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ORIGINAL ARTICLE

Can donors with high donor risk indices be used cost-effectively in liver transplantation in US Transplant Centers?

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Summary

In an effort to quantify the impact of donor risk factors on recipient outcomes, the donor risk index (DRI) was developed. A high DRI correlates with poorer post-transplant survival. In this study, high-DRI donors are classified as those having DRIs >2.0, while low-DRI donors have DRIs <2.0. The aim of this study was to evaluate the cost-effectiveness of high-DRI donor use in US Transplant Centers. A Markov-based decision analytic model was created to simulate outcomes for an allocation scheme using only low-DRI donors versus a scheme using both low- and high-DRI donors. Baseline values and ranges were determined from published data and Medicare cost data. Sensitivity analyses were conducted to test model strength and parameter variability. An allocation scheme in which only low-DRI donors were used generated 5.2 quality-adjusted life years (QALYs) at a cost of $83 000/QALY. An allocation scheme using both low- and high-DRI donors generated 5.9 QALYs at a cost of $66 000/QALY. Sensitivity analyses supported the use of an allocation scheme using both low- and high-DRI donors. The overall contribution of high-DRI grafts to the donor pool and the resultant reduction in wait-list mortality make them cost-effective.

Introduction

In the United States, there are over 18 000 people on the liver transplant waiting list; however, there are only about 6000 organs available for transplant annually. Unfortunately, this gap between recipients and donors will likely not change significantly in the near future. Transplant centers must find ways to optimize organ allocation. With the inception of the Model for End-Stage Liver Disease (MELD) liver allocation system in the United States on February 27, 2002, the manner in which livers are allocated changed to a system that objectively ranks recipients based on their clinical need for transplant and risk of short-term mortality. The MELD score has helped the transplant community better identify those recipients who would benefit the most from earlier transplantation. This resulted in a decrease in wait-list mortality; however, it has not eliminated wait-list death and has resulted in a national push to expand access to transplantation through the increased utilization of "marginal donors" [1].

The MELD system greatly optimized recipient selection and insured that those with the greatest need should be given an opportunity to be transplanted, but what about optimizing the use of these "marginal donor" organs? There has been a great deal of work in this area recently, most notable, that of Feng and colleagues and the development of a donor risk index (DRI) [2]. The DRI encompasses seven donor factors that were found to accurately depict graft failure after transplantation: age, cause of death, race, donation after cardiac death, height, split allograft, and location. Decreased graft and patient survival is strongly correlated with an increasing DRI. Recipients receiving high-DRI donors have been shown to have twice the length of stay and a twofold increase in hospital costs when compared to recipients of low-DRI donors [3]. Through the use of this index, transplant centers are trying

to identify high-DRI donors or "marginal" organs and define their role in the present allocation scheme to optimize the use of the limited organ supply available.

The purpose of this study is to examine the use of organ allocation schemes that incorporate high- and low-DRI donors. The cost and effectiveness of these schemes will be evaluated as well as their impact on wait-list mortality. To do this, we employed a Markov model. Markov modeling is a dynamic modeling tool that allows multiple facets of clinical scenarios to be varied simultaneously and the most cost-effective solution to a problem identified. These methods are essential when studying processes that are not amenable to randomized controlled trials or events with low rates of occurrence.

Methods

Design overview

A cost-effectiveness decision model was created comparing an allocation scheme using low-DRI donors only with an allocation scheme that uses both low- and high-DRI donors. For the purposes of this study, High-DRI donors were classified as those having DRIs >2.0, while low-DRI donors had DRIs less than or equal to 2.0. A DRI of 2.0 or greater was chosen as the cutoff for high-DRI donors because this represents the 10% of organs that are considered to be associated with the highest risk of poor post-transplant outcomes and highest costs [3]. Base-case analysis with incremental cost-effectiveness determination was performed for an ideal transplant recipient. One-way, two-way, and multiway sensitivity analyses were undertaken to incorporate the uncertainty in model parameters and to determine the impact of key variables on cost-effectiveness. Guidelines set forth by the Panel on Cost-Effectiveness in Health and Medicine were followed for performance of cost-effectiveness analysis [4].

Decision model

TreeAge Pro 2010 software (TreeAge Software, Inc, Williamstown, MA, USA) was used to construct a Markov model of transplantation with alternate donor allocation schemes. In a Markov model, subjects of a cohort are divided among several mutually exclusive health states. Movements of the cohort across these health states are modeled over time (time horizon) into a series of cycles of predetermined lengths. The health states are defined to capture the salient features of the disease and the interventions under consideration. For those potential recipients on the wait list, mortality and quality of life were assessed at the end of each 1-year cycle. At the end of each cycle, the cohort subjects are reallocated across health states guided by transition probabilities that characterize the natural history of the disease until all members of the cohort have reached an absorbing state (i.e., death) or completed the predetermined time horizon. In this study, the time horizon was 10 years with each cycle lasting 1 year. The effects of an intervention can be modeled by altering certain transition probabilities of the model. The total number of years lived by the cohort (life expectancy) and average lifetime health-care costs are accrued at the end of the analysis [5].

The strategies

We compared the costs and outcomes associated with the following two strategies.

1. Transplantation with low-DRI donors only: The entire cohort undergoes transplantation with low-DRI donor organs, trading a higher wait-list mortality for decreased complications and increased patient survival.
2. Transplantation with low- and high-DRI donors: The cohort undergoes transplantation with low-DRI and high-DRI donor organs, accepting more post-transplant complications and decreased patient survival for lower wait-list mortality.

The model developed for this simulation considers 4 health states that exist for patients with end-stage liver disease any time over a 10-year time horizon. Figure 1 displays the health states and transitions represented in the model.

Patient population and base case

The intended population for this analysis was the US liver transplant wait list, and the base case was a man 45 years of age with a BMI of 30 and a MELD score of 25 and end-stage liver disease secondary to hepatitis C. Base-case health preferences and probabilities are summarized in Table 1. Base-case probabilities were derived from exact calculations when available from SRTR data. When actual data were not available, data were abstracted from the literature concentrating on controlled trials or reviews. To create a conservative model, survival probabilities on the lower end of expected were used and complication rates on the higher end of expected were used to populate the model.

Cost

Cost estimates from a societal perspective were derived from published data of Medicare cost [6,7]. Direct and indirect costs of transplantation were incorporated. All monetary values were adjusted to 2012 US dollars using the consumer price index for medical care [8]. Base-case costs are summarized in Table 1.

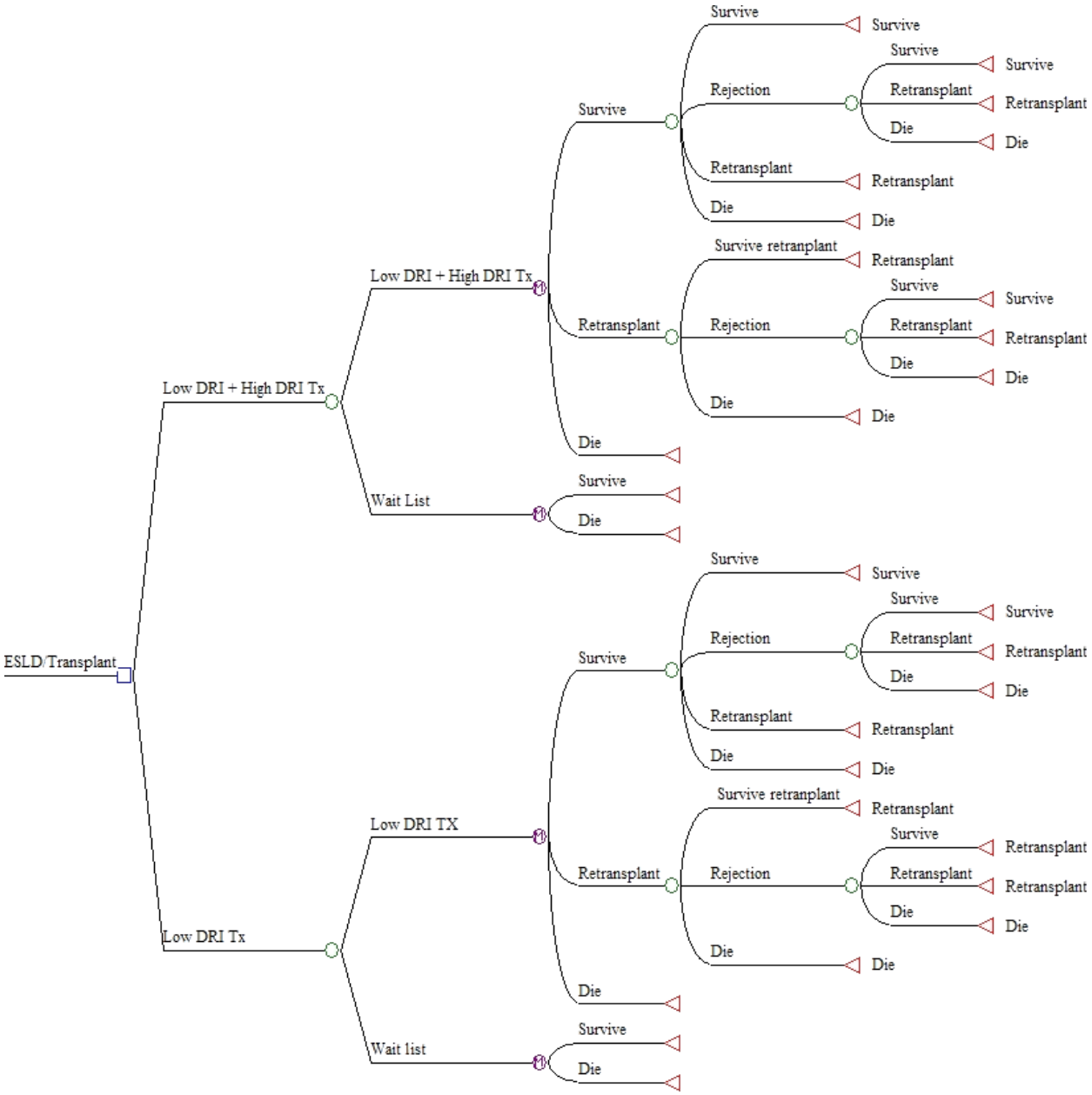

Figure 1 Markov decision tree representing the choice of strategies for organ donation. The two clinical strategies to be chosen from are represented at the square decision node. The probabilities and estimates of their probabilities are listed in Table 1. = the choice between strategies (decision node); M = the point of yearly cycling of patients (Markov node); and = a logic check in the simulation (terminal node). DRI, donor risk index; ESLD, end-stage liver disease.

Effectiveness or utility

Effectiveness was measured in terms of quality-adjusted life years (QALYs) that provide a composite value of both quality of life and time. QALYs are calculated based on health utilities determined by standard methodology assigning procedures and diagnoses a value ranging from 0 (utility of death) to 1 (utility of perfect health). QALYs incorporate both quality of life (health utility) and time (years) and are calculated by multiplying the health utility by the total time spent in a given health state. In this study, the cohort moved through health states yearly over a 10-year horizon. Discounting of quality-adjusted life expectancy was performed at a rate of 3% per year. Base-case utilities are summarized in Table 1.

Table 1. Literature-based probabilities and costs.

Baseline parameters	Value	Range	References
3-year survival (%)			
Low-DRI OLT	75	50–90	[2,3,9,10]
High-DRI OLT	60	45–85	
Re-Tx	45	35–75	
Probability high-DRI donor	10	3–20	
Retransplantation rate (%)			
Low-DRI OLT	5	2–8	[2,3,9,10]
High-DRI OLT	15	5–35	
Wait-list mortality (%)			
Low-DRI list	15	5–25	[2,3,9,10]
Low-DRI/ High-DRI list	10	5–25	
Utility			
Cirrhosis on wait list	0.6 QALY	0.3–0.8 QALY	[11–15,22,23]
Low-DRI OLT	0.8 QALY	0.5–0.9 QALY	
High-DRI OLT	0.7 QALY	0.4–0.9 QALY	
Re-Tx	0.7 QALY	0.3–0.8 QALY	
Cost			
Wait-list death	$50 000	$25 000–75 000	[5–7,11–15,
Low-DRI OLT	$150 000	$100 000–200 000	21–23]
High-DRI OLT	$200 000	$150 000–250 000	
Re-Tx	$215 000	$150 000–250 000	

DRI, donor risk index; QALY, quality-adjusted life year; OLT, orthotopic liver transplant; Re-Tx, retransplant.

Sensitivity analyses

Sensitivity analyses were performed to explore the degree to which our base-case analyses were influenced by uncertainty regarding parameter values used in the model. DRI ranges were varied in sensitivity analyses, and multiple recipient characteristics were explored in sensitivity analyses including MELD, ESLD etiology, and BMI. In one-way sensitivity analyses, the results were recalculated as the values of model parameters were individually varied. Additionally, two-way sensitivity analyses were performed to examine the effects of varying pairs of influential variables simultaneously. To integrate higher levels of uncertainty often encountered in clinical practice, multiway probabilistic sensitivity analysis was used with Monte Carlo methods.

Results

Base-case analysis

In the base-case scenario, a transplantation scheme that incorporated the use of only low-DRI donors generated 5.2 QALYs and cost $432 000 (Table 2 and Fig. 2). This equated to a cost of $83 000 per QALY. A transplantation scheme that incorporated the use of both low- and high-DRI donors generated 5.9 QALYs and cost $392 000. This equated to a cost of $66 000 per QALY. The low- and high-DRI donor scheme was $40 000 less costly and yielded 0.7 more QALYs over the 10-year study horizon. Therefore, the low- and high-DRI donor scheme is the dominant or most cost-effective strategy.

One-way and two-way sensitivity analyses

Figure 3 demonstrates the results of a one-way sensitivity analysis in which the rate of wait-list death in the low-DRI donor only strategy is varied. The yearly rate of survival on the wait list is varied between 50% and 99%. The threshold

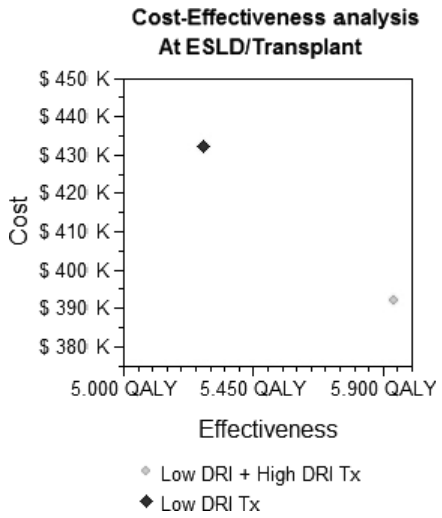

Figure 2 Results of the base-case analysis in the Markov model comparing the cost-effectiveness of wait-list strategies using low-DRI donor only versus low- and high-DRI donors in liver transplant. The strategy using both low- and high-DRI donors is the dominant strategy meaning that is costs the least and generates the most QALYs. DRI, donor risk index; QALY, quality-adjusted life year.

Table 2. Costs and cost-effectiveness of organ donors.

Strategy	Cost ($)	Incremental cost ($)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Cost/effectiveness ($/QALY)
Low DRI + High DRI	$392 000	–	5.9 QALY	–	$66 000/QALY
DBD Only	$432 000	$40 000	5.2 QALY	−0.70 QALY	$83 000/QALY

DRI, donor risk index; QALY, quality-adjusted life year.

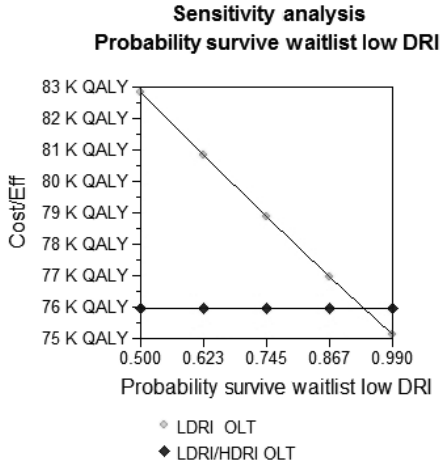

Figure 3 One-way sensitivity analysis where the rate of wait-list death is varied in the low-DRI donor only strategy. When the wait-list mortality is <7% for those awaiting low-DRI donors only, it becomes the preferred strategy. DRI, donor risk index.

value at which the low- and high-DRI donor strategy is no longer dominant (superior) is 93%. Therefore, wait-list mortality would have to be <7% annually before the low-DRI donor only becomes the preferable strategy.

A one-way sensitivity analysis was performed in which the probability of receiving a high-DRI donor transplant from the wait list is varied, as shown in Fig. 4. The threshold value at which the low- and high-DRI donor strategy is no longer the dominant strategy is 82%. Therefore, if a center uses more than 18% high-DRI donors, the low-DRI donor only strategy becomes preferable.

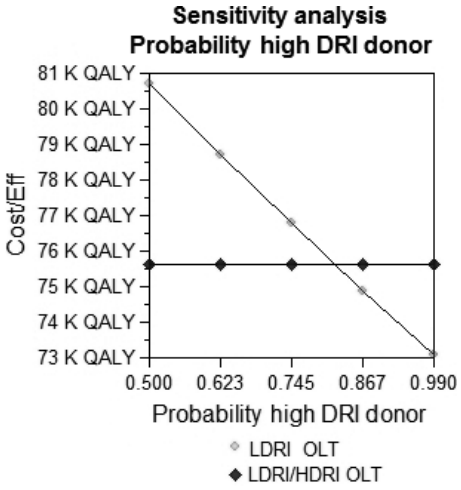

Figure 4 One-way sensitivity analysis in which the probability of receiving a high-DRI donor is varied. The low DRI only strategy is the best strategy when the rate of high-DRI donor transplant exceeds 18%. DRI, donor risk index.

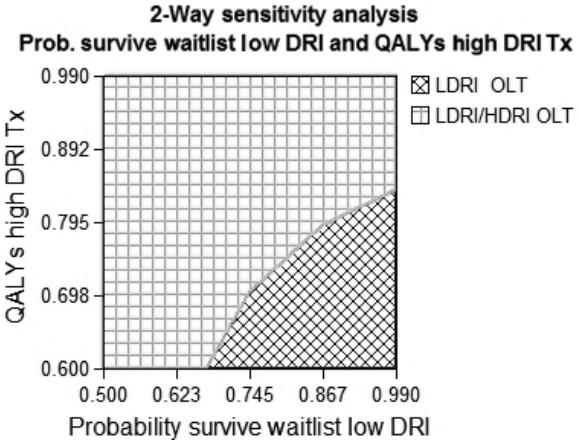

Figure 5 Two-way sensitivity analysis varying both rates of wait-list death in the low-DRI donor only strategy and QALYs after receiving a high-DRI donor transplant were simultaneously varied. The low-DRI donor only transplant strategy becomes dominant at low rates of low-DRI donor wait-list death and low QALYS after high-DRI donor transplantation. DRI, donor risk index; QALY, quality-adjusted life year.

In a two-way sensitivity analyses (Fig. 5), the rates of wait-list death in the low-DRI donor only strategy and the QALYs after receiving a high-DRI donor transplant were simultaneously varied. The low-DRI donor only transplant strategy becomes dominant at very low rates of death on the low-DRI donor only wait list and when the QALYs generated by transplanting high-DRI donor organs is low.

One-way sensitivity analyses were performed for a range of DRI and recipient MELD and etiology of liver disease (HCC, HCV, etc.). In all, the most influential factor on cost-effectiveness was donor DRI over 2.0.

One-way and two-way sensitivity analyses were performed for a variety of ranges for costs and utilities and the low- and high-DRI donor wait list was the dominant strategy at all clinically relevant values. Additionally, multiway probabilistic sensitivity analyses using Monte Carlo methods also proved low- and high-DRI donor transplants to be the dominant strategy at all clinically relevant values.

Multiway sensitivity analysis

In a multiway sensitivity analysis, 10 discrete cost, utility, and probability values were replaced with triangular distributions to incorporate plausible ranges of these values within the model. Essentially, all 10 variables were changed simultaneously in the model to encompass a high level of uncertainty with the decision to choose the use of a low- and high-DRI donor scheme or a scheme that uses only low-DRI donors. Similar to the base-case analysis, a strategy that used both low- and high-DRI donors was generally less costly and more effective than a strategy that used only low-DRI donors.

Discussion

In this cost-effectiveness analysis of two transplantation schemes utilizing different donor use strategies, the use of both low- and high-DRI donors was found to be less costly and more effective than using only low-DRI donors. We characterized high-DRI donors as those with a DRI over 2.0. This represented the 10% of donors who were very high risk and associated with extremes of post-transplant cost and survival. Therefore, it was demonstrated that although these riskier donors may individually result in more costs, their inclusion in the donor scheme and resultant decrease in wait-list death were more cost-effective for society. These results were robust to reasonable levels of uncertainty in the decision model. The most important factors to choosing the best strategy for donor use included the percentage of high-DRI donors in the donor pool and the rate of wait-list death. A higher percentage of high-DRI donors is used in Europe compared with US transplant centers [24,25]. The sensitivity analyses allowed the modeling of the use of high-DRI donors over a wide range of probabilities and demonstrated that if centers use more than 18% of donors with a DRI over 2.0, then transplantation will likely not be cost-effective. Also, unless a center had a very low rate of wait-list morality of <7%, then the use of high-DRI donors benefited their population. Therefore, unless centers excessively use high-DRI donors or have very low wait-list death, then the use of high-DRI donors in the general donor pool is cost-effective.

There have been multiple studies over the last two decades analyzing the risk of graft failure after liver transplantation [16–18]. Feng and colleagues developed the DRI to focus on donor characteristics while adjusting for multiple recipient and transplant characteristics [2]. A reliable decrease in graft and patient survival was demonstrated with increasing DRI. In looking at the economic impact of the use of donors with a high DRI, Axelrod and colleagues demonstrated that the use of high-DRI donors results in an increase in hospital length of stay and hospital cost [3]. In the present study, we sought to analyze the societal impact of the use of DRI donors. We found that when high-DRI donors are incorporated into the donor pool with low-DRI donors, their use should help to decrease wait-list death and make transplantation less costly over all.

These results are supported by work from Schaubel *et al.*[19] in an analysis of survival benefit as a function of candidate disease severity and donor quality. While transplantation of high-DRI donors into low-MELD score patients negatively impacted survival, transplantation of high-DRI donors into recipients with MELD scores >20 provided a significant survival advantage. Amin and colleagues explored a similar concept and looked at whether recipients should accept expanded criteria donor (ECD) livers or wait for more ideal standard criteria donor livers (SCD) [20]. In this study, the authors found that in patients with MELD scores >30, there was a survival benefit with immediate ECD transplants despite higher rates of primary graft failure.

In a paper by Salvalaggio *et al.* [21], the authors again demonstrated the increased costs associated with the use of high-DRI donors. They found that MELD and DRI interact synergistically. Patients with high MELD scores who received high-DRI donor organs experienced significantly more costly care post-transplant. This is compounded in centers in highly competitive regions where it is essential to use high-DRI donors in high-MELD score patients to minimize wait-list death. The authors agree that despite the increase cost of these transplants, there is a life-saving advantage to using high-DRI donors.

The results of this study must be interpreted within the contexts of its limitations. We used a model to simulate the complex process of an individual's progression from end-stage liver disease to wait list. Their progression from wait list to transplantation and death was then modeled. Throughout this progression, we made educated assumptions backed by the literature. We also incorporated wide variations in these assumptions through sensitivity analyses. However, there remains a great deal of complexity between donor and recipient interactions that are difficult to quantitate and model. Another limitation of this study and the concept of DRI in general is that the DRI is based on calculations made on a subset of the US SRTR database from 1998 to 2002. The DRI has not been recalculated with a newer dataset, and survival characteristics have likely changed in the last 10 years. Additionally, this model is based on the US transplant population. Therefore, careful consideration of the conclusions must be observed by transplant centers outside the United States as their transplant practices and outcomes may differ significantly. Despite these limitations, this type of modeling is extremely effective in situations in which randomized controlled trials can never be performed.

Authorship

DEM: designed and performed the research/study and wrote the manuscript. CDK and LAD: performed the research/study and wrote the manuscript.

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References

1. Marks WH, Wagner D, Pearson TC, *et al.* Organ donation and utilization, 1995–2004: entering the collaborative Era. *Am J Transplant* 2006; **6**: 1101.

2. Feng S, Goodrich NP, Bragg-Gresham JL, *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783.
3. Axelrod DA, Schnitzler M, Salvalaggio PR, *et al.* The economic impact of the utilization of liver allografts with high donor risk index. *Am J Transplant* 2007; **7**: 990.
4. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996; **276**: 1253.
5. Roberts DN, Arguedas MR, Fallon MB. Cost-effectiveness of screening hepatopulmonary syndrome in liver transplant candidates. *Liver Transpl* 2007; **13**: 206.
6. Best JH, Veenstra DL, Geppert J. Trends in expenditures for Medicare liver transplant recipients. *Liver Transpl* 2001; **7**: 858.
7. Northup PG, Abecassis MM, Englesbe MJ, *et al.* Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost. *Liver Transpl* 2009; **15**: 148.
8. Consumer price index for medical care. United States Department of Labor Bureau of Labor Statistics. http://www.bls.gov/cpi. Accessed on July 3, 2012.
9. OPTN. Liver-only National Data 2002-2008: Organ Procurement and Transplantation Network. Accessed April 2009.
10. VUMC Liver Transplant Database 2002-2008. Accessed June 2008.
11. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan Criteria. *Am J Transplant* 2008; **8**: 839.
12. Younossi ZM, Singer ME, McHutchison JG, Shermock KM. Cost effectiveness of interferon alpha 2b combined with ribavirin for the treatment of chronic hepatitis C. *Hepatology* 1999; **30**: 1318.
13. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and cost in the United States. *Am J Public Health* 2000; **90**: 1562.
14. Bennett WG, Inoue Y, Beck R, *et al.* Estimates of the cost-effectiveness of a single course of interferon-alpha2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997; **127**: 855.
15. Wong LL, McFall P, Wong LM. The cost of dying of end-stage liver disease. *Arch Intern Med* 1997; **157**: 1429.
16. Markman JF, Markman JW, Markman DA, *et al.* Preoperative factors associated with outcome and their impact on resource use in 1148 consecutive primary liver transplants. *Transplantation* 2001; **72**: 1113.
17. Ghobrial RM, Gornbein J, Steadman R, *et al.* Pretransplant model to predict posttransplant survival in liver transplant patients. *Ann Surg* 2002; **236**: 315.
18. Rull R, Vidal O, Momblan D, *et al.* Evaluation of potential liver donors: limits imposed by donor variables in liver transplantation. *Liver Transpl* 2003; **9**: 389.
19. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *Am J Transplant* 2008; **8**: 419.
20. Amin M, Wolf MP, Tenbrook JA, *et al.* Expanded criteria donor grafts for the deceased donor liver transplantation under the MELD system: a decision analysis. *Liver Transpl* 2004 Dec; **10**: 1468.
21. Salvalaggio P, Dzebisashvili N, MacLeod K, *et al.* The interaction among donor characteristics, severity of liver disease, and the cost of liver transplantation. *Liver Transpl* 2011; **17**: 233.
22. Landman MP, Feurer ID, Pinson CW, Moore DE. Which is more cost-effective under the MELD system: primary liver transplant, or salvage transplantation after hepatic resection or after loco-regional therapy for hepatocellular carcinoma within Milan Criteria? *HPB (Oxford)* 2011; **13**: 783.
23. Dageforde LA, Feurer ID, Pinson CW, Moore DE. Is liver transplantation using organs donated after cardiac death cost-effective or does it decrease wait list death by increasing recipient death? *HPB (Oxford)* 2013; **15**: 182.
24. Avolio AW, Cillo U, Salizzoni M, *et al.* Balancing donor and recipient risk factors in liver transplantation: the value of D-MELD with particular reference to HCV recipients. *Am J Transplant* 2011 Dec; **11**: 2724.
25. Braat AE, Blok JJ, Putter H, *et al.* The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012 Oct; **12**: 2789.

