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Comparing Simultaneous Liver-Kidney Transplant Strategies: A Modified Cost-Effectiveness Analysis

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Abstract

Background: The proportion of patients with kidney failure at time of liver transplantation is at an historic high in the United States. The optimal timing of kidney transplantation with respect to the liver transplant is unknown.

Methods: We used a modified cost-effectiveness analysis to compare four strategies: the old system ("pre-OPTN"), the new Organ Procurement Transplant Network (OPTN) system since August 10, 2017 ("OPTN"), and two strategies which restrict simultaneous liver-kidney transplants ("safety net" and "stringent"). We measured "cost" by deployment of deceased donor kidneys (DDKs) to liver transplant recipients and effectiveness by life years (LYs) and quality-adjusted life years (QALYs) in liver transplant recipients. We validated our model against Scientific Registry for Transplant Recipients data.

Results: The OPTN, safety net and stringent strategies were on the efficient frontier. By rank order, OPTN > safety net > stringent strategy in terms of LY, QALY and DDK deployment. The pre-OPTN system was dominated, or outperformed, by all alternative strategies. The incremental LY per DDK between the strategies ranged from 1.30 to 1.85. The incremental QALY per DDK ranged from 1.11 to 2.03.

Conclusion: These estimates quantify the "organ"-effectiveness of various kidney allocation strategies for liver transplant candidates. The OPTN system will likely deliver better liver

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transplant outcomes at the expense of more frequent deployment of DDKs to liver transplant recipients.

Introduction

In 2002, the United States (US) Organ Procurement and Transplant Network (OPTN) adopted the Model for End-stage Liver Disease (MELD) score for assigning priority in liver transplantation[1]. The presence of kidney failure increases the MELD score and thus liver transplant priority. Due to broader acceptance criteria for liver transplant candidates and universal application of the MELD score, the proportion of patients with kidney failure at time of liver transplant has risen, leading to a surge in simultaneous liver-kidney (SLK) transplants. OPTN data show that 531, or 5%, of all deceased donor kidneys (DDKs) transplanted in 2014 were allocated as SLK. Of these kidneys, approximately half were allocated to recipients with conventional indications for kidney transplantation, *i.e.* metabolic disease (*e.g.* primary hyperoxaluria) or prolonged dialysis-dependence (Table 1). However, the rest were allocated without meeting any formal criteria[2]. Given the ongoing scarcity of organs, every organ allocated to one patient is necessarily withheld from another[3]. The practice of SLK transplantation has come under considerable scrutiny in recent years and was reformed on August 10, 2017 by the OPTN.

For those liver transplant candidates without a conventional indication for kidney transplantation, four strategies for liver-kidney transplantation are possible (Figure 1a). In the old US system (“pre-OPTN”), they undergo SLK or liver transplantation alone (LTA) at the transplant center’s discretion. Common indications include varying dialysis duration, varying degrees of chronic kidney disease, and varying duration of acute kidney injury, although regional differences abound[4]. Since August 10, 2017, the OPTN has implemented a new system (“OPTN”), by which[5]:

1. Patients will be accepted for SLK transplantation only by meeting certain medical eligibility criteria based on the duration and extent of acute and chronic kidney disease. In theory, these criteria identify patients at a high risk of irreversible kidney failure after LTA.
2. An express kidney transplant waitlist (“safety net”) will be in place: any LTA recipient whose kidneys fail within one year of transplant will receive priority on the kidney transplant waitlist.

These eligibility criteria were arrived at via consensus, and many patients who met them have received LTA with acceptable outcomes[6]. These criteria are to be interpreted as minimal acceptability criteria, rather than designating hard indications for SLK. Two scenarios are thus possible under the new system: 1) only patients who absolutely need SLK are listed for SLK and the remainder receive LTA (“low-utilization scenario”); 2) all patients who meet medical eligibility criteria for SLK are listed for SLK (“high-utilization scenario”) by their transplant centers.

Members in the nephrology and transplant community have proposed a third strategy (“safety net”)[2,7]. This strategy reserves SLK only to liver transplant candidates with conventional kidney transplant indication. All other candidates will undergo LTA backed by

"safety net" allocation, as per the second half of OPTN's new system. A fourth strategy ("stringent") is similar to "safety net" strategy, but eliminates "safety net" allocation altogether. These two strategies form the most conservative kidney transplant strategies for liver transplant candidates.

Controversy exists regarding whether OPTN's criteria for SLK are too broad and will utilize too many DDKs, leading to diminished access for patients with end-stage kidney disease (ESKD) without liver disease who are awaiting kidney transplantation, a far larger pool, already strained by wait times that typically exceed life expectancy[6,8]. We therefore set out to compare four transplantation strategies—pre-OPTN, OPTN, safety net, and stringent—that span the full range of strategies for liver transplant recipients, and included both scenarios within the new OPTN system in the evaluation. Since a prospective randomized controlled trial comparing allocation strategies is not feasible, we turned to decision modeling to fulfill our objective.

Methods

This study consisted of two parts: 1) development and validation of a Markov model for liver transplant candidates, using inputs from a cohort assembled from Scientific Registry of Transplant Recipients (SRTR) 2002–2013 data to recreate the post-SLK and liver transplant trajectories over the same time period; and 2) an assessment of the patient outcomes (life years [LYs] and quality-adjusted life years [QALYs]) and organ costs of the strategies outlined above using this model. We used a simulated study cohort consisting of 55-year-old first-time liver transplant candidates *without* a conventional indication for kidney transplant (primary diagnosis of metabolic disorder or dialysis-dependent for ≥6 weeks). Age 55 was selected, as it is the mean and median age for first-time liver transplant recipients in 2002–2013.

Cohort Definition

Characteristics and outcomes of the simulated cohort were obtained from first-time liver and SLK transplant recipients assembled from SRTR, March 1 2002 through December 31, 2013. March 2002 marks the beginning of the MELD era. The cut-off at December 2013 ensured that we had at least 1-year follow-up for all patients. The SRTR contains de-identified data on all solid organ transplants in the US, including status history (clinical information from the pre-transplant period), recipient information collected at the time of transplant, and dates of graft failure and death. Liver status history forms record pre-transplant serum creatinine and dialysis-dependence at set time intervals, which are required submissions from transplant centers to maintain waitlist priority. We used this information to divide patients into three strata based on their kidney function at time of the liver transplant: little or no kidney disease (estimated glomerular filtrate rate ≥60 mL/min), kidney disease that meets OPTN's criteria for SLK[5] (OPTN+), and kidney disease that does not meet OPTN's criteria (OPTN-). We sequentially excluded 454 recipients of multi-organ transplants other than SLK transplant and 2,036 recipients with a conventional indication for kidney transplant, as noted above. We further excluded 6,365 (11%) patients whose status history forms did not contain sufficient information to place them into the OPTN− *versus*

OPTN+ group. We included these patients as separate stratum in a secondary analysis. Meanwhile, the primary analysis cohort consisted of three strata (Table 2) with outcomes modeled separately by stratum.

Model Structure

We followed patients in each stratum for a lifetime in a discrete-time Markov model. We calculated each outcome in each stratum, and the overall population mean as a weighted average across the three strata. The outcomes included post-transplant life years (LYs), quality-adjusted life years (QALYs), and number of DDKs utilized. A 3% annual discount rate was applied to outcomes and costs.

We modeled four strategies: pre-OPTN, OPTN (both scenarios), safety net, and stringent (Figure 2a). In the high-utilization scenario of OPTN system, *all* patients who met the SLK eligibility criteria received a SLK transplant. In the low-utilization scenario, only the patients who received SLK transplant in the pre-OPTN system *and* met the SLK eligibility criteria received a SLK transplant. The probability of receiving a SLK transplant pre-OPTN was derived from the stratum-specific proportions in 2013 (Table 2).

The model was run in monthly cycles for 30 years, at which point <10% of the cohort remained alive. In each cycle, a patient could transition from one health state to another based on a probability placed into the model. As can be seen in Figure 2b, at any point after the index transplant (LTA or SLK), a patient could die or undergo liver graft failure or kidney (native or graft) failure. Liver graft failure led to liver re-transplantation. Kidney failure led to dialysis and/or entering the kidney transplant waitlist. Kidney failure followed by liver allograft failure led to SLK re-transplantation. To approximate real-life scenarios, we allowed no more than one liver and one kidney transplant after the index transplant. DDK transplant occurred when time-on-waitlist equaled time-to-transplant and the subject had not experienced a competing event (death or liver graft failure). Living donor kidney transplant occurred at 3 months after onset of kidney failure, if a donor were available.

Model Inputs

We derived values for model parameters, especially transition probabilities, from two data sources:

1. Post-LTA and post-SLK transplant outcomes, analyzed based on the SRTR dataset.
2. Published literature, which consisted of registry-based analyses (similar to SRTR) and single-center reports.

Table 3 details parameters used in the model. A detailed discussion of each parameter is included Supplemental S0: Technical Appendix. To reflect uncertainty in average patient risks and costs, each parameter was represented by a continuous probability distribution. We determined the distribution with non-parametric assumptions from simulation (as detailed in Supplemental S0: Technical Appendix), or with back-calculation, using parametric assumptions from the expected value (base model) and 95% confidence interval (range). Some assumptions were necessary; we arrived at them through consensus among the

clinician co-authors and stated them explicitly in Supplemental S0: Technical Appendix. In general, we tried to select assumptions such that they biased the model in one direction: favoring strategies utilizing SLK transplantation more liberally. We selected this direction of bias to counteract the bias in observational literature: the benefit of SLK versus LTA may be underestimated in observational studies, because SLK recipients may be sicker[4]. Biasing the model in one direction, toward less stringent use of SLK, also enhances the interpretability of our results.

We tested a series of assumptions in sensitivity analyses (Supplemental S1). Kidney waitlist length and therefore wait-time to transplant vary regionally, but transplant policies are national. We therefore assessed the strategies across assumptions regarding wait-time to transplant and effects of safety net allocation on wait-time and living donation rate. Because all available studies detailing the mortality risk after SLK *versus* LTA are observational, there is uncertainty surrounding the probability of death after LTA when the patient might have otherwise received SLK. We therefore assessed the direction of strategies across a range of assumptions regarding this death risk.

Some parameters were correlated with others in the model. For instance, in a world where patients experience a higher probability of death after LTA, we would expect that the probability of death is also higher after SLK transplant, *i.e.* the two rates are correlated. We induced a modest correlation (ρ=0.5) using a published rank order approach to create joint distributions for correlated parameters[16], and then built the model based on these joint distributions.

Model Validation

To augment model credibility, we validated the model[17] by plotting the actual *versus* modelled patient outcomes (survival, liver re-transplant-free survival, and death-censored ESKD-free survival) using the Kaplan-Meier method. We used three related SRTR cohorts for actual clinical outcomes:

1. Derivation cohort: First-time adult LTA and SLK transplant recipients, March 1 2002 through December 31 2013, meeting the exclusion criteria as defined in “Cohort Definition”, with follow-up until December 31 2014 (N=53,648);
2. Validation cohort 1: Same cohort as the derivation dataset, with extended follow-up until December 31 2016 (N=53,648);
3. Validation dataset 2: first-time adult LTA and SLK transplant recipients, January 1 2014 through December 31 2015, meeting the exclusion criteria as defined in “Cohort Definition”, with follow-up until December 31 2016 (N=10,147).

Comparison of model output to the derivation cohort tests internal validity, *i.e.* whether the model is able to reproduce the same outcomes from its derivation dataset. The two validation cohorts enable a test external validity, i.e. whether the model is able to predict outcomes in a different dataset.

Outcomes and Analysis

Main outcomes are LYs, QALYs, and number of DDKs deployed to liver transplant recipients. To capture a key aspect of the SLK controversy, *i.e.*, whether the increase in DDK allocated to SLK provides sufficient benefit to justify the practice, we calculated an incremental LY/QALY gained per DDK deployed when comparing one strategy to another. This is a modified form of the incremental cost-effectiveness ratio commonly used in economic analyses: instead of monetary cost, we focus on the organ "cost". For comparison purposes, a metric developed for kidney and kidney-pancreas transplants is the life year from transplant (LYFT)[18]. This may be seen also as an incremental LY gained per DDK when we compared two strategies for treating ESKD: transplantation and dialysis.

We calculated the outcomes as follows. For each patient stratum, we performed 1,000,000 simulations (1,000 microsimulations, nested within 1,000 probability sensitivity analyses [PSAs]). Each microsimulation represented an individual patient's post-transplant course. Each PSA represented a "parallel universe," in which a set of parameters, *e.g.* probability of death after liver transplant, were sampled independently from distributions defined in Table 3. The 1,000,000 simulations therefore represent 1,000 "parallel universes," each of which contains 1,000 individual patients and their unique trajectories. Thus we propagated the uncertainty in the parameters to uncertainty in outcomes modelled. For each study outcome, we constructed the population average within each PSA. We then bootstrapped these population averages to arrive at a pooled result that represented the weighted-average of the three strata: little or no kidney disease (estimated glomerular filtrate rate ≥60 mL/min), kidney disease that meets OPTN's criteria for SLK[5] (OPTN+), and kidney disease that does not meet OPTN's criteria (OPTN-)

Simulations and calibrations to generate model inputs were conducted in SAS 9.4 (Cary, NC). Model validations and simulations were performed in TreeAge Pro 2016 (Williamstown, MA). Stanford University's Institutional Review Board approved this study in accordance with the Declaration of Helsinki (protocol number IRB-40876). The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US government. Findings in this manuscript were partly reported in abstract form at the National Kidney Foundation Young Investigator Forum in April, 2017 and American Transplant Congress in May, 2017.

Results

Model Validation

As internal validation, actual *versus* modelled Kaplan-Meier curves for post-transplant outcomes are virtually superimposable (Figure S3). As external validation, our model slightly overestimates death and liver re-transplant, but closely approximates kidney-specific outcomes (Figure 3). The overestimation is slightly more pronounced in LTA than in SLK transplants.

Analysis

Table 4 summarizes our primary outcomes. The stringent strategy results in the fewest DDKs deployed to liver transplant recipients (3.6 per-100-persons) and the lowest LYs and QALYs per person (9.56 and 7.09, respectively). Moving from the stringent strategy to the safety net strategy results in more LYs and QALYs per person at the expense of more DDKs, with an incremental effectiveness of 1.85 LYs or 2.03 QALYs per DDK deployed. The OPTN and pre-OPTN strategies deploy yet more DDKs. In the low-utilization scenario, wherein an expansion in SLK transplantation does not occur as a result of the new rule, the OPTN strategy generates more LYs/QALYs per person using fewer DDKs, compared to the pre-OPTN strategy. In the high-utilization scenario, where an expansion in SLK transplantation occurs, and every liver transplant candidate eligible for SLK receives one, the pre-OPTN strategy is also not favored. Assuming a starting point with a slightly worse clinical outcome (*i.e.*, safety net), we can choose to move to the pre-OPTN or OPTN strategy by deploying more DDKs to liver transplant recipients. With every additional DDK deployed, we gain 1.15 (1.08–1.22) LY by moving to the OPTN strategy, compared to only 0.89 (0.81–0.98) LY by moving to the pre-OPTN strategy. Thus under no circumstance would we prefer the pre-OPTN over the other strategies, given the set of trade-offs. In sensitivity analysis, these results are robust to the discount rate used, adjustment for the liver transplant counterfactual, wait time to DDK transplant, varying effectiveness of safety net allocation and live kidney donation rate for safety net-eligible patients (Supplemental S1).

Table 5 summarizes detailed organ utilization per strategy. The OPTN strategy has the potential to increase the number of SLKs significantly (high-utilization scenario), but may also decrease the number of SLKs somewhat compared to the pre-OPTN strategy (low-utilization scenario). DDK utilization tracks SLK numbers. Live kidney donation rates are comparable under all the strategies. Activation on safety net is more common in strategies that are more conservative with SLKs. The proportion of patients activated on safety net who ultimately receive DDK transplantation is 70–72%. Average liver graft lifespan ranges from 11.92 (11.90–11.94) years under stringent strategy to 12.02 (11.99–12.04) years under OPTN strategy (high-utilization scenario).

Discussion

In the past few decades, health policy experts have used decision analysis with Markov models to approach problem where an intervention modifies an ongoing risk. In the present study, we compared kidney allocation strategies, which modify the ongoing risks of death and kidney failure after the initial liver transplant. Because organ scarcity lies at the heart of this problem, we used a modified cost-effectiveness analysis approach to evaluate the expected clinical benefit (life year and quality-adjusted life years) as well as the organ “cost,” herein expressed in terms of DDKs deployed per strategy, rather than conventional currencies. We hypothesized a trade-off between maximizing clinical benefit and minimizing DDK deployment[1,19,20], and our objective was to quantify this trade-off.

Our first important finding is that the new OPTN system has the potential to substantially *increase* the number of DDKs deployed to liver transplant recipients, both in the form of SLK transplants and subsequent kidney transplants (3.6 [3.5–3.6] per 100-persons, or 167

kidneys in 2013 terms). Our estimates likely *under*estimate the true number of patients who will qualify for SLK transplants for two reasons. First, we excluded from the analysis patients for whom we could not establish SLK eligibility based on liver status form data, but a proportion of whom likely *will* meet criteria for SLK transplantation by additional data to which transplant centers would have access. Furthermore, we used the 4-variable Modification of Diet in Renal Disease (MDRD4) equation, which has been shown to *over*estimate kidney function in cirrhosis[21–23]—and therefore *under*qualify patients for SLK. These two factors increase the theoretical upper bound of proportion of patients who will qualify for SLK transplants under OPTN's eligibility criteria. The extent to which transplant centers will pursue SLK listing for these eligible patients is unknown. We modelled the OPTN strategy under two scenarios: one in which transplant centers do not expand their indication for SLK transplants, and one in which they do, assuming that the truth will lie somewhere in between. Nonetheless, given that all metrics for transplant centers focus on post-transplant outcomes, we hypothesize that the truth will lean slightly toward the high-utilization scenario in which centers expand their indication for SLK transplants in the hope of improving survival after liver transplant in their sickest patients. As the supply of DDKs has remained rather constant over the past decade, we project that the increase in DDK deployment to liver transplant candidates may diminish access to DDKs for kidney transplant candidates without liver disease, an opportunity cost we have formerly quantified at 5.92 years (1st-3rd quartile: 5.50–6.39 years) per DDK[24], the LYFT[18] that would be expected if we used each DDK deployed to SLK to transplant kidney transplant candidates without liver disease.

Our second important finding is that in both scenarios of OPTN system, all strategies, except the pre-OPTN system, are efficient uses of DDKs with a specific trade-off between liver transplant outcomes and DDK deployment. In the low-utilization scenario, the OPTN system increases LY/QALY per person and decreases DDK deployment compared to pre-OPTN system, so in no scenario would we choose the pre-OPTN system. In the high-utilization scenario, the four strategies are ranked as OPTN > pre-OPTN > safety net > stringent strategy in both liver transplant outcomes and DDK deployment. For any level of DDK use, the OPTN, safety net and stringent strategies are all deploy DDKs more efficiently than the pre-OPTN system. We have additional confidence in our results because our model is biased, as previously discussed, to favor strategies more liberal with SLK transplants: that more restrictive strategies still perform well is therefore all the more striking. Our decision analysis therefore fully supports changing the pre-OPTN system to the new system, even as controversy over the specifics exist[6,8]. Future modifications of the OPTN system may consider setting stricter eligibility criteria for SLK, and our analysis provides the quantification of trade-offs to inform these policy modifications.

Two possible mechanisms account for the relative efficiency of the OPTN system and safety net strategy: 1) in patients who do not meet OPTN's SLK medical eligibility criteria, SLK transplant may yield little appreciable benefit over LTA[5], and thus eliminating these "low-value" SLK transplants reduces DDK deployment without too much adverse effect on patient outcomes; 2) certain patients develop severe kidney failure after LTA due to stochastic peri- and post-operative events, and these patients benefit greatly from the earlier kidney transplants that the OPTN system and safety Net strategy afford.

Our model performed well in internal and external validation. Rates of death and liver re-transplantation are slightly overestimated, especially for LTA recipients. We anticipate that this would bias our results toward policies more liberal with SLK transplants and lead us to understate the effectiveness of the OPTN system (restricted use) and the safety net strategy. This bias thus does not alter our conclusion.

To our knowledge, this is the first comprehensive evaluation of the OPTN's new liver-kidney transplantation strategy, and the first comparison of the new system to the pre-OPTN system and alternative strategies. Compared to prior decision analyses[7,20,25], advantages of this study include the inclusion of *all* liver transplant candidates who might be affected by a change in allocation policy, comparison of clearly defined allocation strategies, and incorporation of SRTR data to provide the highest degree of assurance that the model faithfully mimics reality.

Our study has several important limitations. We relied on observational data, where any comparison of SLK *versus* LTA suffers from confounding by indication, and had to exclude many patients whose kidney status are not as well-defined. We considered some of these factors in sensitivity analyses, which did not alter our qualitative results. Factors we did not consider included different rates of native kidney failure or alternative criteria to define SLK eligibility. Conceivably, there may be biases in the opposite direction. In one study, a subset of liver transplant recipients was listed for, but too unstable to undergo, SLK transplant[26]. The desire to avoid futile kidney transplants in extremely sick liver transplant recipients[27] may also bias the studies by enriching the liver transplant pool with sicker patients, although this is unlikely to overcome the powerful incentive that the SRTR program-specific reporting —which excludes SLK from liver transplant report cards—provides. These biases may lead us to overestimate the effectiveness of the OPTN system and underestimate the effectiveness of the safety net and stringent strategies. Nonetheless, they are unlikely to alter our conclusion that all of these strategies are preferable to the pre-OPTN system. The use of past data to "predict" future outcomes in a complex system is, at best, an imperfect endeavor. For instance, we did not account for changes in future patient mix, future organ supply, technologic changes that may substantially change the field of transplantation, or other policy or structural changes in the transplant field (including liver allocation re-districting). Discounting both benefits and costs, as we have done, is a partial safeguard against weighing the unpredictable future too heavily. Finally, we made the overly simplistic assumption that all liver transplant recipients with kidney failure will move to the kidney transplant waitlist. The scarcity of data on the proportion of such patients who are eligible for kidney transplant *versus* not and their differential rates of survival drove this decision. This bias may lead us to overestimate the effectiveness of the OPTN and the safety set strategy.

In summary, both the new liver-kidney transplantation system put forth by OPTN and competing strategies far more parsimonious in SLK allocation are preferable to the pre-OPTN system of SLK allocation. The net effect on patient outcomes and organ utilization will require further study. We raise concerns over aspects of the current proposal, including a potential increase in the number of DDKs required. Our modelling provides a quantification of the trade-off between liver transplant outcomes and DDK deployment which may inform future modifications to the OPTN SLK allocation system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AKI	Acute kidney injury.
CKD	Chronic kidney disease.
DDK	Deceased donor kidney.
ESKD	End-stage kidney disease.
LTA	Liver transplant alone.
LY	Life year.
LYFT	Life year from transplant.
MELD	Model for End-stage Liver Disease.
MMRF	Minneapolis Medical Research Foundation.
OPTN	Organ Procurement and Transplant Network.
PSA	Probability sensitivity analysis.
QALY	Quality-adjusted life year.
SLK	Simultaneous liver-kidney.
SRTR	Scientific Registry of Transplant Recipients.
US	United States.

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Liver transplant candidate categories	Pre-OPTN	OPTN		Alternative Strategies	
		Low-Utilization Scenario	High-Utilization Scenario	Safety Net Only	Stringent
Dialysis-dependent kidney failure ≥6 weeks	SLK	SLK	SLK	SLK	SLK
Metabolic disease (e.g. hyperoxaluria)	SLK	SLK	SLK	SLK	SLK
Kidney failure[a] meeting OPTN proposed criteria	SLK or LTA	SLK or LTA + Safety Net	SLK	LTA + Safety Net	LTA
Kidney failure[a] not meeting above criteria	SLK or LTA	LTA + Safety Net	LTA + Safety Net	LTA + Safety Net	LTA
No kidney failure[a]	LTA	LTA + Safety Net	LTA + Safety Net	LTA + Safety Net	LTA

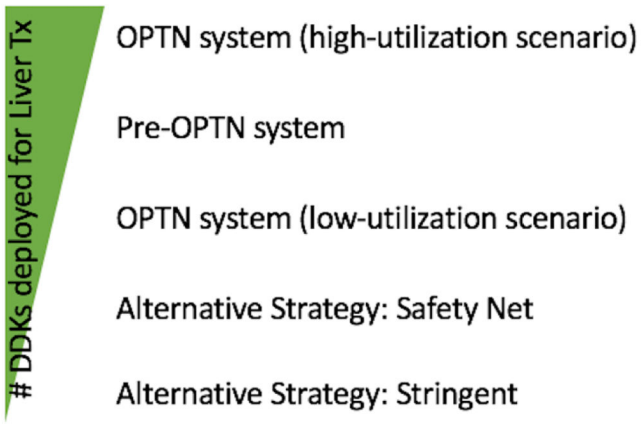
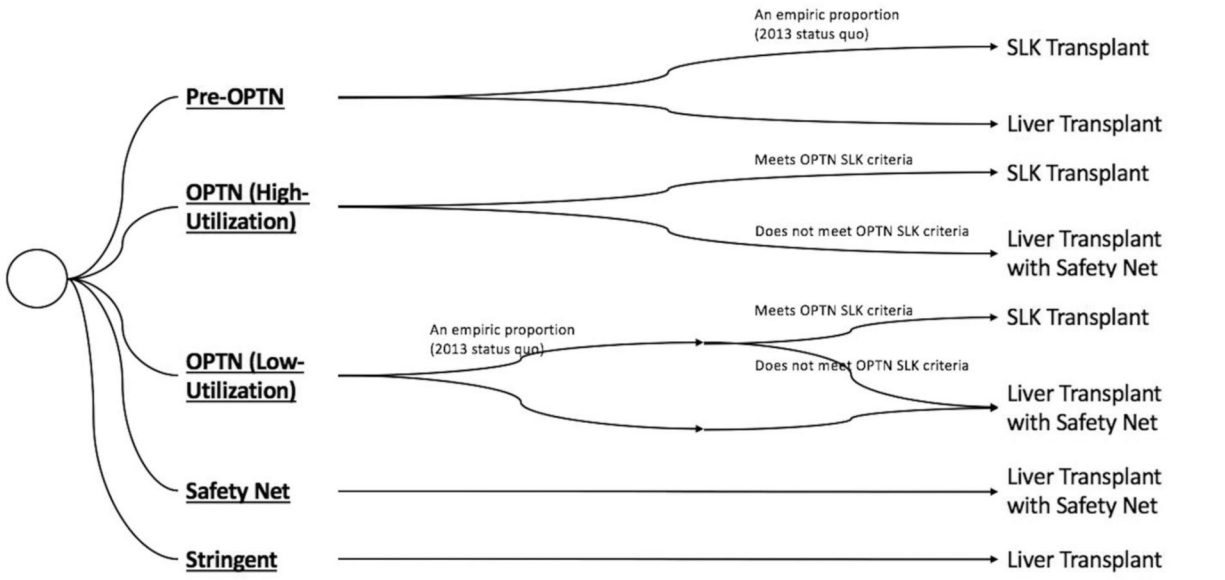
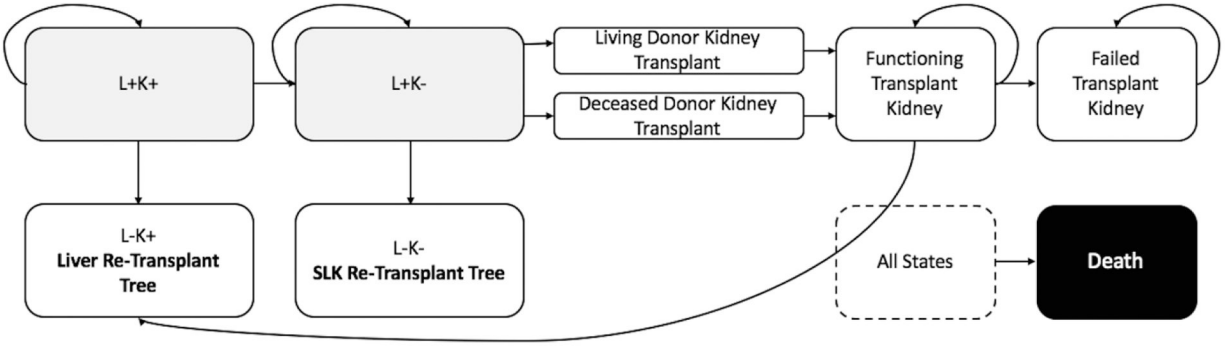


Figure 1.

Kidney transplant strategies for liver transplant candidates, in detail (**panel A**) and ranked by number of deceased donor kidneys needed (**panel B**).



Safety Net: Patients who develop irreversible kidney failure within 1 year of the liver transplant are afforded priority on the kidney transplant waitlist



L+: Functioning liver graft. **L-**: Liver graft failure necessitating liver re-transplant.
K+: Functional kidney (native or graft), dialysis-independence. **K-**: Kidney failure necessitating dialysis.

Figure 2.

Decision model layout. **Panel A**: Decision tree schematic depicting the four strategies. **Panel B**: Schematic diagram depicting the health states and their flow post-transplant in the Markov model. Death could happen in any health state.

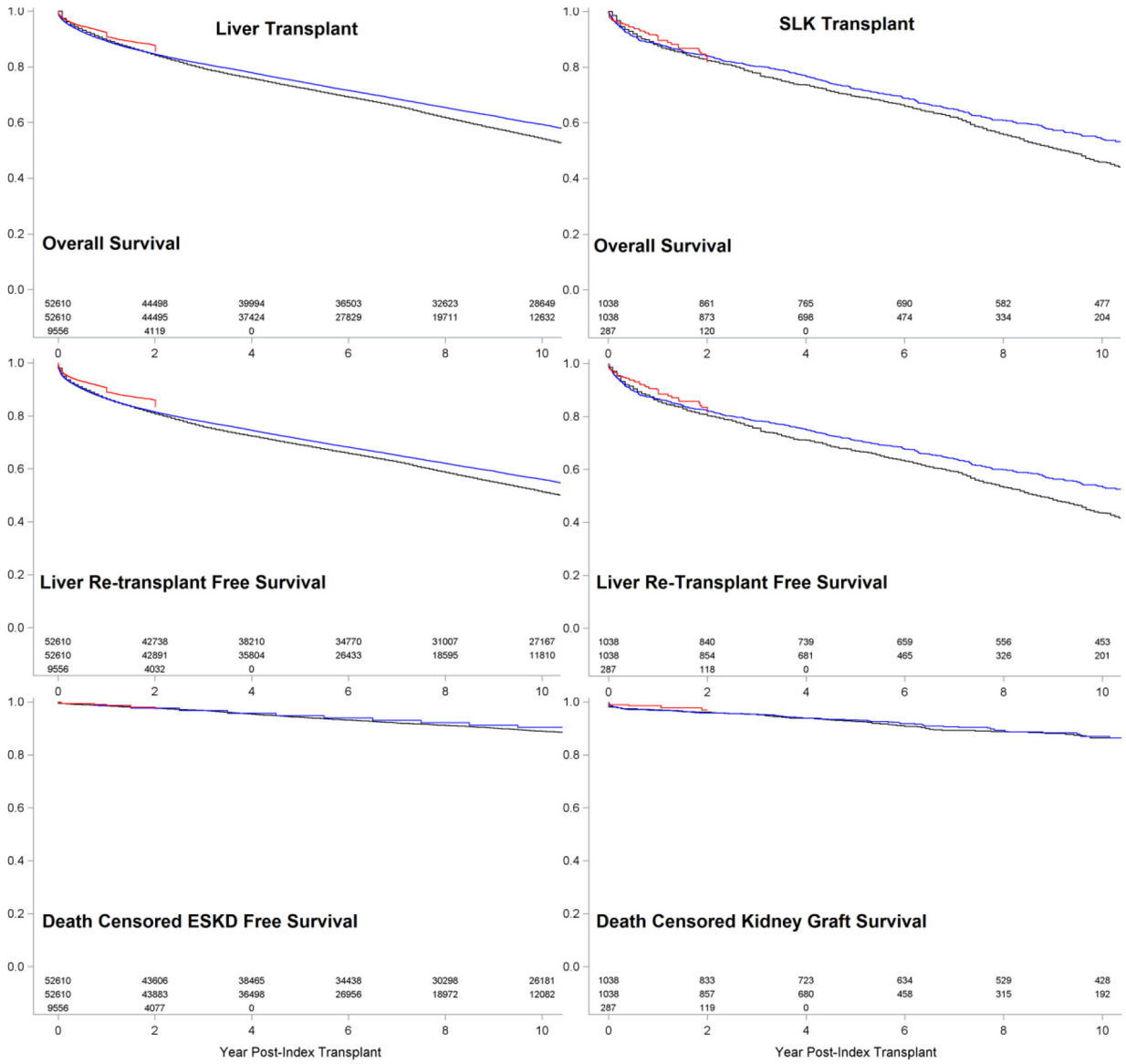


Figure 3.

External validation: Actual SRTR (blue: validation set #1; red: validation set #2) *versus* modelled (black) outcomes after LTA or SLK transplantation.

Table 1.

Indications for first-time simultaneous liver-kidney transplantation (SLK) in adults, March 1 2002 – December 31 2013.

Indication	Number
Dialysis duration ≥6 weeks	1640 (44%)
Metabolic disorder, e.g. primary hyperoxaluria	96 (3%)
Triple-organ transplant (heart-liver-kidney or liver-intestine-kidney)	10 (<1%)
Other	1943 (53%)
Meeting OPTN AKI criteria for SLK	433 (11%)
Meeting OPTN CKD criteria for SLK	267 (7%)
Not meeting OPTN criteria for SLK	351 (10%)
Unknown if meeting OPTN criteria for SLK	892 (24%)
Total	**3689**

OPTN = Organ Procurement and Transplant Network. AKI = acute kidney injury. CKD = chronic kidney disease.

Table 2.

A theoretical cohort is assembled based on adult, first-time liver transplant recipients from Scientific Registry of Transplant Recipients (SRTR), 2013 data.

Stratum	SRTR Cohort (N=4649)		Proportion in Theoretical Cohort
	Received LTA	Received SLK	
1: No kidney failure	2826	0	0.6079
2: Kidney failure (OPTN−)	1510	34	0.3321
3: Kidney failure (OPTN+)	188	91	0.0600

OPTN+ and OPTN− refer to whether the patient's degree of kidney disease qualifies them for simultaneous liver-kidney (SLK) or liver transplant alone (LTA) based on Organ Procurement and Transplant Network's proposed SLK criteria.

Table 3.

Parameter inputs for decision tree and Markov model. L+/−: functioning or non-functioning liver allograft. K +/−: functioning or non-functioning kidney, allograft (if initial transplant is SLK) or native (if initial transplant is liver). KD: Kidney disease. OPTN-: Kidney disease not meeting OPTN criteria for SLK. OPTN+: Kidney disease meeting OPTN criteria for SLK.

Parameter	Stratum	Base Model	Range	Distribution	Source	Technical Appendix
Probability of outcome at month 1 post-index transplant						
Post-SLK transplant:						
L+K−	OPTN−	0.012	0.003–0.026	beta (4,334)	SRTR cohort	A
	OPTN+	0.019	0.010–0.030	beta (13,687)		
L−K+	OPTN−	0.003	0.000–0.011	beta (1,337)	SRTR cohort	A
	OPTN+	0.013	0.006–0.022	beta (9,691)		
Death	OPTN−	0.024	0.010–0.042	beta (8,330)	SRTR cohort	A
	OPTN+	0.020	0.011–0.032	beta (14,686)		
Post-liver transplant:						
L+K−	No KD	0.003	0.001–0.005	beta (11,3289)	[9]	A
	OPTN−	0.006	0.005–0.007	beta (215,34185)		
	OPTN+	0.033	0.019–0.046	beta (23,680)		
L−K+	No KD	0.022	0.020–0.023	beta (722,32933)	SRTR cohort	A
	OPTN−	0.018	0.016–0.020	beta (306,16758)		
	OPTN+	0.013	0.009–0.019	beta (25,1866)		
Death	No KD	0.023	0.021–0.024	beta (759,32896)	SRTR cohort	A
	OPTN−	0.036	0.033–0.038	beta (609,16455)		
	OPTN+	0.044	0.036–0.054	beta (84,1807)		
Transition probabilities per cycle, month 1 and beyond post-index transplant						
Post-SLK transplant:						
Death (L+K+ → death)	time-dependent, see Table A5			non-parametric	SRTR cohort	A
Liver graft fails (L+K+ → L−K+L+K− → L−K−)	time-dependent, see Table A5			non-parametric	SRTR cohort	A
Kidney graft fails (L+K+ → L+K−)	time-dependent, see Table A5			non-parametric	SRTR cohort	A
Post-liver transplant:						
Death (L+K+ → death)	time-dependent, see Table B5			non-parametric	SRTR cohort	A
Liver graft fails (L+K+ → L−K+L+K− → L−K−)	time-dependent, see Table A5			non-parametric	SRTR cohort	A
Native kidneys fail (L+K+ → L+K−)	time-dependent, see Table A5			non-parametric	[9]	A
Post-both transplants:						
Death on dialysis (L+K− → death)	all	death rate without dialysis	hazard ratio: 2.96–3.71	hazard ratio: log-normal (1.200,0.058)	[10]	A

Parameter	Stratum	Base Model	Range	Distribution	Source	Technical Appendix
		× hazard ratio (3.32)				
Liver graft failure on dialysis (L+K− → L−K−)	all	liver failure rate without dialysis × hazard ratio (1.49)	hazard ratio: 1.10–2.04	hazard ratio: log-normal (0.3988,0.1573)	[11]	A
Death after second transplant (kidney)	all	death rate without second transplant × time-dependent hazard ratio	time-dependent, see Figure B2	non-parametric	[12]	B
Kidney graft failure after second transplant (kidney)	time-dependent, see Table B2			non-parametric	[12]	B
Kidney wait-list information						
Proportion of patients who have matching living donors	all	0.059	0.049–0.069	beta (132,2105)	[12]	B
Adjustment for liver / SLK re-transplantation						
Hazard ratio for death (compared to first transplant)	all	1.7	1.56–1.84	log-normal (0.531,0.042)	[13]	A
Probability of receiving SLK pre-OPTN (based on 2013 data)						
	No KD	0.000	0	none	2013 SRTR cohort	
	OPTN−	0.022	0.015–0.030	beta (34,1510)		
	OPTN+	0.326	0.272–0.382	beta (91,188)		
Utility weights						
Post-liver transplant:						
No kidney failure	all	0.747	0.720–0.774	beta (742,251)	[14]	D
With kidney failure	all	0.573	0.523–0.624	beta (210,156)	[14,15]	D

[a] Gamma distribution is described here by a shape parameter, α, and an inverse scale parameter, β.

Table 4.

"Cost"-effectiveness of each kidney allocation strategy, with 3% annual discounting. LY: life year. QALY: quality-adjusted life year. DDK: deceased donor kidney. Dom: Dominated completely (*i.e.* there is another strategy present which delivers more LY or QALY using fewer DDKs). DomEx: Dominated by extension (*i.e.* other strategies present provide more LY or QALY at the same incremental increase in DDK). Highlighted cells indicate the dominated strategy.

Low-Utilization Scenario for OPTN Implementation					
Strategy	*LY (year)*	*QALY (year)*	*# DDK*	*Incremental LY per DDK**	*Incremental QALY per DDK**
Stringent	9.56 (9.55–9.57)	7.09 (7.08–7.10)	0.036 (0.036–0.037)	-	-
Safety Net	9.57 (9.56–9.59)	7.10 (7.09–7.11)	0.042 (0.041–0.042)	1.85 (1.77–1.94)	2.03 (1.97–2.09)
OPTN	9.61 (9.59–9.61)	7.12 (7.11–7.13)	0.061 (0.060–0.061)	1.59 (1.52–1.66)	1.22 (1.17–1.27)
Pre-OPTN	9.59 (9.57–9.60)	7.11 (7.10–7.12)	0.062 (0.062–0.063)	Dom	Dom
High-Utilization Scenario for OPTN Implementation					
Strategy	*LY (year)*	*QALY (year)*	*# DDK*	*Incremental LY per DDK**	*Incremental QALY per DDK**
Stringent	9.56 (9.55–9.57)	7.09 (7.08–7.10)	0.036 (0.036–0.037)	-	-
Safety Net	9.57 (9.56–9.59)	7.10 (7.09–7.11)	0.042 (0.041–0.042)	1.85 (1.77–1.94)	2.03 (1.97–2.09)
Pre-OPTN	9.59 (9.57–9.60)	7.11 (7.10–7.12)	0.062 (0.062–0.063)	DomEx: 0.89 (0.81–0.98)	DomEx: 0.54 (0.48–0.60)
OPTN	9.64 (9.62–9.65)	7.15 (7.14–7.16)	0.098 (0.098–0.099)	1.30 (1.21–1.38)	1.11 (1.05–1.17)

*Current strategy compared to the immediately preceding strategy.

Table 5.

Expected organ usage (per liver transplant recipient) under each kidney transplant strategy. SLK: simultaneous liver-kidney. For Safety Net, activation refers activation under the Safety Net system, and transplant refers to receiving a deceased donor kidney transplant under the Safety Net system.

	SLK	Liver	Kidney		Safety Net	
			Deceased Donor	Living Donor	Activation	Transplant
Stringent	-	1.07	0.05	0.006	-	-
Safety Net	-	1.07	0.06	0.006	0.02	0.01
OPTN:						
Low-utilization	0.02	1.07	0.07	0.006	0.02	0.01
High-utilization	0.06	1.07	0.11	0.006	0.01	0.01
Pre-OPTN	0.03	1.07	0.08	0.006	-	-