
Monthly probability of having encephalopathy requiring treatment	0.070	0.018-0.135	(36, 89)
Probability of death from an episode of encephalopathy	0.115	0.045-0.185	(90, 91)
Monthly probability of developing HCC	0.030	0.005-0.069	(36, 92)
Probability of developing contraindication to transplantation with HCC	0.217	0.081-0.354	(36, 93)
Probability of death with HCC	0.097	0.025-0.157	(36, 93)
Monthly probability of variceal hemorrhage	0.064	0.011-0.120	(36, 94-96)

Probability of death from an episode of variceal hemorrhage	0.142	0.012-0.356	(95-97)
Monthly probability of remaining stable, without complications	0.04	0.008-0.083	(98)
Monthly probability of death once a contraindication to transplant has occurred	0.067	0.010-0.150	(99-102)
Monthly probability of receiving a LDLT	Table		(75) and expert opinion
Average monthly probability of receiving a DDLT	0.0625	0.025-0.12	(36)
Post DDLT			
Probability of DDLT recipient death within 30 days of transplant	0.039	0.0157-0.0720	(36, 103, 104)
Probability of DDLT graft pnf requiring retransplantation	0.0372	0.009-0.062	(36, 103, 104)
Probability of death within 30 days after DDLT while awaiting retransplantation	0.3618	0.33-0.57	(15, 36, 105, 106)
Monthly probability of severe disease recurrence after DDLT	0.002	0.001-0.018	(36)
Probability of retransplantation for severe disease recurrence after DDLT	0.015	0.007-0.030	(36)
Monthly probability of sepsis from non-biliary infection after DDLT	0.003	0.001-0.0113	(107-109)
Probability of death from a sepsis event after DDLT	0.240	0.140-0.400	(107-109)
Monthly probability of needing non-transplant reoperation more than 30 days after DDLT	0.0025	0.001-0.080	(110)

Probability of death after non-transplant reoperation after DDLT	0.105	0.050-0.200	(110)
Monthly probability of biliary complications after DDLT	0.007	0.001-0.028	(64, 111-114)
Probability of death from biliary complications after DDLT	0.034	0.004-0.070	(64, 111, 112, 115)
Probability of receiving retransplantation due to biliary complications after DDLT	0.031	0.011-0.085	(113, 116, 117)
Probability of requiring non-transplant, non-endoscopic reoperation after DDLT because of biliary complications	0.053	0.011-0.150	(64, 111, 113, 118)
Monthly probability of acute rejection severe enough for hospitalization after DDLT	0.010	0.003-0.050	(21, 119, 120)
Probability of death from an episode of acute rejection after DDLT	0.0016	0.00002-0.003	(120)
Probability of requiring retransplantation because of severe acute rejection after DDLT	0.005	0.0003-0.010	(120)
Post LDLT			
Probability of donor death after LDLT procedure	0.0028	0.0012-0.0100	(57-61)
Probability of donor having major complications after LDLT procedure	0.12	0.03-0.19	(58-60, 121-125)
Probability of LDLT recipient death within 30 days of transplant	0.029	0.010-0.040	(36, 126)
Probability of LDLT graft PNF requiring retransplantation	0.045	0.030-0.060	(36, 127)
Probability of death within 30 days after LDLT while awaiting retransplantation	0.3618	0.33-0.57	(15, 36, 105, 106)

Monthly probability of severe disease recurrence after LDLT	0.004	0.001-0.018	(76-80)
Probability of retransplantation for severe disease recurrence after LDLT	0.025	0.010-0.060	(36)
Monthly probability of recipient sepsis from non-biliary infection after LDLT	0.003	0.001-0.0113	(107-109)
Probability of recipient death from a sepsis event after LDLT	0.240	0.140-0.400	(107-109)
Monthly probability of recipient requiring non-transplant reoperation after LDLT	0.0028	0.0011-0.080	(57, 122)
Probability of recipient death after non-transplant reoperation after LDLT	0.105	0.050-0.200	(110)
Monthly probability of recipient biliary complications after LDLT	0.015	0.001-0.040	(57, 64, 118, 126, 128, 129)
Probability of recipient death from biliary complications after LDLT	0.034	0.004-0.0070	(64, 111, 112, 118, 126, 128, 129)
Probability of getting retransplantation due to biliary complications after LDLT	0.031	0.011-0.085	(64, 111, 112, 126, 128, 129)
Probability of recipient requiring non-transplant, non-endoscopic reoperation after LDLT because of biliary complications	0.053	0.011-0.150	(64, 126, 128, 129)
Monthly probability of having acute rejection severe enough for hospitalization after LDLT	0.010	0.003-0.050	(21, 80, 119, 120, 130)
Probability of death from an episode of acute rejection after LDLT	0.0016	0.00002-0.003	(21, 80, 120, 130)
Probability of requiring retransplantation because of severe acute rejection after LDLT	0.025	0.01-0.06	(21, 80, 120, 130)

Table 2: Cost data used in model. All costs are reported in year 2002 adjusted U.S. dollars.

	Monthly Costs	Monthly Cost Range*
Baseline Health State Costs		
Baseline average monthly outpatient costs for patient with compensated cirrhosis	63	31-126
Baseline average monthly costs for patients with permanent contraindication to transplant	777	389-1554
Baseline average monthly costs for recipients post transplantation	772	386-1544
Cost Tolls for Specific Events		
Average cost of TIPS procedure. Includes revisions, complications, hospitalizations, imaging, and outpatient follow-up	18,192	9,096-36,384
Average cost of having had SBP. Includes treatment, hospitalization, complications, and imaging	10,248	5,124-20,496
Average monthly cost of medically controlled symptomatic ascites. Includes admissions, treatment costs, and procedures.	516	258-1,033
Average monthly cost of clinical encephalopathy. Includes treatments, outpatient visits, and hospitalizations.	358	179-716

Average monthly cost of HCC. Includes imaging, procedures, and follow-up	313	156-626
Average monthly cost of clinically significant variceal bleeding. Includes hospitalization, procedures, and follow-up	997	499-1,994
One-time cost of DDLT procedure. Includes deceased donor expenses, hospitalization, and pharmacy (131).	103,806	51,903-207,612
One-time cost of LDLT procedure. Includes workup costs for 1.5 potential donors (55, 56), donor procedure without complications, hospitalization, and pharmacy (131).	129,144	64,572-258,288
One-time cost for donor having major complications. Includes hospitalization, procedures, pharmacy, and follow-up.	16,892	8,446-33,784
One-time cost for donor death. Estimated at 75% of the cost of a major complication.	12,669	6,335-25,338
One-time cost for recurrent disease causing graft failure. This is only applied to patients not eligible for re-transplantation. Based on costs incurred for care when transplant is contraindicated.	4,662	2,331-9,324
Average monthly cost for post-transplant patients with serious non-biliary infectious complications. Includes hospitalization, imaging, pharmacy, and follow-up.	2,139	1,070-4,280
Average monthly cost for post transplant recipients that require non-transplant re-operation. Based on the cost of laparotomy.	2,034	1,017-4,067
Average monthly cost for post-transplant patients with clinically significant biliary complications. Includes cost associated with hepatic artery thrombosis, biliary strictures, and 2 ERCP's. (64)	618	309-1,236
One-time cost of post-transplant recipients that require non-transplant reoperation for biliary complication. Does not include ERCP costs. Based on the cost of laparotomy.	18,607	9,303-37,214

Average monthly cost of post-transplant treatment of acute rejection. Includes hospitalization, procedures, pharmacy, and follow-up.	2,019	1,010-4,038

* Ranges are derived as 50% and 200% of calculated costs.

Table 3: Utility data used in the model.

	Base Case Utility	Utility Range	Sources
Baseline Health State Utilities			
Utility of compensated cirrhosis (Childs B)	0.71	0.44-0.98	(47-54)
Utility of decompensated cirrhosis (Childs C)	0.56	0.30-0.67	(47-54)
Utility of recipient post liver transplantation	0.80	0.63-0.87	(48, 50, 52, 54, 132)
Utility penalty accrued every month after transplant when donor dies secondary to donation complication. Donors are assumed to be in perfect health before donation.	Recipient utility – 1.0	0.75-1.0	Expert opinion
Utility penalty accrued every month after transplant when donor has major complications secondary to donation complication (133). Donors are assumed to be in perfect health before donation.	Recipient utility – 0.3	0.25-1.0	Expert opinion

Utility Tolls for Specific Events	**Percent Toll From Baseline**		
Monthly utility penalty for refractory ascites	-25%	0-80%	(51)
One-time utility penalty from TIPS	-25%	0-80%	(49)
One-time utility penalty for SBP. Based on utility for refractory ascites.	-25%	0-80%	(51)
Monthly utility penalty for HCC	-10%	0-50%	(48, 50, 51)
Monthly utility penalty for encephalopathy	-25%	0-80%	(49, 51)
Monthly utility penalty for variceal bleeding	-25%	0-80%	(49, 51)
One-time utility penalty for recent major surgery	-20%	0-80%	(62)

Monthly utility penalty for major complication of transplantation	-25%	0-80%	(48, 50, 52, 54, 132)
One-time utility penalty for undergoing DDLT	-50%	25-75%	(48, 50, 52, 54, 132)
One-time utility penalty for undergoing LDLT. Includes combined donor and recipient penalties	-75%	25-90%	(48, 50, 52, 54, 132) and expert opinion

Table 4: Model validation and survival data. Results from a 120-month Monte Carlo simulation of 1,000 theoretical patients with base case values for all variables.

Variable	No transplant available	DDLT only	LDLT only	DDLT and LDLT available
Mean cost per patient (year 2002 USD)	15,903	116,378	143,467	160,719
Mean lifespan (months)	40.7	73.5	69.2	80.2
Number receiving DDLT	-	670	-	305
Number receiving LDLT	-	-	726	527
Number dead after 10 years	950	534	637	508
Number dead pre-transplant	950	306	256	138
Number (% of patients transplanted) dead post-transplant	-	228 (34.0)	381 (52.4)	370(44.4)

Table 5: Results of the cost-effectiveness analysis. Dominated strategies are both more costly and less effective than alternative treatments. Expected costs are those expected for someone entering the treatment strategy arm, including all outcomes and complications in year 2002 USD. Effectiveness is expressed in quality-adjusted life years.

Treatment Strategy	Expected Cost	Marginal Cost	Effect.	Marginal Effect.	C/E Ratio	Incremental C/E Ratio
No Transplant	$17,000	-	2.0	-	$8,430	-
DDLT-Only	$121,000	$104,000	4.1	2.1	$29,512	$49,920
LDLT-Only	$143,000	$23,000	3.8	-0.3	$37,223	(Dominated)
DDLT/LDLT	$162,000	$41,000	4.4	0.3	$36,679	$129,474

Figure 1: The basic health states of the Markov model.

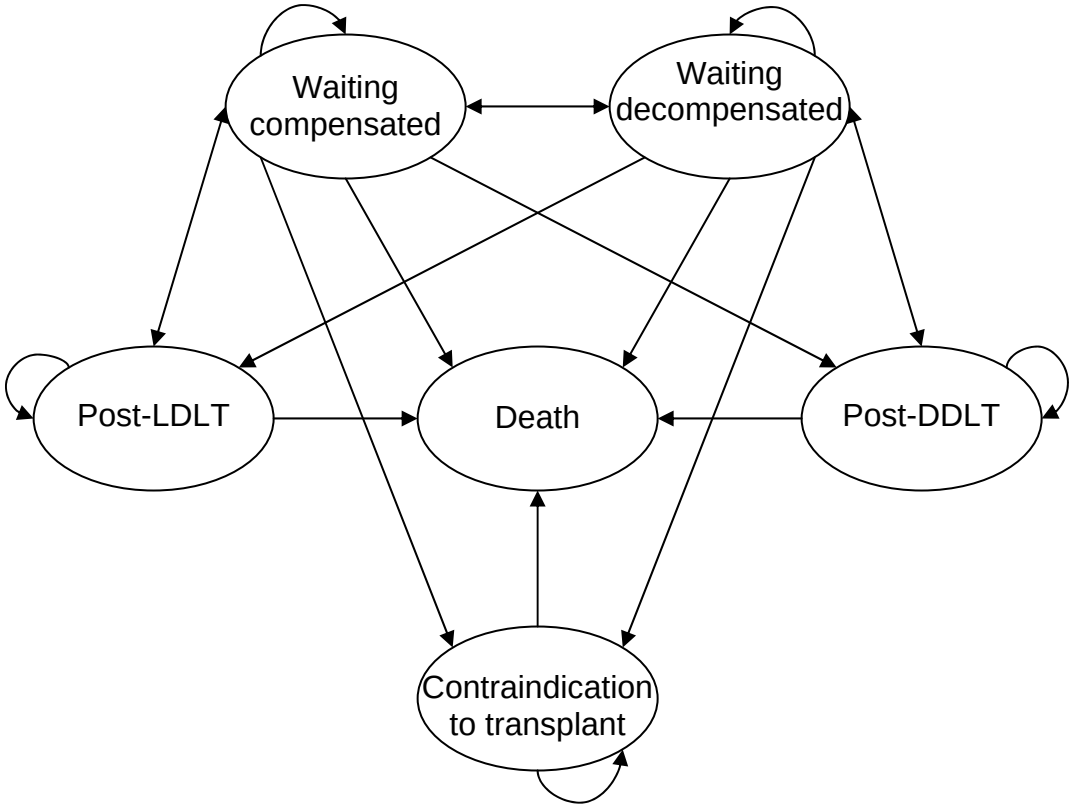


Figure 2: Simplified pre-transplant complication event tree

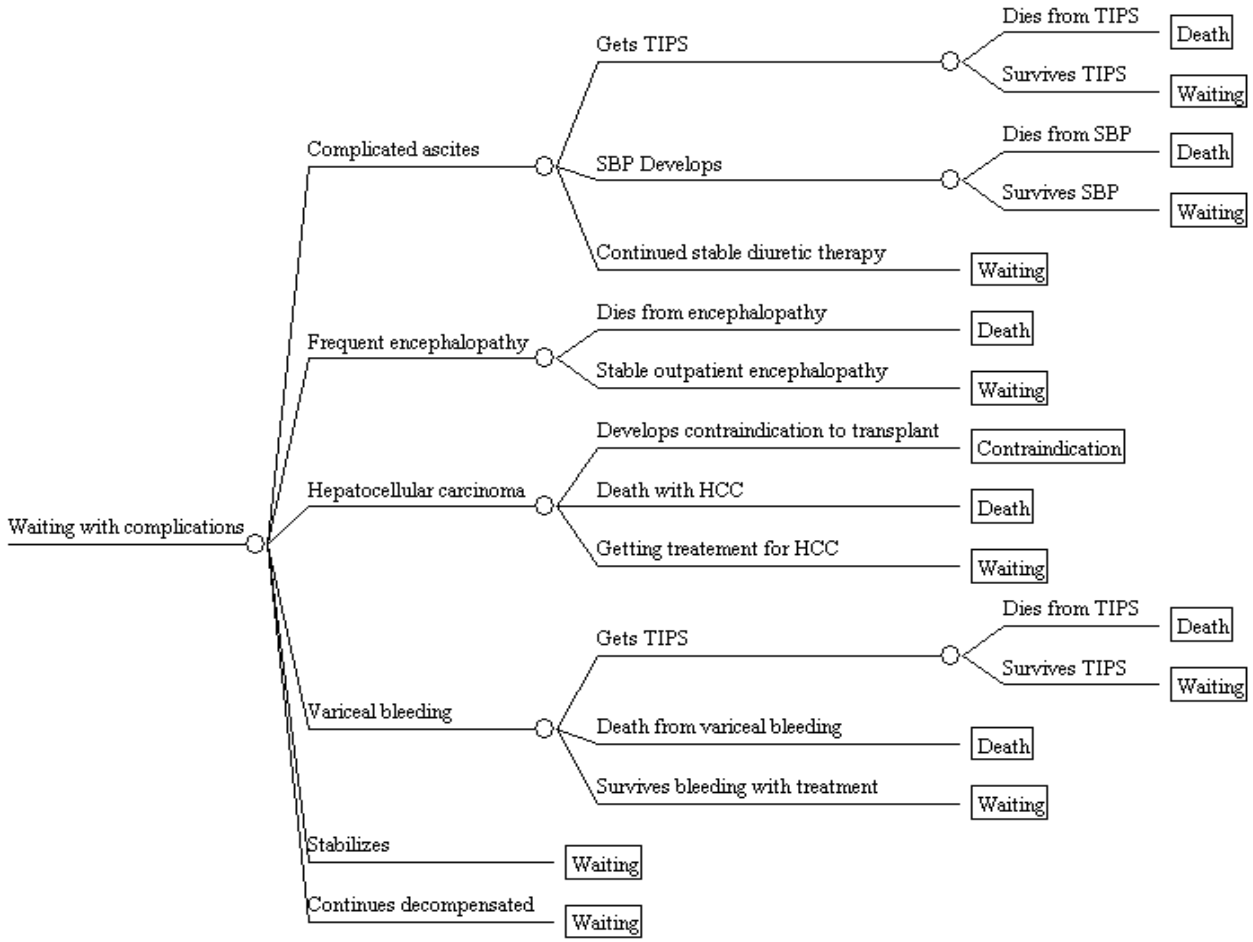


Figure 3: Simplified transplantation event tree

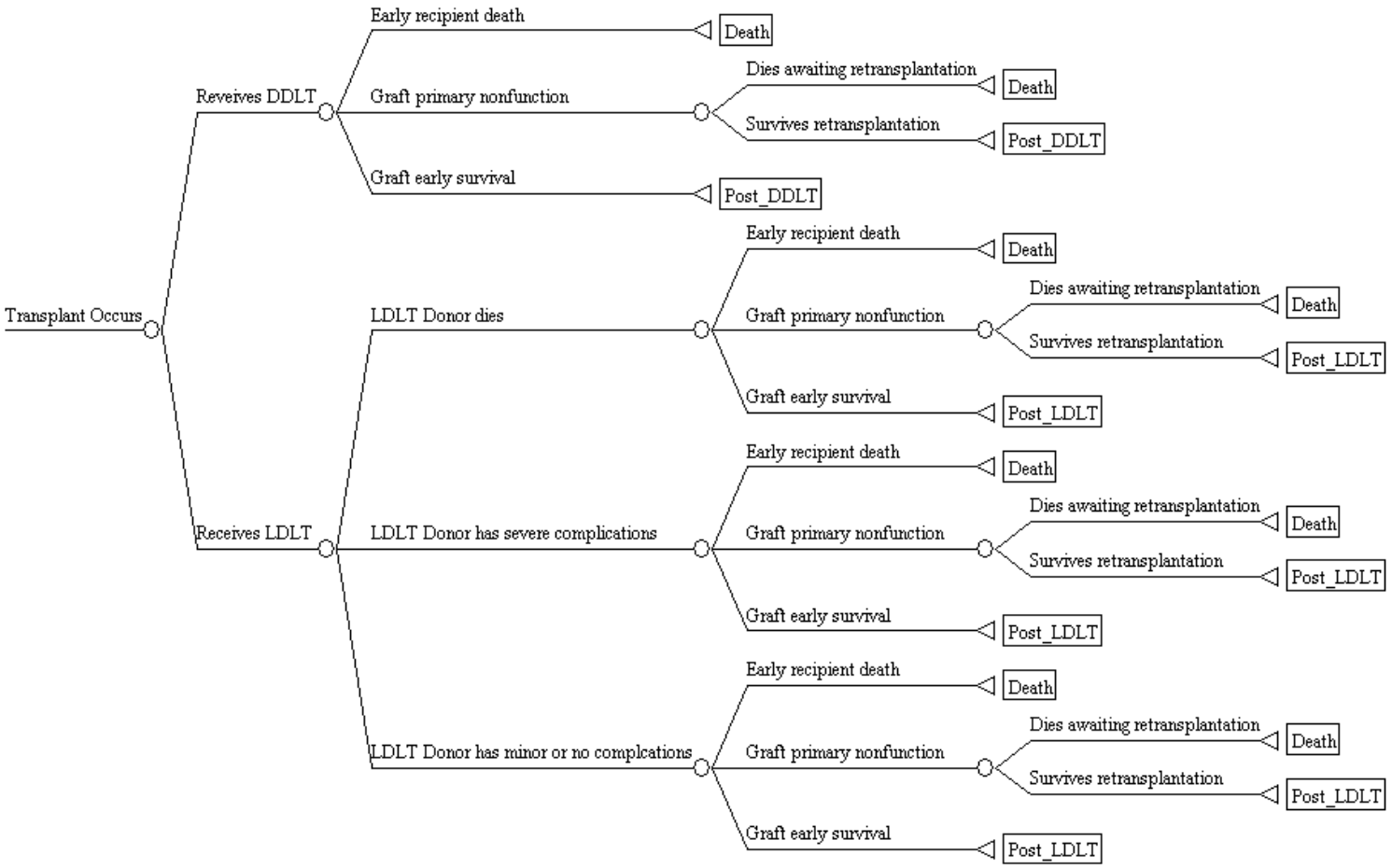


Figure 4: Simplified post-transplantation event tree

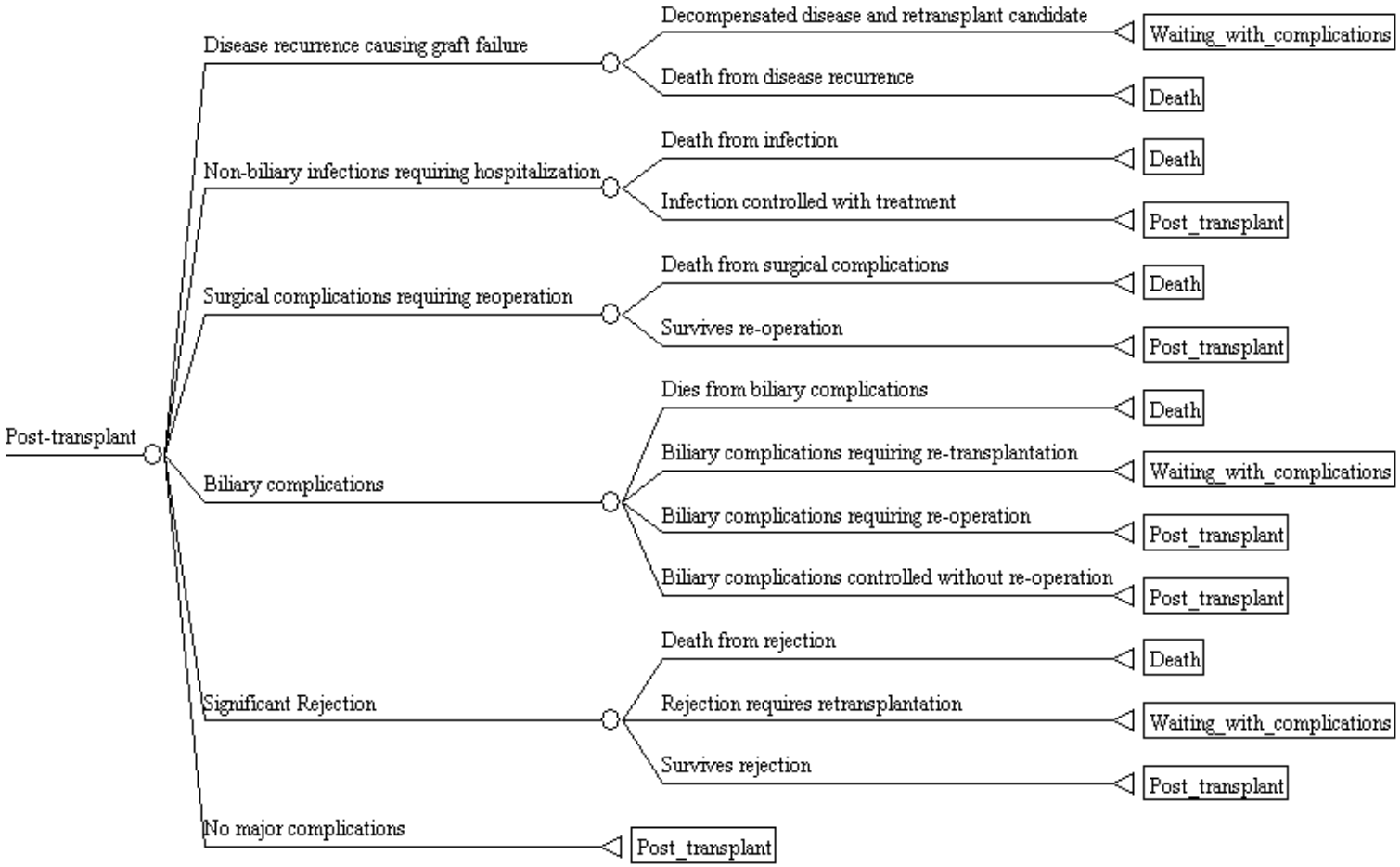


Figure 5: Monthly transplantation rates used in the model simulation. DDLT rates are based on average monthly waitlist transplantations reported by UNOS in the STAR dataset. LDLT rates are based on expert opinion and local experience. After 24 months, rates of LDLT and DDLT remained constant.

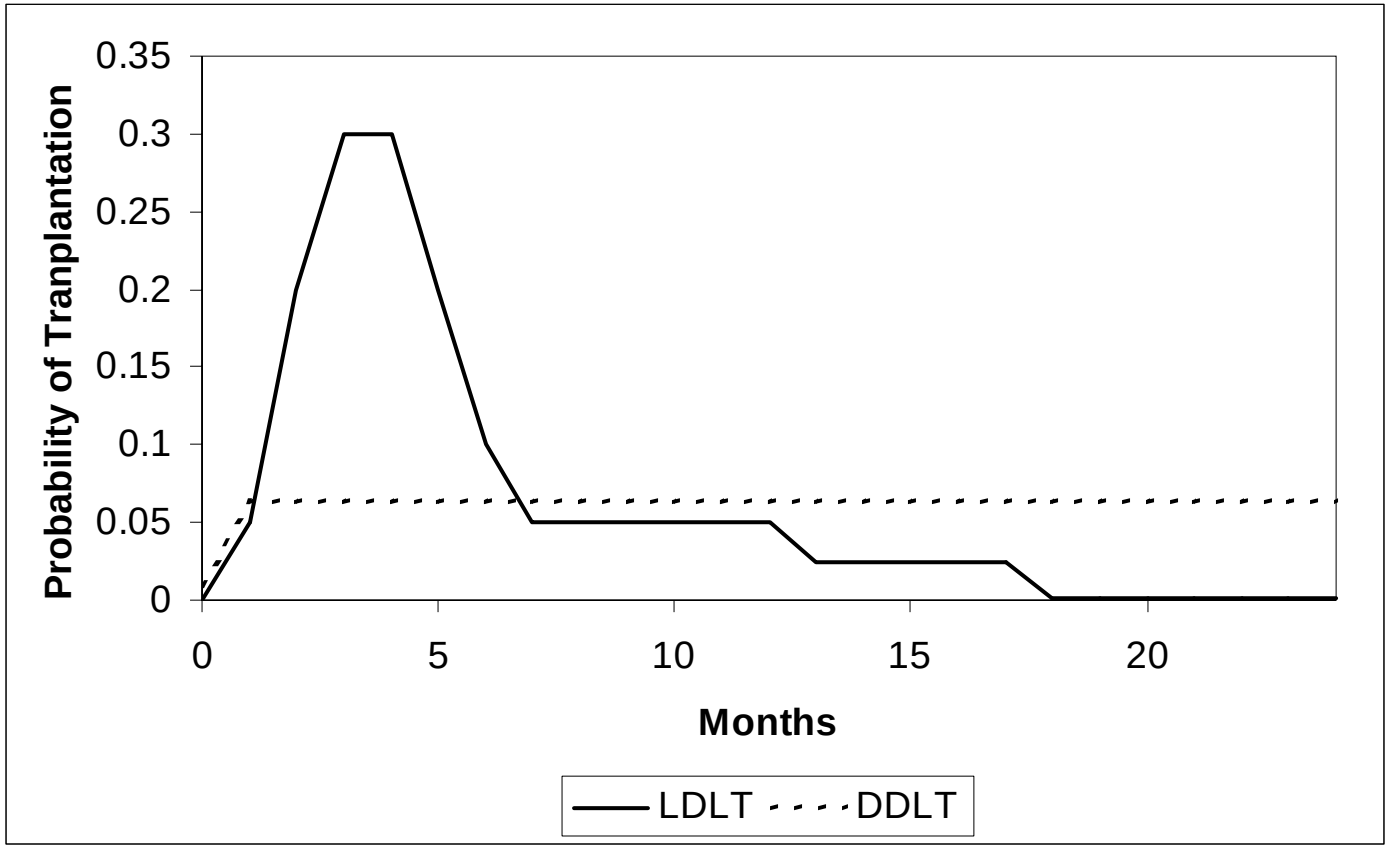


Figure 6: Monthly Markov health state probabilities for DDLT-only treatment arm. Probabilities represent the monthly probability of the simulation cohort to exist in each of the five possible health states for the DDLT-only treatment arm. By definition, existing in the post-LDLT health state is not possible in this treatment arm.

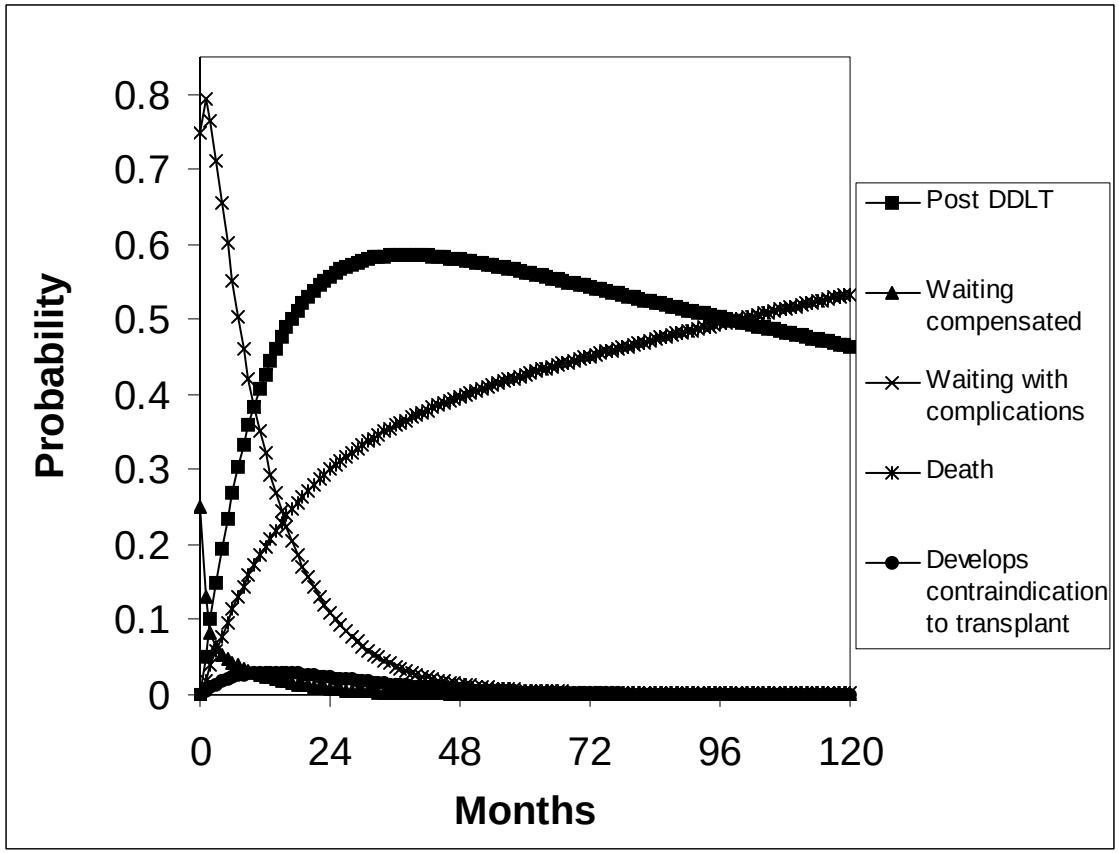


Figure 7: Monthly Markov health state probabilities for combined DDLT/LDLT treatment arm.
Probabilities represent the monthly probability of the simulation cohort to exist in each of the six possible health states for the combined DDLT/LDLT treatment arm.

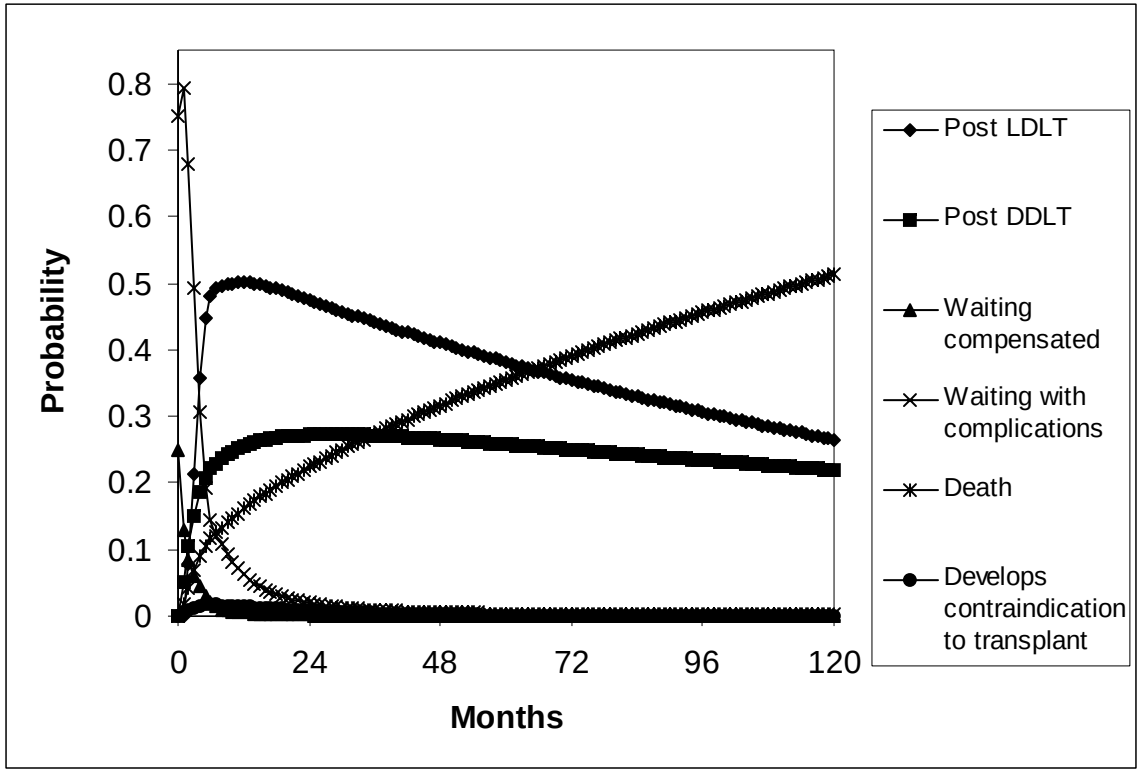


Figure 8: One-way sensitivity analysis on the probability of recurrent disease causing graft failure after LDLT with adjusted survival as the outcome. The threshold value where DDLT-only becomes the preferred strategy over the combined DDLT/LDLT approach was a recurrence rate of 0.0088 per month or equivalent to approximately 11% per year. The treatment strategies of "no transplant" and "LDLT-only" are omitted for clarity.

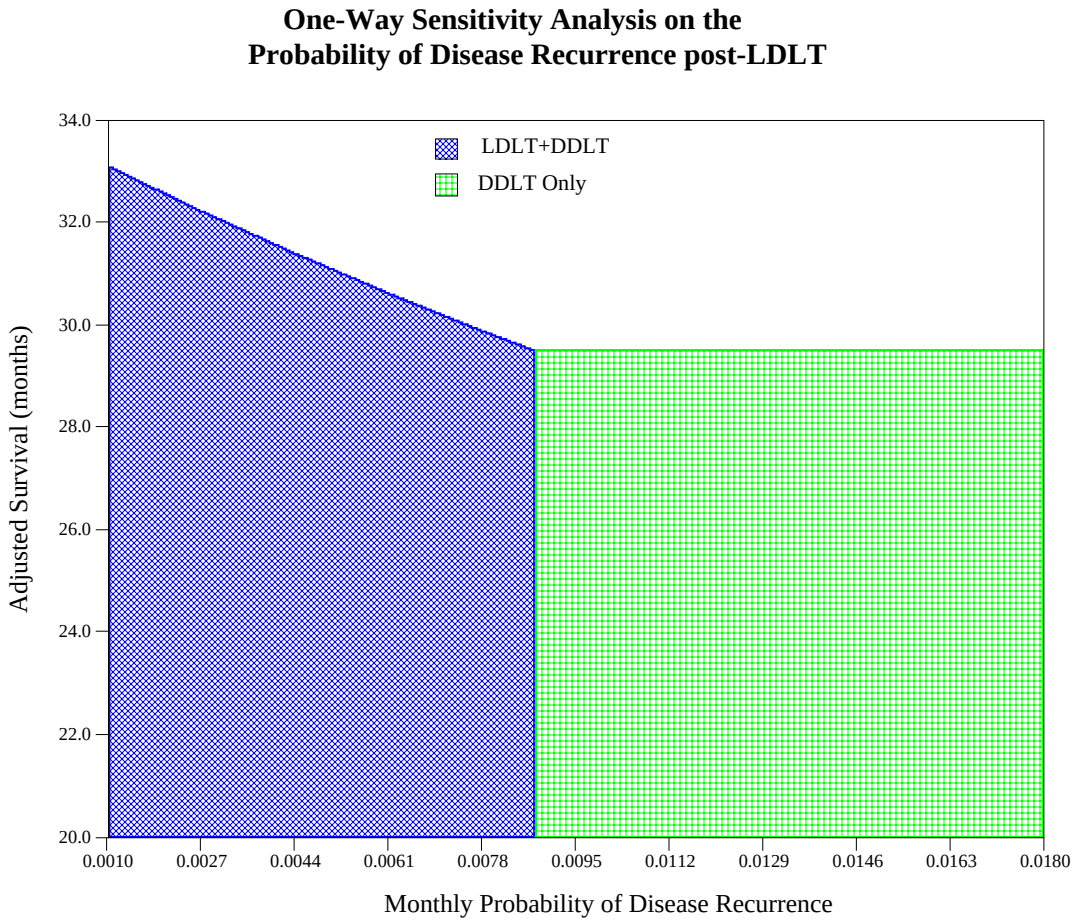


Figure 9: One-way sensitivity analysis of the probability of donor death after LDLT with adjusted survival as the outcome.
The combined DDLT/LDLT strategy is preferred until donor death rates exceed 6.7%, after which DDLT-only becomes the preferred treatment. Adjusted survival is a composite survival accounting for both donor and recipient survival and quality of life.

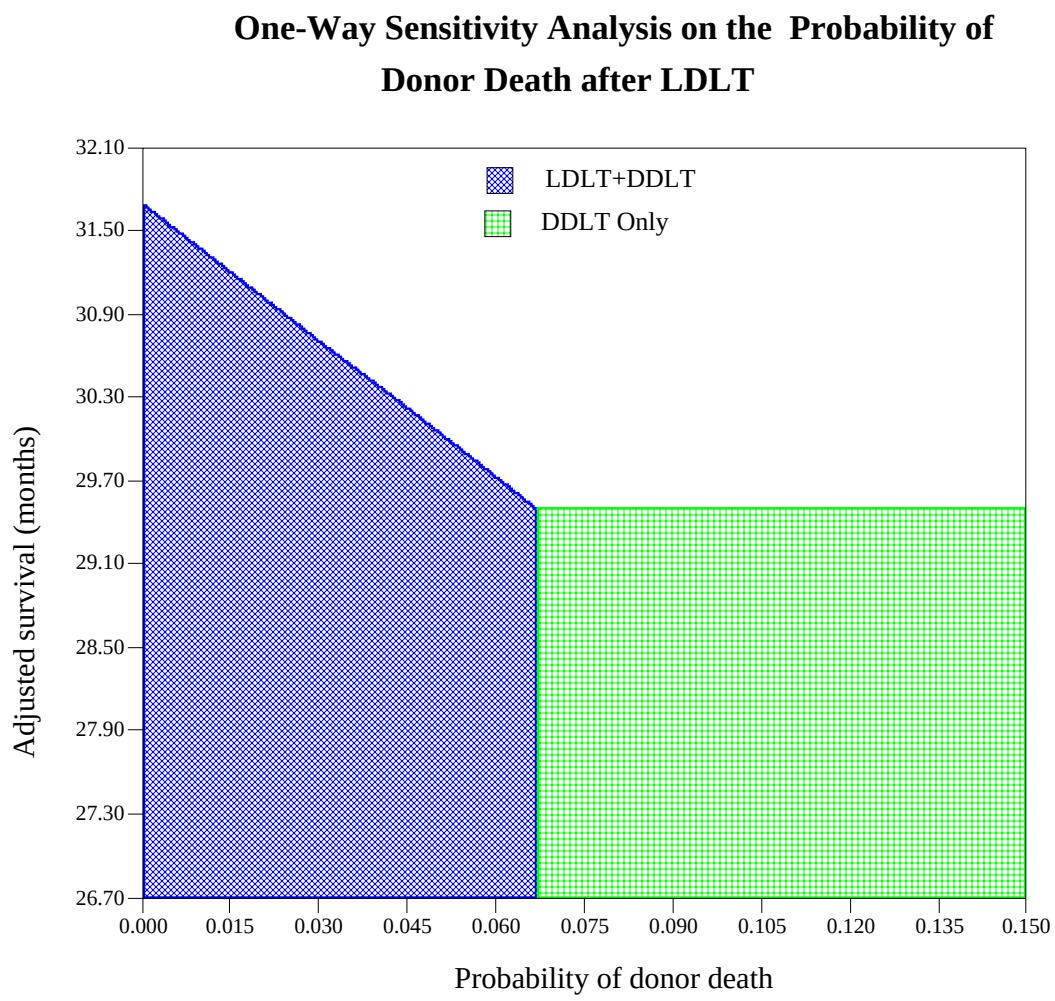


Figure 10: One-way sensitivity analysis on the cost of the DDLT procedure with cost-effectiveness as the outcome measure. DDLT is the preferred procedure until the cost exceeds approximately $152,000 after which LDLT becomes the preferred procedure. Costs are presented in adjusted year 2002 USD.

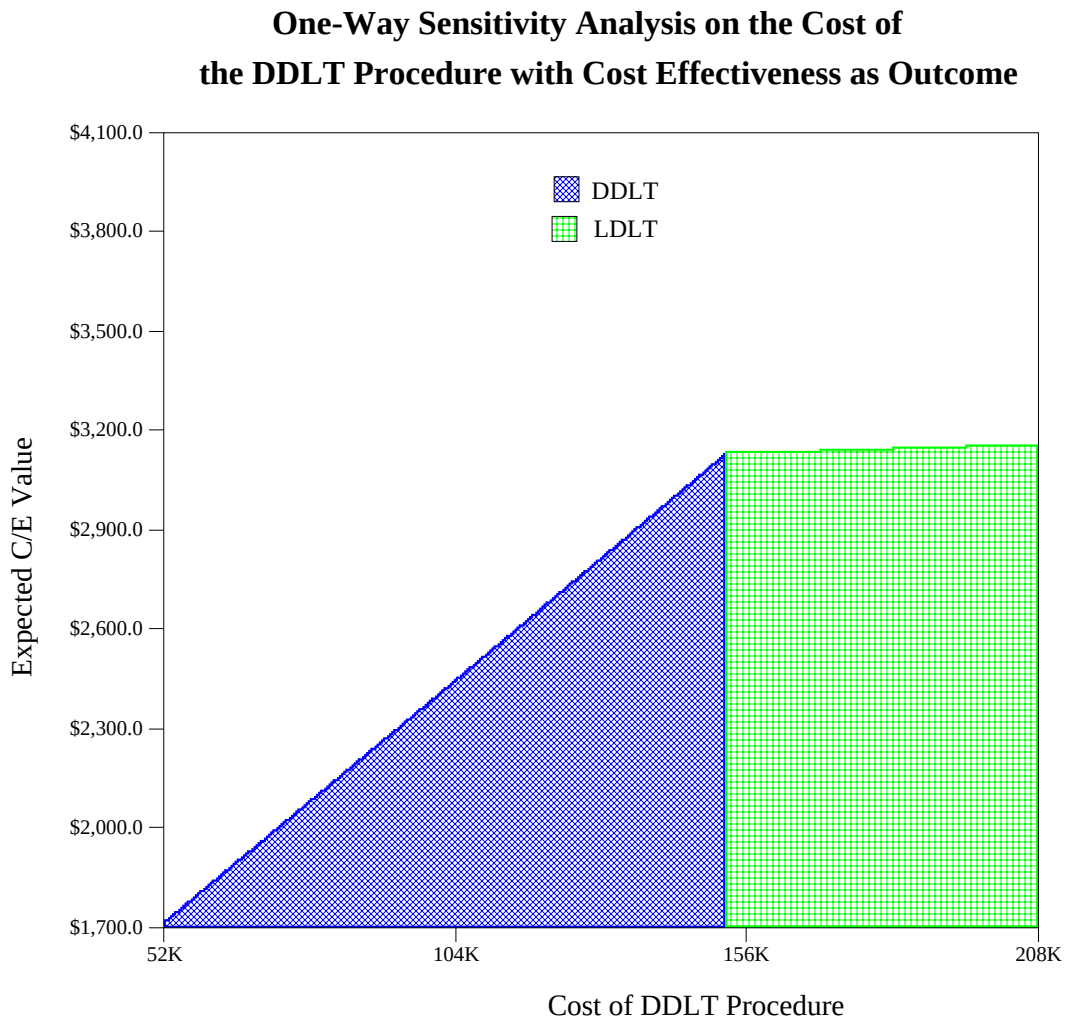
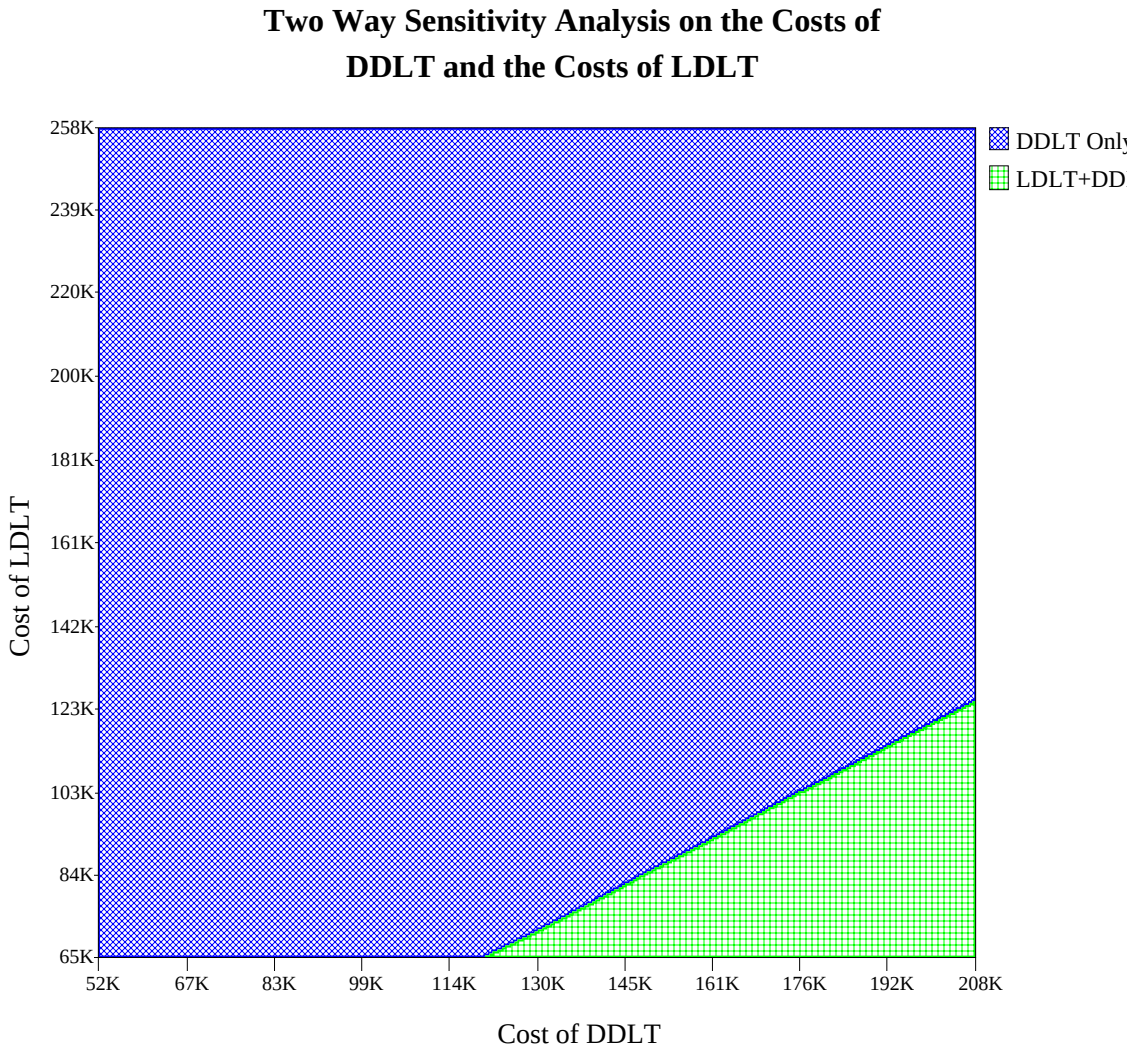


Figure 11: Two-way sensitivity analysis comparing the costs of the DDLT procedure versus the costs of the LDLT procedure with cost-effectiveness as the outcome. As the costs of LDLT are varied at the same time as the costs of DDLT, LDLT costs must be comparably low while DDLT costs are high to make combined DDLT/LDLT a more cost effective strategy than DDLT-only. Costs are reported in adjusted year 2002 USD.



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