

ORIGINAL ARTICLE

Is liver transplantation using organs donated after cardiac death cost-effective or does it decrease waitlist death by increasing recipient death?

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Abstract

Objectives: The aim of this study was to evaluate the cost-effectiveness in liver transplantation (LT) of utilizing organs donated after cardiac death (DCD) compared with organs donated after brain death (DBD).

Methods: A Markov-based decision analytic model was created to compare two LT waitlist strategies distinguished by organ type: (i) DBD organs only, and (ii) DBD and DCD organs. The model simulated outcomes for patients over 10 years with annual cycles through one of four health states: survival; ischaemic cholangiopathy; retransplantation, and death. Baseline values and ranges were determined from an extensive literature review. Sensitivity analyses tested model strength and parameter variability.

Results: Overall survival is decreased, and biliary complications and retransplantation are increased in recipients of DCD livers. Recipients of DBD livers gained 5.6 quality-adjusted life years (QALYs) at a cost of US\$69 000/QALY, whereas recipients on the DBD + DCD LT waitlist gained 6.0 QALYs at a cost of US\$61 000/QALY. The DBD + DCD organ strategy was superior to the DBD organ-only strategy.

Conclusions: The extension of life and quality of life provided by DCD LT to patients on the waiting list who might otherwise not receive a liver transplant makes the continued use of DCD livers cost-effective.

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Introduction

Liver transplantation (LT) is the treatment of choice in end-stage liver disease. Despite the adoption of the Model for End-stage Liver Disease (MELD) system of organ allocation, which prioritizes those who are most ill or have hepatocellular carcinoma (HCC), waitlist mortality has remained stable for many years because the number of candidates for LT continues to rise, but the number of organs available for transplant has reached a plateau.¹ As the gap between numbers of donor organs and LT candidates continues to widen, strategies that maximize the use of all available grafts while maintaining optimal outcomes are

required. From 1968, when criteria for establishing brain death were developed, to the end of the 20th century, the only reliable source of livers was derived from subjects who donated after brain death (DBD).² However, organs donated after cardiac death (DCD) have now become widely accepted as an alternative source of organs for transplant and the use of DCD organs has been encouraged by the United Network for Organ Sharing. Although the use of DCD organs has increased the number of potentially available organs, questions about outcomes related to the use of organs from cardiac death donors remain. These concerns have tempered acceptance of the use of DCD organs in the USA, where the proportion of LTs using DCD organs has plateaued at about 6% despite the lengthy candidate waitlist.³⁻⁵

Historically, both patient and graft survival in DCD LT have been significantly lower than in DBD LT.³⁻¹⁶ Other adverse outcomes, such as post-transplant acute kidney injury, hepatitis C virus recurrence and biliary complications, have also been shown

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to be higher after DCD LT.^{7,8,10,15,17–21} Recently published data indicate that outcomes following DCD LT may approach those of DBD LT when there is careful attention to donor and recipient selection and limited cold ischaemic time.^{14,21,22} Despite these encouraging clinical findings, the potential financial burden and societal benefits of DCD LT are unknown.

The current study sought to elucidate the cost-effectiveness, from a societal perspective, of using DBD and DCD organs in LT. The objective of this study was to develop a Markov model to evaluate the cost-effectiveness, including potential outcomes, associated costs and recipient quality of life, of incorporating two different options for LT into waitlist management strategies that: (i) limited potential recipients to receiving DBD organs only, or (ii) allowed potential recipients to receive either DBD or DCD organs. Results from this study may guide surgeons in decision making for individual LT candidates, as well as informing policy making and future planning.

Materials and methods

Markov decision model

The Markov decision analysis technique is used to model outcomes for groups of hypothetical patients and to analyse time, value and costs of patients in each state of health. Outcomes are simulated for each hypothetical patient group over prespecified time intervals or cycles. Initially, hypothetical patients are assigned to a health state but can change health states each time the model is cycled. An 'absorbing state' is a state, such as death, that the patient cannot leave once it is entered. The model is run iteratively either until all hypothetical patients have reached an absorbing state or over a dictated time horizon (such as 10 years in the present model). When the time horizon is limited, the model does not run until all patients reach an absorbing state, but instead stops when the predetermined time is complete. A comprehensive literature review is used to determine the likelihood that, in any model cycle, a patient will either remain in his or her current state or transition to a new health state. A value, most commonly expressed in quality-adjusted life year (QALY) units, is assigned to a patient within a given health state. These values accumulate over each cycle and the net valuation is calculated for each patient after all cycles have been completed. The financial cost per value (QALY) of each health state can be computed and compared with the values of the other treatment strategies.^{23,24}

A Markov-based decision analytic model was constructed to simulate outcomes from a societal perspective for two different waitlist strategies: (i) a strategy that limited potential recipients to receiving DBD organs only, and (ii) an alternative approach that permitted potential recipients to receive either DBD or DCD organs. In this model, the determined cost for each type of donor included the direct costs of transplantation to the hospital or the payer, such as the costs of the procedure, materials and length of hospitalization. Indirect costs of transplantation such as lost earning potential of the recipient, out-of-hospital expenses and the costs of immunosuppressants were also included.

TreeAge Pro 2010 (TreeAge Software, Inc., Williamstown, MA, USA), software that is specifically designed to create and evaluate decision trees and models, was used to construct and run the model using methods similar to those reported previously by the present group.²⁵ The cost-effectiveness analysis was performed and reported according to the Panel on Cost-Effectiveness in Health and Medicine guidelines.^{26–27}

Health states

The Markov decision model shown in Fig. 1 included two waitlist strategies which: (i) limited potential recipients to receiving DBD organs only, or (ii) allowed potential recipients to receive either DBD or DCD organs. In each arm of the model, candidates were placed on the waitlist and were then transplanted (or not transplanted) at different rates depending on the waitlist strategy. Following LT, the hypothetical patient experienced one of the following scenarios based on predetermined probabilities as determined from the literature: uneventful recovery; ischaemic cholangiopathy; retransplantation, or death.

Model assumptions

Several assumptions were made in the creation of this model. The patient in the base case scenario was a 56-year-old man with non-alcoholic steatohepatitis. All costs associated with LT were assumed to be the same for both DBD and DCD LT. In addition, for the DCD organ, all donor qualities, such as age and body mass index (BMI), as well as procedure-related characteristics, such as procurement techniques and warm and cold ischaemia time, were not varied. Wait-listed candidates for both the DBD organ-only and DBD + DCD organs were modelled to be identical. The recipient pools for both DBD organ-only and DBD + DCD organs were assumed to be homogeneous in terms of characteristics such as age, MELD score and aetiology of liver failure distributions. All retransplanted livers were modelled as DBD organs.

Probability and cost data

The probabilities and rates for the baseline analysis and the ranges of these values for all sensitivity analyses are reported in Table 1. These values were determined through a systematic review of the MEDLINE/PubMed database for all reports on deceased donor LT from 2000 to 2011, especially reviews of Scientific Registry of Transplant Recipients (SRTR) data and meta-analyses. Table 1 also presents all cost estimates and ranges. Published data for specific institutional costs, the Medicare database, or similar databases were used for the cost analysis. Cost data were also obtained from published studies identified in the systematic review of the literature. All monetary values were adjusted for inflation to 2010 US dollars using the Consumer Price Index for medical care (US Bureau of Labor Statistics²⁸). To account for the cost of spending money now vs. in the future, health benefits and future costs were discounted at a constant rate of 3%.²⁶

All costs were approached from a societal perspective.²⁹ Modelling from the societal perspective allows for comparisons with

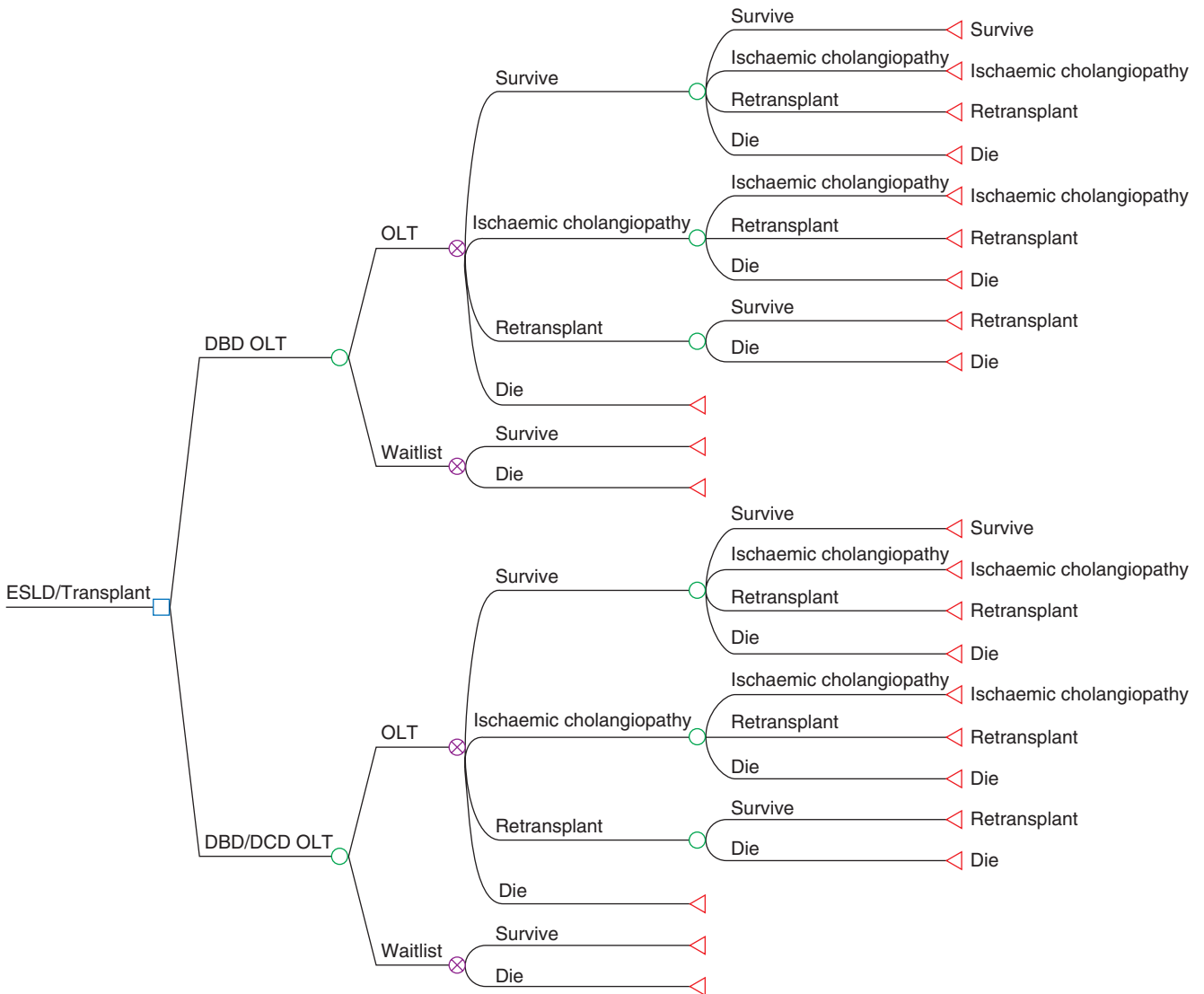


Figure 1 Markov decision tree representing the choice of strategies for organ donation. The two clinical options are represented at the decision node. Probabilities and estimates of probabilities are listed in Table 1. □, choice between strategies (decision node); ○, occurrence of chance events (chance node); ◁, logic check in the simulation (terminal node). DBD, donated after brain death; DCD, donated after cardiac death; ESLD, end-stage liver disease; OLT, orthotopic liver transplant

findings in similar studies that focus on patient outcomes and costs to society. Both positive and negative cost changes resulting from an intervention were considered. Furthermore, rather than being limited to interpretation for a particular patient population, the present findings can be interpreted from the public or societal point of view.

Utilities

The effectiveness of different waitlist strategies was measured in terms of QALYs. This measure of health value incorporates both quality of life and time into a composite statistic that allows for comparison between health interventions. Quality of life is

determined by health utilities reported in the literature, which usually range from 0 (utility of death) to 1 (utility of perfect health). Utilities represent the reported health preferences of groups of patients in the various health states of the model³⁰ (Table 1).

Sensitivity analysis

One- and two-way sensitivity analyses were performed to test the model conclusions based on variations in the range of values and costs reported in the literature. The ranges utilized for these analyses are described in Table 1. Multi-way probabilistic sensitivity analyses using Monte Carlo methods, which change

Table 1 Probabilities and costs based on reports in the literature

Baseline parameters	Value	Range	References
3-year survival, %			3-16,20,32
DBD OLT	75%	50–90%	
DCD OLT	65%	45–85%	
Retransplantation	45%	35–75%	
Probability of DCD organ	5%	3–20%	
Retransplantation rate, %			3,6,7,9–16,18,20,33,34
DBD OLT	5%	2–8%	
DCD OLT	15%	5–35%	
Ischaemic cholangiopathy rate, %			7,8,17–22,28,34
DBD OLT	1%	0–5%	
DCD OLT	20%	15–40%	
Waitlist mortality, %			32,35–39
DBD organ-only list	15%	5–25%	
DBD + DCD organ list	10%	5–25%	
Utility			4,25,29,33,34,40–51
Cirrhosis on waitlist	0.6 QALY	0.3–0.8 QALY	
OLT	0.8 QALY	0.5–0.9 QALY	
Retransplantation	0.7 QALY	0.4–0.9 QALY	
Ischaemic cholangiopathy	0.6 QALY	0.3–0.8 QALY	
Cost, US\$			3,4,16,25,27,33,34,41–54
Waitlist death	50 000	25 000–75 000	
OLT	150 000	100 000–200 000	
Retransplantation	200 000	150 000–250 000	
Ischaemic cholangiopathy	30 000	15 000–50 000	

DBD, donated after brain death; DCD, donated after cardiac death; OLT, orthotopic liver transplant; QALY, quality-adjusted life year.

Table 2 Costs and cost-effectiveness of donated organs

Strategy	Cost, US\$	Incremental cost, US\$	Effectiveness	Incremental effectiveness	Cost-effectiveness, US\$
DBD + DCD organs	366 000	–	6.0 QALYs	–	61 100/QALY
DBD organs only	386 000	18 000	5.6 QALYs	–0.450 QALY	69 300/QALY

DBD, donated after brain death; DCD, donated after cardiac death; QALY, quality-adjusted life year.

all probabilities and costs within the model simultaneously,³¹ provided additional tests of model sensitivity to changes in model parameters.

Results

Base case analysis

The previously described model assumptions and the base case probabilities and costs from Table 1 were used in the base case analysis. When the model is run, the program simulates the transition of hypothetical patients through the model. The results of the reference case analysis in the Markov model are essentially the averages associated with the different outcomes of these hypothetical patients, and are listed in Table 2 and depicted graphically in Fig. 2.

The base case patient in this model was a 56-year-old man with non-alcoholic steatohepatitis. Five-year survival was modelled at 65% in recipients of DCD livers and 75% in recipients of DBD livers. Using a 10-year time horizon, the waitlist strategy that relied exclusively on DBD organs resulted in costs of US\$386 000 to achieve 5.6 QALYs, or approximately US\$69 000/QALY. The waitlist strategy that employed both DBD and DCD organs resulted in costs of US\$366 000 to achieve 6.0 QALYs, or approximately US\$61 000/QALY. Therefore, the DBD + DCD organ waitlist strategy was superior to, and dominated, the DBD organ-only strategy.

Sensitivity analysis

Because the baseline probabilities and costs used in this model vary among the centres and regions in which these procedures are

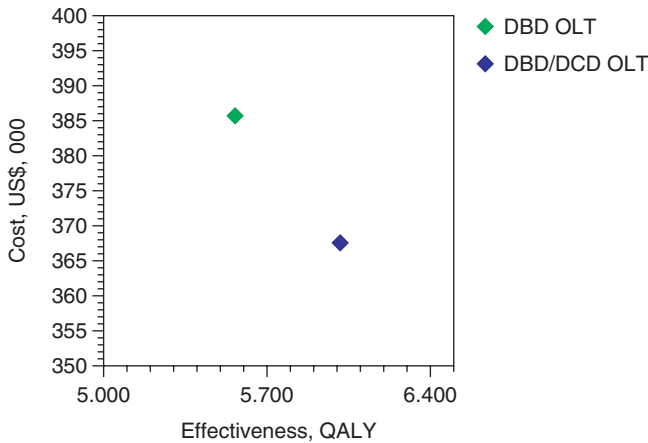


Figure 2 Results of the base case analysis in the Markov model comparing the cost-effectiveness of liver transplantation in end-stage liver disease using organs donated after brain death (DBD) and donated after cardiac death (DCD). The DBD + DCD organ strategy was superior to the DBD organ-only strategy. OLT, orthotopic liver transplant; QALY, quality-adjusted life year

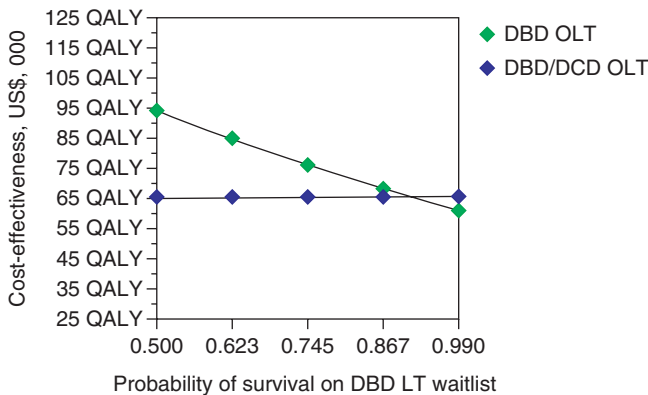


Figure 3 One-way sensitivity analysis in which the rate of waitlist death is varied in the strategy utilizing only organs donated after brain death (DBD). When waitlist mortality is <7% for those awaiting DBD organs only, this becomes the preferable strategy. DCD, donated after cardiac death; OLT, orthotopic liver transplant; QALY, quality-adjusted life year

performed, one- and two-way sensitivity analyses were conducted to test the validity of the conclusions over a range of probabilities and costs. Figure 3 demonstrates the results of a one-way sensitivity analysis in which the rate of waitlist survival in the DBD organ-only strategy is varied. Annual rates of survival on the waitlist vary between 50% and 99%. The threshold value at which DBD + DCD organ use is no longer the dominant (superior) strategy is 93%. Therefore, if waitlist mortality is <7%, the use of only DBD organs becomes the preferable strategy. Figure 4 demonstrates the results of a one-way sensitivity analysis in which the annual rate of survival after DCD LT is varied. The threshold value

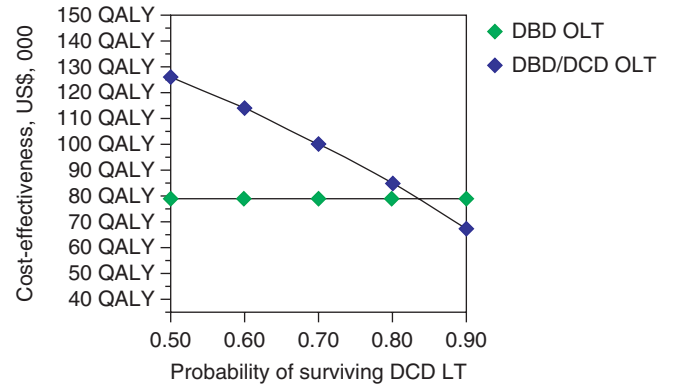


Figure 4 One-way sensitivity analysis in which yearly survival after transplant utilizing organs donated after cardiac death (DCD) is varied. The strategy utilizing only organs donated after brain death (DBD) is the better strategy when the annual mortality rate after DCD organ transplant exceeds 17%. OLT, orthotopic liver transplant; QALY, quality-adjusted life year

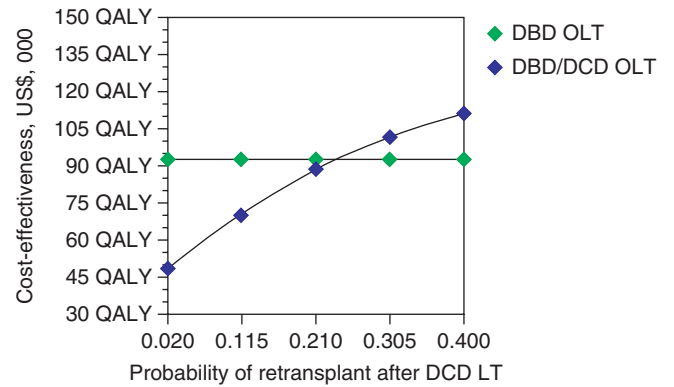


Figure 5 One-way sensitivity analysis in which the probability of retransplantation in the strategy using organs donated after brain death (DBD) and organs donated after cardiac death (DCD) is varied. The DBD organs-only strategy is preferable if retransplantation after DCD liver transplantation exceeds 21%. OLT, orthotopic liver transplant; QALY, quality-adjusted life year

at which DBD + DCD organ use is no longer the dominant strategy is 83%. Therefore, the DBD organ-only strategy becomes preferable if annual mortality after DCD LT exceeds 17%. Figure 5 demonstrates the results of a one-way sensitivity analysis in which the probability of retransplantation after DCD LT is varied. The threshold value at which the DBD + DCD LT strategy no longer dominates is 21%, which means the DBD organ-only strategy is preferable if the retransplantation rate after DCD LT exceeds 21%. In Fig. 6, the probability of receiving a DBD organ in the DBD + DCD LT strategy is varied. When the rate of DBD organs reaches a threshold value of 90%, the DBD organ strategy dominates. Therefore, if DCD organs represent >10% of the donor organ pool, the DBD + DCD waitlist strategy is no longer preferable. In

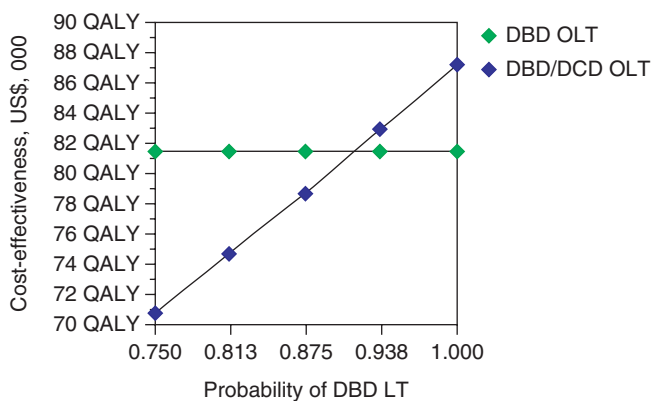


Figure 6 One-way sensitivity analysis in which the probability of receiving an organ donated after cardiac death (DCD) in the strategy utilizing organs donated after brain death (DBD) + DCD is varied. When DCD organs comprise >10% of the organ pool, the DBD + DCD waitlist strategy is no longer the most cost-effective. OLT, orthotopic liver transplant; QALY, quality-adjusted life year

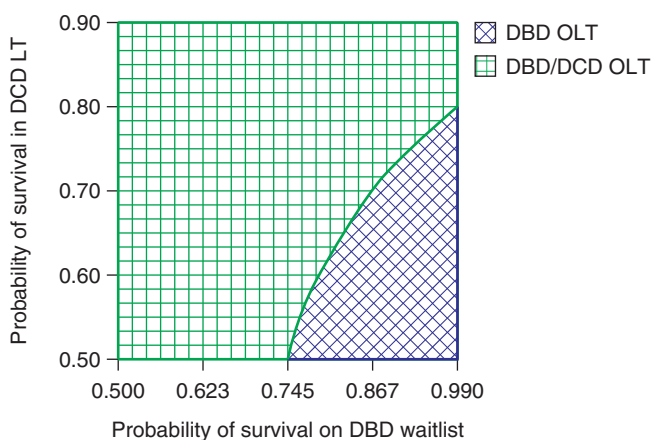


Figure 7 Two-way sensitivity analysis in which rates of waitlist death in the strategy using only organs donated after brain death (DBD) and yearly survival after transplant using organs donated after cardiac death (DCD) are simultaneously varied. The DBD organ-only strategy becomes dominant at low rates of DBD waitlist death and high rates of DCD post-transplant mortality. OLT, orthotopic liver transplant

two-way sensitivity analyses in Fig. 7, rates of waitlist survival in the DBD organ-only strategy and annual post-transplant survival after DCD LT are varied simultaneously. The DBD organ-only transplant strategy becomes dominant at very low rates of DBD organ-only waitlist death and very high rates of post-DCD LT mortality.

One- and two-way sensitivity analyses were performed for a variety of ranges for costs and utilities; the DBD + DCD organ waitlist was the dominant strategy at all clinically relevant values. Additionally, multi-way probabilistic sensitivity analyses using

Monte Carlo methods indicated that DBD + DCD LT was the preferable strategy at all clinically relevant values.

Discussion

Donation after cardiac death is a reasonable solution to address, in part, the well-recognized shortage of organs. The provision of DCD organs can expand the potential donor organ pool by as much as 20%. Outcomes following LT with DBD organs are typically reported as being better than those of LT with DCD livers; however, recent publications indicate that careful pairing of recipients with DCD organs and optimized procurement and transplant procedures may narrow this disparity.^{14,21,22} The aim of this study was to evaluate the cost-effectiveness of a waitlist strategy that included the use of both DCD and DBD organs compared with one that relied on DBD organs exclusively. The present analyses indicated that, although the modelled 3-year survival in DCD LT was less than that in DBD LT, the improvement in waitlist survival and quality of life that occurred when DCD organs were included in a waitlist strategy made their use cost-effective. Sensitivity analyses demonstrated that the use of both DBD and DCD organs continued to be cost-effective as long as DCD organs did not account for >10% of the organs transplanted and the retransplantation rate after DCD LT did not exceed 21%. At most US transplant centres, rates of use of DCD organs and retransplantation fall within these parameters.

According to the present model, individual patients who received a DCD liver had a decreased 3-year modelled survival. Decreased patient survival has also been reported by other groups in both single-centre reports^{4,6,11,14,15} and in a recent review of Scientific Registry of Transplant Recipients (SRTR) data by Jay *et al.*¹¹ Similarly, Mathur and colleagues' review of SRTR data demonstrated that increased donor age, donor weight and cold ischaemia time were associated with poor outcomes.¹⁴

There is substantial variability in reported rates of biliary complications and graft failure associated with DCD LT. The present model indicates that individual patients receiving organs from cardiac death donors encounters a three-fold increase in biliary complications in comparison with patients who receive a liver from a brain death donor. These findings are consistent with those of previously published reports.^{1,7,9,15,19} Foley and colleagues reported single-centre overall rates of biliary complications of 47% in recipients of DCD organs and 26% in those receiving DBD organs.⁸ DeOliveira and colleagues reported a recent European experience of lower overall rates of biliary complications, but noted that higher rates persisted among patients receiving DCD organs (19.7%) in comparison with those receiving DBD organs (12.5%).⁷

In head-to-head comparisons of costs associated with DBD and DCD LT, DCD LT is usually shown to incur higher costs for transplant procedures and post-transplant care. For example, recent analyses of data from the UK demonstrated an increased cost of GBP97 400 per LT when the organ was sourced from a

cardiac death donor, largely as a result of an increased hospital length of stay and rates of acute renal failure requiring inpatient dialysis.^{4,5} In the present model, the cost per QALY gained by using organs from the DCD + DBD organ pool was lower than the equivalent cost in the DBD organ-only strategy. By contrast with the UK analyses,^{4,5} the present model evaluated the costs and benefits in a cohort of hypothetical waitlist patients from a societal perspective, rather than an individual patient perspective. The decreased cost per QALY gained in the DBD + DCD LT strategy results from the inclusion of more potential donors in the donor pool. The costs are lower in this donor strategy because of the decreases in waitlist mortality and pre-transplant morbidity associated with an increased number of donors.

The present cost-utility model provides a new and necessary perspective on societal-level implications of the use of DCD organs in LT. Increasingly, health care cost minimization considerations are balanced with outcome optimization to determine the best options for providing health care at the lowest cost. From the societal perspective, recipients in the DBD + DCD organ waitlist group gained, on average, more QALYs at a lower average cost per QALY in comparison with those in the DBD organs-only group.

A limitation of this study is that LT and donor type considerations have been distilled into a very basic model. The authors recognize that transplant outcomes depend on several recipient characteristics and procedural factors that are not accounted for in the current model. Future studies might include separate models of the use of DCD organs in select recipient populations incorporating pertinent clinical factors such as cold ischaemia time, warm ischaemia time, MELD score, age, and donor and recipient BMI, to model the complexity of DCD LT outcomes.

The present study used published data and meta-analyses to approximate the most likely clinical scenarios, probabilities and costs associated with different types of organ sources. Any publication bias that exists in the peer-reviewed literature on this topic would therefore be reflected in the present model estimates.

A strength of the cost-effectiveness model is that it is adaptable to a wide range of clinical scenarios. The current model helps to elucidate factors that contribute to determining the optimal economic strategy for LT in the face of a substantial disparity between the numbers of candidates and donors. It provides data that can inform future discussions at the patient, institutional and societal levels. Additionally, in an era of increasing health care costs, this model allows policymakers to further understand the costs associated with various options of organ source and utilization in LT and helps to identify policies that are most likely to optimize patient care and minimize societal costs.

Conflicts of interest

None declared.

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