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ORIGINAL ARTICLE

Addition of Adult-to-Adult Living Donation to Liver Transplant Programs Improves Survival but at an Increased Cost

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Using outcomes data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study, we performed a cost-effectiveness analysis exploring the costs and benefits of living donor liver transplantation (LDLT). A multistage Markov decision analysis model was developed with treatment, including medical management only (strategy 1), waiting list with possible deceased donor liver transplantation (DDLT; strategy 2), and waiting list with possible LDLT or DDLT (strategy 3) over 10 years. Decompensated cirrhosis with medical management offered survival of 2.0 quality-adjusted life years (QALYs) while costing an average of $65,068, waiting list with possible DDLT offered 4.4-QALY survival and a mean cost of $151,613, and waiting list with possible DDLT or LDLT offered 4.9-QALY survival and a mean cost of $208,149. Strategy 2 had an incremental cost-effectiveness ratio (ICER) of $35,976 over strategy 1, whereas strategy 3 produced an ICER of $106,788 over strategy 2. On average, strategy 3 cost $47,693 more per QALY than strategy 1. Both DDLT and LDLT were cost-effective compared to medical management of cirrhosis over our 10-year study period. The addition of LDLT to a standard waiting list DDLT program is effective at improving recipient survival and preventing waiting list deaths but at a greater cost. ***Liver Transpl 15: 148-162, 2009.*** © **2009 AASLD.**

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Living donor liver transplantation (LDLT) is an alternative to traditional deceased donated transplants, but there is little reliable outcomes data for adult-to-adult LDLT on which to base clinical decisions, patient counseling, or health policy. Of primary concern, the exposure to potential donor morbidity and mortality has not been evaluated, and case series reported in the literature vary in claims of donor morbidity in the immediate perioperative period from minimal[1] to 18%.[2,3] Although analyses of costs,[4-9] outcomes,[1,2,10-12] and quality of life[13-22] in relation to LDLT have been published, few have evaluated the true cost effectiveness of LDLT with a formal medical decision analysis.[23-26] Previously published studies were also hindered by a lack of ac-

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; CDR, Clinical Data Repository; DDLT, deceased donor liver transplantation; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LDLT, living donor liver transplantation; OPO, organ procurement organization; QALY, quality-adjusted life year; SBP, spontaneous bacterial peritonitis; STAR, Standard Transplant Analysis and Research; TIPS, transjugular intrahepatic portosystemic shunt; UNOS, United Network for Organ Sharing.

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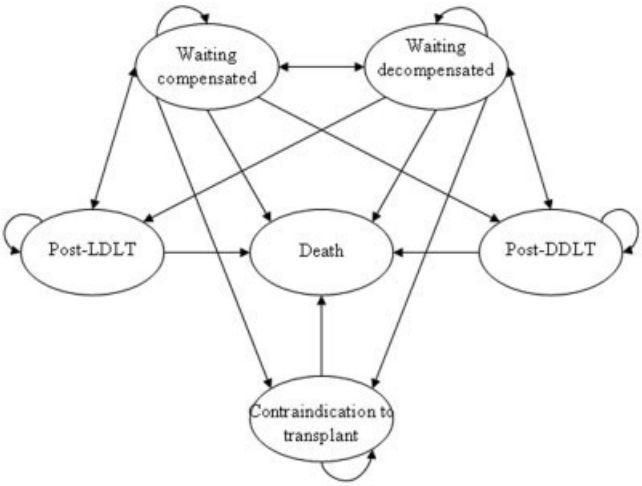

Figure 1. The basic health states of the Markov model. Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.

curate data with respect to donor outcomes and incomplete accounting of donor morbidity.

In the year 2000, the US National Institutes of Health organized a multicenter prospective cohort study of adult-to-adult LDLT performed at several large transplant centers in the United States over a 5-year period.[27,28] This cohort study has been given the name Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL). When completed in 2009, the study will report all significant surgical and clinical outcomes for adult-to-adult LDLT candidates, recipients, and donors at 9 major transplant centers in the United States. This data assessment by the A2ALL consortium is the largest and most current systematic report of the LDLT experience in the United States and includes outcomes from 819 transplant candidates, 1011 potential living donors, and 392 successful living donors. The aim of the current study is to evaluate the cost effectiveness of adult-to-adult LDLT versus deceased donor liver transplantation (DDLT) using the most comprehensive and current data on variables such as donor morbidity and mortality, complication events, and quality-of-life estimates derived from A2ALL, the United Network for Organ Sharing (UNOS), and the latest published literature.

MATERIALS AND METHODS

Decision Analysis Model

Cost-effectiveness analysis using Markov models has been described elsewhere.[29] The model developed for this simulation considers 6 health states that can occur for patients with end-stage liver disease any time over a 10-year time horizon, including the pretransplantation, perioperative, and posttransplant time periods. Figure 1 graphically displays the health states and transitions represented in the model. The model provides a conceptual framework for organizing the relationship of events and costs and the utility of different outcomes for patients with end-stage liver disease.

Three separate treatment strategies are simulated in the model: (1) supportive care/medical management only for decompensated liver disease, (2) standard Model for End-Stage Liver Disease–based wait listing for DDLT, and (3) DDLT wait listing in addition to an evaluation of prospective donors for LDLT. A Monte Carlo simulation of the Markov decision model was used to estimate the distribution of events that would occur for 1000 subjects (cohort members) over 10 years. All event probabilities in the model were calculated with a 1-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 cycles) to account for mid-cycle cost and utility accumulation.[29] In the model, members cycle through 1 of 6 basic health states, as shown in Fig. 1. By definition, every candidate entering the model is referred for transplantation with a potential living donor available for assessment. Patients can remain compensated on the waiting list or can have various complications of cirrhosis, including esophageal variceal bleeding, hepatocellular carcinoma (HCC), and ascites flare. When these acute events resolve, they are returned to the theoretical stable waiting list after appropriate costs and utility tolls are assigned for the events. A similar construct of a stable health state interrupted by complications is used in the posttransplant section of the model. To account for inflation, all costs are represented in adjusted year 2002 US dollars. All utilities and costs are discounted by 3% yearly in order to account for the decreased present value of future costs and benefits.[30] Data for Healthcare, version 3.5 (TreeAge Software, Williamstown, MA), was used for modeling, and SAS, version 9.1 (Cary, NC), was used for statistical analysis and dataset manipulation. The University of Virginia Institutional Review Board for Human Research approved this study.

Event Probabilities

All major events in the pretransplant, peritransplant, and posttransplant treatment of cirrhosis were modeled. Table 1 lists the baseline estimates for event probabilities used in the model, the range of values used for sensitivity analysis, and the sources of the data. LDLT events, especially those related to donor complications, were derived from the A2ALL dataset when available. A complete description of the A2ALL cohort patient population is published elsewhere.[31] DDLT event probabilities were drawn from data supplied by the UNOS transplant registry.[32] The UNOS supplied database, the Standard Transplant Analysis and Research (STAR) data set, was queried to calculate actual event rates and distributions that occurred during all adult liver transplants between January 1, 1999 and November 16, 2003. A complete population description of the STAR data set is outlined at www.unos.org or www.ustransplant.org. Base case probabilities were derived

TABLE 1. Event Probabilities in the Model

	Base Case	Range Used in Sensitivity Analysis	Sources
Before transplantation			
Yearly percent chance of developing symptomatic ascites on waitlist	20.3%	10%-40%	32, 72, 73
Percent chance of receiving TIPS for ascites or bleeding	20.5%	5%-40%	32, 72, 74
Percent chance of death related to each TIPS procedure	3.8%	1%-8%	72, 74
Yearly percent chance of contracting SBP in patients with symptomatic ascites	4.3%	2%-8%	72, 75-78
Percent chance of death related to each episode of SBP	20.0%	10%-40%	72, 75, 77-79
Yearly percent chance of having encephalopathy requiring admission	23.5%	11%-46%	32, 80
Percent chance of death from each episode of encephalopathy	11.5%	5%-25%	81, 82
Yearly percent chance of developing HCC on waitlist	10.3%	5%-20%	32, 83
Yearly percent chance in patients with HCC of progression resulting in delisting (equivalent to 5.4% per 90 days on the waiting list)	21.7%	10%-40%	32, 84
Yearly percent chance of variceal hemorrhage	22.4%	11%-44%	32, 85-87
Percent chance of death from each episode of variceal hemorrhage	14.2%	7%-28%	86-88
Yearly percent chance of remaining stable on waitlist, without complications	18.7%	9%-36%	89
Yearly percent chance of death once delisted for a contraindication to transplant	32.4%	16%-64%	90-93
Post-DDLT			
Percent chance of DDLT recipient death within 30 days of transplant	4.1%	2%-9%	32, 94, 95
Percent chance of graft failure due to disease recurrence	2.0%	1%-10%	32
Percent chance of successful retransplantation in patient with graft failure secondary to recurrent disease	24.9%	12%-50%	32
Yearly percent chance of admission for nonbiliary sepsis post-DDLT	9.9%	4%-20%	96-98
Percent chance of death from each sepsis event after DDLT	14.1%	7%-28%	96-98
Percent chance of needing nontransplant, no-biliary reoperation more than 30 days after DDLT	22.5%	11%-45%	99
Percent chance of death after each nontransplant reoperation after DDLT	10.5%	1%-20%	99
Percent chance of a biliary complication after DDLT	21%	10%-40%	100-104
Probability of death from biliary complications after DDLT	4.7%	2%-9%	100, 101, 104, 105
Percent chance of receiving retransplantation in a recipient with biliary complications after DDLT	4.8%	2%-9%	102, 106, 107
Percent chance of requiring nontransplant reoperation in a recipient with biliary complications after DDLT	8.0%	4%-16%	100, 102, 104, 108
Percent chance of acute rejection severe enough for hospitalization after DDLT	35.9%	15%-60%	11, 109, 110
Percent chance of death from an episode of acute rejection after DDLT	0.2%	0.1-0.5%	110
Percent chance of requiring retransplantation because of severe acute rejection after DDLT	1.3%	0.5%-3%	110
Post-LDLT			
Donor			
Probability of donor death after LDLT procedure	0.28%	0.01%-1%	51-55
Probability of donor having major complications (Clavien grade 3 or 4) after LDLT procedure	1.5%	0.5%-4%	A2ALL,52-54, 56, 57, 111-116
Probability of donor having minor or major complications (Clavien grade 2 or greater) after LDLT procedure	13%	6%-25%	52-54, 56, 57, 111-116
Recipient			
Percent chance of LDLT recipient death within 30 days of transplant	4.6%	2%-9%	A2ALL, 31, 32, 117
Percent chance of graft failure due to disease recurrence	3.2%	1.5%-7%	A2ALL, 31, 118-122
Percent chance of successful retransplantation in patient with graft failure secondary to recurrent disease	21.4%	12%-50%	A2ALL, 32

TABLE 1. (CONTINUED)

	Base Case	Range Used in Sensitivity Analysis	Sources
Yearly percent chance of recipient admission for nonbiliary sepsis post-LDLT	9.9%	4%-20%	A2ALL, 31, 96-98
Percent chance of recipient death from each sepsis event after LDLT	14.5%	7%-28%	A2ALL, 31, 96-98
Percent chance of recipient requiring nontransplant, nonbiliary reoperation after LDLT	22.5%	11%-45%	A2ALL, 31, 51, 112
Percent chance of recipient death after each nontransplant reoperation after LDLT	10.5%	1%-20%	99
Percent chance of a recipient biliary complication after LDLT	37%	15%-60%	A2ALL, 31, 51, 104, 108, 117, 123, 124
Percent chance of recipient death from biliary complications after LDLT	9.7%	4%-19%	A2ALL, 31, 100, 101, 104, 108, 117, 123, 124
Percent chance of receiving retransplantation in a recipient with biliary complications after LDLT	4.9%	2%-10%	100, 101, 104, 117, 123, 124
Percent chance of requiring nontransplant reoperation in a recipient with biliary complications after LDLT	54.9%	20%-90%	A2ALL,104, 117, 123, 124
Chance of having acute rejection severe enough for hospitalization after LDLT	33.9%	15%-60%	A2ALL, 11, 109, 110, 122, 125
Percent chance of death from an episode of acute rejection after LDLT	0.2%	0.1-0.5%	A2ALL, 11, 110, 122, 125
Percent chance of requiring retransplantation because of rejection after LDLT	1.3%	0.5%-3%	A2ALL, 11, 110, 122, 125

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

from exact calculations when they were available from the UNOS data set or from A2ALL data. When exact calculations were not available, data were abstracted from the literature. In a few cases, mainly the complications of cirrhosis in the pretransplant phase, enough data were available from the literature to calculate weighted averages for probabilities. When none of these choices were available, a point prevalence or percentage was used based on the published literature. Sensitivity margins attempted to encompass the span of the available literature on the event.

Financial Costs

All costs represented in the model are based on the medical center cost point of view. All direct and indirect outpatient and inpatient costs accrued over the 10-year study period are accounted for in the model. Abstract costs such as lost wages and emotional costs are not measured in this model. Accurate, easily generalized liver transplantation cost data were not available from the literature, A2ALL data set, or the STAR data set. Cost data for this analysis were obtained from mean values derived from liver transplant patient hospitalizations and physician administrative data abstracted from the University of Virginia Health System Clinical Data Repository (CDR).[33] The CDR is a secure comprehensive clinical database that captures all inpatient and outpatient clinical contacts in the University of Virginia Health System. The CDR uses microcosting algorithms to capture extensive cost data in an actual utilization (non–diagnosis-related group) framework. Financial transactions are recorded in the CDR as both third-party charges and actual costs and are calculated with real-time discharge utilization algorithms. The development, accuracy, and validity of the University of Virginia CDR have been published elsewhere.[34-37] Cost data from the CDR have been used successfully in other decision analysis models and publications, and costs calculated with the CDR have been shown to be comparable to adjusted national costs.[38] Table 2 shows the estimated cost data components for the model.

Health-Related Utility Measures

Health outcomes research and health decision analysis depend on analyzing not only the length of time spent in a health state but also the quality of life, or utility, associated with that 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.[39] Several studies have reported health

TABLE 2. Cost Data Used in the Model

	Monthly Costs	Monthly Cost Range*
Baseline health state costs		
Baseline average monthly outpatient costs for patients with compensated cirrhosis	63	31-126
Baseline average monthly costs for subjects 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	9096-36,384
Average cost of an episode of SBP (includes treatment, hospitalization, complications, and imaging)	10,248	5124-20,496
Average cost of ascites and peripheral edema requiring admission to the hospital	6,197	3,098-12,394
Average cost of encephalopathy admission	4,297	2,148-8,594
Average monthly cost of HCC (includes imaging, procedures, and follow-up)	3,755	1,877-7,510
Average cost of variceal bleeding (includes hospitalization, procedures, and follow-up)	11,964	5,892-23,928
One-time cost of DDLT procedure (includes deceased donor expenses and organ acquisition costs from OPO, hospitalization, and pharmacy[126])	103,806	51,903-207,612
One-time cost of LDLT procedure [includes workup costs for 1.23 potential donors,[49,50] donor procedure without complications, hospitalization, and pharmacy[126]; donor costs are normalized to DDLT OPO charges to avoid double-charging living donors; the actual estimated costs for a 1-time live donor procedure without complications is $129,144]	103,806	51,903-207,612
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 applied only to subjects not eligible for retransplantation; based on costs incurred for care when transplant is contraindicated)	4,662	2,331-9,324
Average cost for posttransplant subjects with nonbiliary infectious complications (includes hospitalization, imaging, pharmacy, and follow-up)	6,952	3,476-13,904
Average cost for posttransplant recipients that require nontransplant reoperation (based on the cost of laparotomy)	16,892	8,446-33,784
Average cost for posttransplant subjects with clinically significant biliary complications (includes cost associated with chronic biliary strictures, and 2 ERCPs[104])	7,292	3,646-14,584
One-time cost of posttransplant recipients that require nontransplant reoperation for biliary complication (does not include ERCP costs; based on the cost of laparotomy)	18,607	9,303-37,214
Average cost of posttransplant treatment of acute rejection (includes hospitalization, procedures, pharmacy, and follow-up)	6,798	3,339-13,596

NOTE: All costs are reported in year 2002 adjusted US dollars. See the text for the derivation of the costs.
Abbreviations: DDLT, deceased donor liver transplantation; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; OPO, organ procurement organization; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.
*Ranges are derived as 50% and 200% of the calculated costs.

TABLE 3. Utility Data Used in the Model

Baseline Health State Utility	Base Case Utility	Utility Range	Sources
Utility of compensated cirrhosis (Child B)	0.71	0.44-0.98	40-47
Utility of decompensated cirrhosis (Child C)	0.56	0.30-0.67	40-47
Utility of recipient post–liver transplantation	0.80	0.63-0.87	41, 43, 45, 47, 127
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[128] (donors are assumed to be in perfect health before donation)	Recipient utility − 0.3	0.25-1.0	Expert opinion
Utility Toll for Specific Events	Percent Toll from Baseline	Range	Sources
Monthly utility penalty for refractory ascites	−25%	0%-80%	44
One-time utility penalty from TIPS	−25%	0%-80%	42
One-time utility penalty for SBP (based on utility for refractory ascites)	−25%	0%-80%	44
Monthly utility penalty for HCC	−10%	0%-50%	41, 43, 44
Monthly utility penalty for encephalopathy	−25%	0%-80%	42, 44
Monthly utility penalty for variceal bleeding	−25%	0%-80%	42, 44
One-time utility penalty for recent major surgery	−20%	0%-80%	58
Monthly utility penalty for major complication of transplantation	−25%	0%-80%	41, 43, 45, 47, 127
One-time utility penalty for undergoing DDLT	−50%	25%-75%	41, 43, 45, 47, 127
One-time utility penalty for undergoing LDLT (includes combined donor and recipient penalties)	−75%	25%-90%	41, 43, 45, 47, 127, and expert opinion

Abbreviations: DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

state utilities associated with chronic liver disease and liver transplantation derived by standardized and validated methods.[40-47] 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.[25,26,48] Evidence from the literature indicates that prospective donors are frequently disqualified from the donation process following discovery of preexisting medical conditions or tissue incompatibilities or by their eventual unwillingness to participate.[49,50] Donor death and serious morbidity 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.[51-55]

Living donor costs are not well accounted for in the current reimbursement system in the United States, and there is little published data on this topic. We performed an informal multicenter survey regarding the costs and charges assigned to the living donor in LDLT. It was generally agreed that typical costs paid to the organ procurement organization (OPO) for DDLT should not be attributed to the living donor. A detailed analysis at 2 of the A2ALL centers showed that the costs attributed to the living donor approximate the costs paid to the OPO for DDLT (unpublished data). Many of the centers, for accounting purposes, assigned a cost to the LDLT recipient that was equal to the OPO charges for DDLT. Therefore, we chose to equalize the costs for the hospitalizations of the living donor to the OPO DDLT costs in the model. This resulted in only a small difference for the actual DDLT and LDLT hospitalizations. Repeated trial runs of the model with both the equalized costs and the individual estimated costs for both procedures yielded nearly the exact same results (see Table 2). Thus, we chose to use the most common accounting practice in the final model. A wide variation was used in the sensitivity analysis to test the impact of this decision.

Our model assumes that all living donors enter the simulation in a state of perfect health. On the basis of the A2ALL experience, for each LDLT recipient, 1.23 prospective donors are evaluated. This accounts for the extra cost of evaluating donors that are eventually deemed ineligible.[49,50] 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 major complication rates for donors were extracted from the A2ALL data set and include all donor compli-

TABLE 4. Model Validation and Survival Data After a 10-Year, 1000-Subject Trial

Variable	No Transplant Available	Listed for DDLT	Listed for DDLT with LDLT Available
Mean cost per patient (2002 US dollars)	65,068	151,613	208,149
Mean unadjusted lifespan (years)	3.1	6.4	7.3
Mean quality-adjusted lifespan (QALYs)	1.9	4.4	4.9
Number receiving DDLT (primary or retransplant)	—	687	233
Number receiving LDLT (primary)	—	—	715
Number dead after 1 year	175	158	136
Number dead after 5 years	630	335	256
Number dead after 10 years	964	454	397
Number receiving primary transplant at 1 year	—	309	520
Number receiving primary transplant at 5 years	—	516	662
Number dead before transplant or on waitlist (%)*	964	309 (30.9)	112 (11.2)
Mean cost to prevent 1 pretransplant death (2002 US dollars)	—	122,516	199,942
Number dead after transplant (%)	—	145 (14.5)	285 (28.5)
Living donor deaths (%)	—	—	2 (0.2)
Living donor serious complications, excluding deaths (%)	—	—	17 (2.4)

NOTE: Results are presented from a 120-month Monte Carlo simulation of 1000 theoretical subjects with base case values for all variables.
Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; QALY, quality-adjusted life year.
*This represents a 10-year cumulative mortality for the entire cohort. The yearly mortality rate on the waiting list is roughly one-tenth of this value.

cations considered grade 3 or above according to the Clavien grading system.[3,56,57] Donor deaths incur a penalty of 1.0 utility point 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 on the documented health utility after complications from major surgery.[58] 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 the loss of 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. The ranges of minimum and maximum values considered for each estimated component in the model are shown in the tables of the model probabilities, costs, and utilities.

RESULTS

Model Validation and Unadjusted Recipient Survival

Table 4 lists results from the Monte Carlo simulation of the Markov decision analysis model iterating 1000 theoretical subjects with decompensated cirrhosis. Ten-year posttransplant survival rates for DDLT recipients (542 of 687, 79.0%) and LDLT recipients (510 of 715, 71.3%) were comparable to reported survival rates in the literature. The 10-year survival rate for subjects with no access to transplantation (3.6%) was comparable to that reported in the literature for end-stage liver disease. The mean waiting time for all candidates was 149 days, which is comparable to the current waiting times for DDLT in the United States. The LDLT simulation yielded 2 donor deaths (0.2%) and 17 major complications in donors (2.4%). The maximum survival was attained in the LDLT-exposed treatment branch. In this branch, there were 715 LDLT and 233 DDLT procedures with 112 subjects (11.2%) dying on the waitlist and 285 subjects (28.5%) dying after transplantation. This treatment branch terminated at 10 years with 24 subjects still alive and awaiting transplantation.

The major contributor to the increased 5-year survival rate in the LDLT-exposed treatment arm compared to the DDLT-only treatment arm was the decreased number of subjects dying on the waiting list. The DDLT-only treatment arm had a 30.9% mortality rate on the waiting list, whereas the LDLT treatment arm had 11.2% waitlist mortality over the 10 years of the simulation. This yielded a relative risk of waitlist mortality of 2.75 in the DDLT-only group compared to the LDLT-exposed group with a relative risk reduction for waitlist death of 63.8%. This is equivalent to a number needed to treat of 5 to prevent 1 waitlist death; that is, for every 5 patients listed at a transplant program with access to LDLT, 1 waitlist death was prevented in comparison with programs with only DDLT access. This finding is in agreement with previously published recipient survival improvements afforded by LDLT.[59,60]

TABLE 5. Results of the Cost-Effectiveness Analysis

Treatment Strategy	Expected Cost (×$1000)	Marginal Cost (×$1000)	Survival (QALY)	Marginal Survival (QALY)	Cost-Effectiveness Ratio	ICER
No transplant	63	—	2.0	—	$32,969	—
Listed for DDLT	150	87	4.4	2.4	$34,648	$35,976
Listed for DDLT with LDLT available	214	64	4.9	0.5	$43,487	$106,788

NOTE: Expected costs are those expected for a subject entering the treatment strategy arm, including all outcomes and complications in year 2002 US dollars. Effectiveness (survival) is expressed in QALYs.
Abbreviations: DDLT, deceased donor liver transplantation; ICER, incremental cost-effectiveness ratio; LDLT, living donor liver transplantation; QALY, quality-adjusted life year.

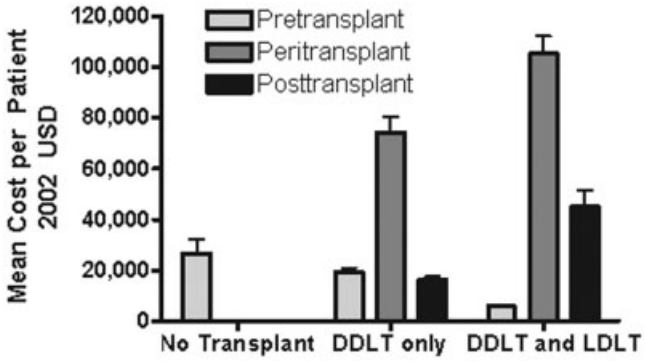

Figure 2. Mean costs per patient for each treatment strategy by phase of simulation. Costs are reported in 2002 US dollars with standard deviations. The addition of LDLT to a transplant program significantly decreases pretransplant costs but increases posttransplant and peritransplant costs. Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.

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 cohort were $87,000 more than those for nontransplant care. The LDLT approach was $64,000 more expensive than the DDLT-only approach. The increased cost of the LDLT strategy was due to fewer waitlist deaths and thus more ongoing posttransplant expenses in the survivors as well as donor procedures and complications (see Fig. 2 for cost details).

Effectiveness is reported as quality-adjusted life years (QALYs). The no-transplant strategy offered a quality-adjusted expected survival of 2.0 QALYs, while DDLT-only offered 4.4 QALYs. The combined LDLT strategy resulted in 4.9-QALY expected survival, which was 0.5 QALYs more than the DDLT-only strategy. Cost-effectiveness ratios are reported in dollars per QALY. The LDLT strategy yielded the highest cost per QALY. Both transplant approaches were more effective and reasonably priced in comparison with pure supportive care/medical management of cirrhosis. The DDLT-only strategy cost an average of $35,976 per QALY over medical management, whereas the availability of the LDLT strategy cost $47,693 per QALY. LDLT quality-adjusted survival was hindered by donor morbidity and, to a lesser extent, donor death. The incremental cost-effectiveness ratio (ICER) of moving from the DDLT-only strategy to the LDLT strategy was approximately $106,788 per QALY.

Sensitivity Analysis

One-way sensitivity analyses were performed on all variables in the model. The basic relationships between DDLT and LDLT and cost effectiveness were not affected by any clinically relevant range of values for any single variable in the model. Repeated analyses using extreme estimates for each of these variables did not change the preferred treatment strategy with respect to cost effectiveness (see Fig. 3). In general, improvement in pretransplant variables decreased the cost effectiveness of both forms of transplantation in proportional amounts. Conversely, improvements in posttransplantation variables moderately improved the cost effectiveness of both forms of transplantation. There were no circumstances in the sensitivity analysis that enabled LDLT to be less costly than DDLT and only with extreme assumptions could their costs approach equality (see Fig. 4). Similarly, because of donor morbidity and mortality, aggregate adjusted quality of life was always only marginally better for LDLT than DDLT, despite the decrease in deaths on the waitlist. The improvement in quality of life and decrease in costs associated with less waitlist death in the LDLT strategy were offset by the increased exposure of recipients to posttransplant complications and costs. Because of this, there were no realistic interventions in the model that could bring the ICER of the LDLT strategy below $50,000 per QALY. This remained true when DDLT waiting times were varied through extreme ranges. When average waiting times for DDLT approached 3 years, the DDLT and LDLT strategies yielded very similar ICER values. Conversely, when DDLT waiting times were less than 2 months, the LDLT strategy was both less effective and more costly than the DDLT approach.

The probability of donor death and complications after LDLT were significant influences on the cost effectiveness of LDLT in the extreme cases. Because of the improved overall recipient quality of life after transplan-

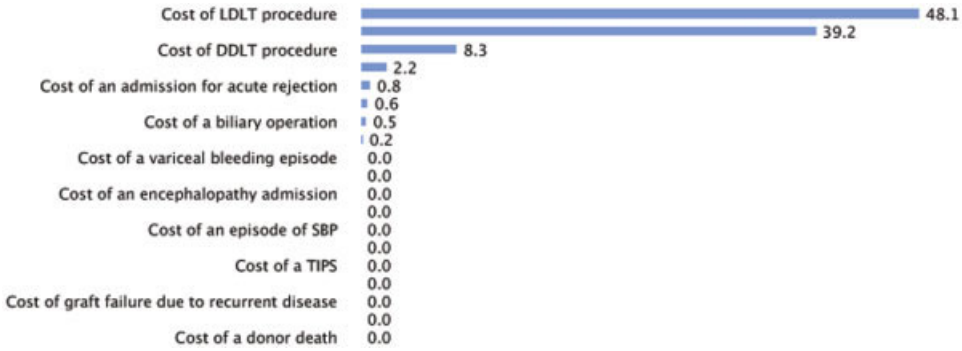

Figure 3. Sensitivity of the model to cost variables. The number shown is the percentage of cost-dependent model variability attributable to the listed cost as determined by a tornado diagram sensitivity analysis. Within the ranges of the sensitivity analysis, none of the cost variability was able to change the fundamental cost effectiveness of the treatment strategies. See the text for details. All values listed as 0.0 were not statistically significant contributors to overall model variability. Abbreviations: DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

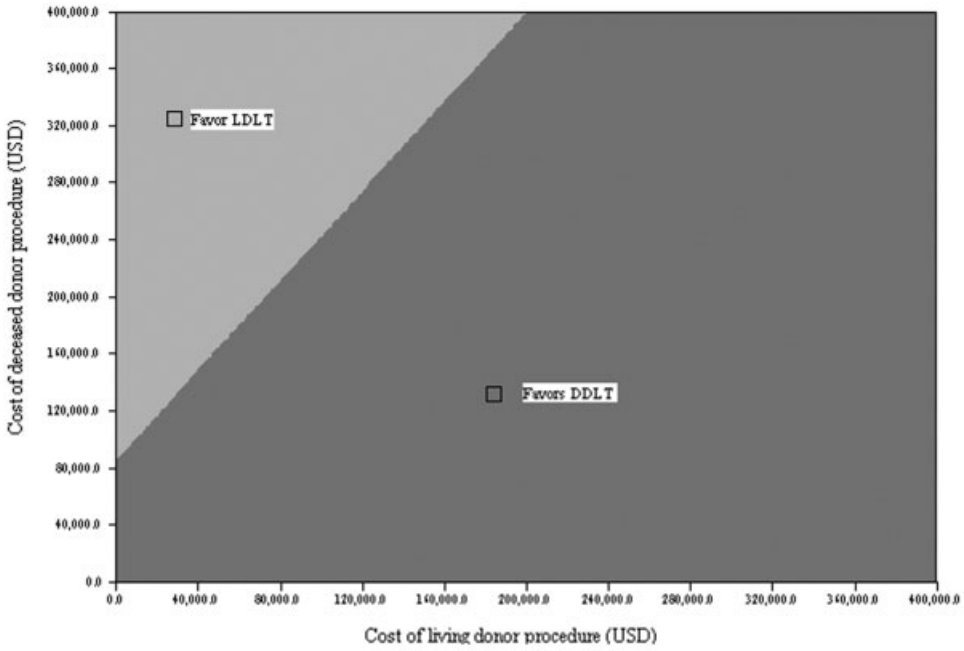

Figure 4. Two-way sensitivity analysis of costs of individual transplant procedures. Only unrealistic differences in the cost of the individual procedures would swing the cost-effectiveness superiority to LDLT. See the text for details. Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.

tation and diminished waitlist death rates, donor death had only a marginal influence on aggregate quality of life and adjusted survival. Only when donor death rates exceeded an unrealistic 24% was the aggregate adjusted survival after LDLT less than that of DDLT. Donor morbidity had little effect on overall adjusted survival and quality of life, although costs were significant. Because of a steep learning curve in performing the LDLT procedure,[31] data regarding complications and outcomes were separately analyzed with a cutoff of 20 LDLT procedures or fewer per center. The assumption was that less experienced centers would have more complications and therefore the cost effectiveness of the procedure would improve after the learning curve was overcome. Despite significant improvements in some complications, cost effectiveness in experienced centers was only minimally improved because the fundamental costs involved with more exposure to the posttransplant health state were not significantly affected.

Hepatocellular carcinoma is one circumstance that may benefit by earlier transplantation. In the present model, if more than 40% of waitlisted subjects have HCC, then the ICER of LDLT approaches the commonly accepted $50,000 per QALY but at the cost of a 17% increase in waitlist death (282 versus 331), mainly in the non-HCC subjects. More comprehensive simulations focused specifically on HCC have been published elsewhere.[48]

The cost-effectiveness measurements of all treatment strategies in the model were highly sensitive to the time horizon (ie, the total observation time for each subject entering the model) chosen for the analysis. Because the majority of expense and morbidity occurs early in the course of liver transplantation, the major cost and

quality of life benefit of liver transplantation is in the long-term survival advantage offered by either form of liver transplantation. In the present model, at the 1-year observation time (from presentation for evaluation with decompensated cirrhosis), neither form of liver transplantation is cost-effective (the ICER of DDLT was greater than $2,252,000 per QALY, whereas LDLT was more costly and had lower survival). With a 2-year time horizon, this trend continued (the ICER of DDLT was greater than $513,000 per QALY, and LDLT was still inferior). Only with a total observation period of 9 years or more does the DDLT strategy become cost-effective with an ICER less than $50,000 per QALY, whereas the ICER of the LDLT strategy remains greater than $135,000 per QALY. Because the mean survival of liver transplant recipients is greater than 10 years in the United States, a time horizon of 10 years was chosen in this model. This idea of accepting early increases in costs and morbidity for a long-term benefit are critical in policymaking decisions about liver transplantation. Conversely, earlier transplantation would be expected to be a cost-effective treatment method only in candidates with a high likelihood of death in the short term. Other researchers have estimated a threshold of survival benefit of liver transplantation to be above a Model for End-Stage Liver Disease score of 17.[61]

DISCUSSION

This simulation 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 decision analysis model to simulate the major events that occur before, during, and after both LDLT and DDLT. Unlike many previous models, extensive consideration was given to costs related to the workup of potential donors that are eventually deemed ineligible for donation, the real impact of donor mortality and morbidity, 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 the course of events reported in the literature.

We have 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 more than $35,000 when measured over a 10-year time frame. Although modestly more effective, mostly because of less time spent on the waiting list for transplantation, the addition of LDLT to the DDLT approach was an expensive but effective alternative. The ICER of the LDLT strategy was approximately $106,000. The interpretation of an ICER based on a simulation is a subjective matter and is influenced by societal willingness to pay and by the validity of the model and its assumptions.[62] Previously reported ICERs for routinely performed medical interventions in the United States include $86,362 for screening for colorectal cancer in people over age 65,[63] $8000 to $900,000 (depending on age and type of drug used) for the treatment of hypertension,[64,65] $112,000 for screening for HCC in cirrhosis patients with ultrasound and alpha fetoprotein,[66] and more than $708,000 for intravenous proton pump inhibitor therapy for peptic ulcers.[67] In contrast, the traditional willingness to pay benchmark in the United States is based on the cost of chronic ambulatory hemodialysis.[68-70] Although an ICER of less than $50,000 has been traditionally accepted as a cost-effective addition to the medical system in the United States, some authors have argued that based on different economic calculations and assumptions, a cost-effective medical intervention could range from as little as $24,000 to as much as $428,000 per QALY.[71] In fact, if cost-effectiveness values associated with hemodialysis derived from studies in the late 1980s are adjusted for year 2004 US dollars, an ICER of $75,000 may be a more proper benchmark for modern cost-effectiveness analyses.

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. Although quite complex, the model is an approximation of reality and cannot truly represent all the possible outcomes in this complicated disease process. However, we have based the probabilities and health state utilities on the best available and most pertinent data. 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 data were insufficient or weak. Finally, when no published data were available, expert opinion and unpublished data were used, but these occurrences were few, and the following sensitivity analyses were conducted over a broad range.

Cost data were center-specific and this inherent weakness was unavoidable in this simulation. Using strong microcosting 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. There have been 2 published analyses from US universities assessing costs in the setting of LDLT and DDLT.[7,8] These studies published not specific costs but related comparative costs on the basis of cost units. Despite this, the costs related to LDLT and DDLT in those reports were comparable to those used in this model. Similarly, European studies have published abridged cost data,[25] and after we accounted for currency conversion rates and inflation, the costs in this model compare similarly.

We chose a 10-year time horizon because data for transplantation in the modern era are available for approximately the last 10 years. It was also felt that ex-

trapolating beyond 10 years with event rates was very speculative and potentially inaccurate. This time frame also yields a reasonable time frame to judge the benefit of transplant beyond the immediate postsurgical complications and waiting list morbidities. Also the A2ALL study period was roughly 10 years as initially funded. In theory, a longer time frame of observation could change our eventual conclusion concerning cost effectiveness, although no solid data are available at the present time to support this speculation, and there is no clear advantage to LDLT or DDLT in this respect. Changing the overall time horizon in the model has two opposite effects: (1) shortening the length of time that candidates are exposed to waiting list mortality and (2) shortening the extension of life in the posttransplant phase that successfully transplanted candidates are allowed to experience. These opposite effects cause a waiting list mortality decrease at the same time as a decrease in posttransplant quality of life benefit. The overall effect on the model is not strong unless very short time horizons are used. Thus, we chose the 10-year time frame to simulate reality as much as possible while still using data that were dependable. Another unexplored factor in this article is regional variation in donor utilization and organ allocation. This model assumes a national distribution of organs,and the fundamental data in this article are based on national averages. Regional variation is a potential source of widely variable practice in the United States, but an investigation of regional changes in cost effectiveness and LDLT practice is beyond the scope of this article. It was the goal of this analysis to combine the representative data from a national sample of transplant programs in order to give a broad view of the practice of LDLT in the United States.

In summary, this article presents an extensive cost-effectiveness model simulating chronic liver disease and cirrhosis with treatment options including the standard-of-care DDLT-only strategy and the addition of LDLT to the treatment paradigm. 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 traditionally defined standards of cost effectiveness were used, the DDLT-only approach 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 modestly more effective but much more expensive than the DDLT-only strategy per QALY saved. This simulation, 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.

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