Choosing Among Living-Donor and Cadaveric Livers

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The only therapy for a patient with end-stage liver disease (ESLD) is liver transplantation, which is performed by using either a cadaveric liver from a deceased donor or a portion of a living-donor’s liver. This study addresses the following decision problem for an ESLD patient with an available living donor. Should she have a transplantation now or wait? If she decides to have the transplantation now, should she use her living-donor liver or a cadaveric liver for transplantation? We formulate this problem as a discrete-time, infinite-horizon Markov decision process model and solve it using clinical data. Because living donors are typically related to the recipient, we incorporate a disutility associated with using the living-donor liver as opposed to using a cadaveric liver. We perform a structural analysis of the model, including a set of intuitive conditions that ensure the existence of structured policies such as an at-most-three-region (AM3R) optimal policy. Our computational experiments confirm that the optimal policy is typically of AM3R type.

Key words: medical decision making; Markov decision processes; control-limit policy; health-care applications; organ transplantation; service operations; optimal stopping; dynamic programming

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1. Introduction

The only therapy for a patient with end-stage liver disease (ESLD) is liver transplantation, which is performed by using either a cadaveric liver from a deceased donor or a portion of a living-donor’s liver. Because nondiseased livers have a unique regenerative ability, in living-donor transplants both livers regain their original sizes within two months of transplantation (Ibrahim et al. 2005, Hayashi and Trotter 2002, Fausto 2001).

To be eligible for a cadaveric liver transplantation, the patient with ESLD must join a waiting list, which is maintained by the United Network for Organ Sharing System (UNOS), the organization responsible for managing the national organ donation and allocation system. UNOS offers each donated liver to the patients using a complex priority system (UNOS 2005) based on geographic location, current health, and, in certain circumstances where other criteria are equal, time spent in the current or worse health states since joining the waiting list. The current liver allocation system is described in detail in Alagoz et al. (2005a). When UNOS makes an offer to a patient, the transplant surgeon acting on behalf of the patient may decline the organ offer without penalty. Howard (2002) reports that 45% of all cadaveric liver offers are declined by the first transplant surgeon and/or patient to whom they are offered. The surgeons decline low-quality organs for relatively healthy patients in the hope that they will receive a better organ offer in the future. Figure 1 shows the waiting list data in the United States between 1996 and 2004. In 2005 alone, 10,434 joined the waiting list (UNOS 2006). As of March 3, 2006, there were 17,274 patients on the waiting list.

The median waiting time for transplantation was approximately 775 days in 2002 and this figure is anticipated to increase in the future (UNOS 2006). For this reason, transplant surgeons are encouraging living-donor liver transplantation more aggressively. There is little evidence that the outcome is better with living-donor liver transplantation over cadaveric liver transplantation. Trotter et al. (2002) report that posttransplant quality of life is generally higher for living-donor recipients than cadaveric liver recipients, whereas Futagawa and Teresaki (2004) note that there was a very small difference in five-year graft survival rates comparing living and deceased donors.
Although there are several advantages of using a living donor over a cadaveric liver for the patient (Broelsch et al. 2003, Colardyn 2003, Maluf et al. 2005, Russo et al. 2004), there are some risks for the donor. The estimated risk of donor mortality due to living-donor liver transplantation is between 0.3% to 1% (Abhinav 2004). It is estimated that the morbidity rate is between 15% and 20%, which includes complications such as a leak in the biliary system, a need for a blood transfusion, and a major postoperative infection (Lo 2003, Abhinav 2004). Furthermore, there may be a financial burden on donors due to the recovery time after the transplantation (Silverman 2004). There are also potential psychiatric issues for the living donors related to organ donation (Beresford 2004) as living donors are typically related to the recipient (Thalheimer and Capra 2002). In a recent survey among transplant surgeons, 77% of them indicated that the risk to the donor causes the surgeons a moral dilemma (Cotler et al. 2003). All of these studies suggest that, all things being equal, there is a disutility associated with using a living-donor liver rather than a cadaveric liver for transplantation.

This study addresses the following decision problem for an ESLD patient with an available living donor. Should she have a transplantation now or wait? If she decides to have the transplant now, should she use her living-donor liver or a cadaveric liver? That is, we seek a policy describing the patient-state/cadaveric liver-type combinations in which cadaveric or living-donor liver transplantation should occur, and those combinations in which waiting is optimal. Currently, there are no guidelines for determining when a patient should accept a living-donor liver versus a cadaveric liver for transplantation. To the best of our knowledge, our study is the first to consider how physicians and/or patients with ESLD should make this transplant decision.

In general, previous studies on organ transplantation take either society’s perspective (Righter 1989; David and Yechiali 1990, 1995; David 1995; Zenios et al. 1999, 2000; Zenios 2002; Roth et al. 2004) or the individual patient’s perspective (David and Yechiali 1985; Ahn and Hornberger 1996; Hornberger and Ahn 1997; Howard 2002; Alagoz et al. 2004, 2007). Su and Zenios (2005) integrate society’s and the individual patient’s perspectives in designing a kidney allocation system. Alagoz et al. (2005a) and Shechter et al. (2005) describe these studies in more detail.

The two most relevant studies in the literature are Alagoz et al. (2004, 2007). Alagoz et al. (2004) consider the problem of optimally timing a living-donor liver transplant to maximize a patient’s total reward, such as quality-adjusted life expectancy. Although patients with available living donors typically join the waiting list, they do not consider the possibility of being offered a cadaveric organ, nor do they incorporate the disutility associated with living-donor liver transplantation. Alagoz et al. (2007) consider the decision faced by liver patients on the waiting list: Should an offered organ of a given quality be accepted or declined? They assume that the patient does not have an available living donor. This paper generalizes these two studies in the sense that the patient both has an available living donor and is waiting on the cadaveric list. Furthermore, we incorporate the disutility associated with using the living donor into our decision models. In fact, both Alagoz et al. (2007, 2004) can be viewed as special cases of the model presented here.

The remainder of this paper is organized as follows. We present a Markov decision process (MDP) model of the problem in §2. We derive several structural properties of this MDP model and its optimal policy in §3. In §4, we present and discuss computational results. We draw some conclusions and discuss future research directions in §5.

2. Model Formulation

We formulate a discrete-time, infinite-horizon MDP model of this problem, in which the objective of the decision maker is to maximize the patient’s total expected discounted reward. In this study, we consider the patient’s perspective in optimizing the organ acceptance decisions. Although there is evidence that ESLD patients are risk averse (Chong et al. 2003), we assume that the decision maker is risk neutral. We assume that the living-donor liver is available at all times and that its quality does not change over time. Note that a patient may have access to multiple living-donor livers, in which case, she simply considers only the best available living-donor liver assuming that her disutility function is the same across all available living donors. We assume that the transition probabilities and the reward function are stationary. The notation used in the model is as follows:

\[ T = \{1, \ldots, \infty\} : \text{time periods.} \]
\( \lambda \): discount factor, \( 0 \leq \lambda \leq 1 \).

\( h_t \): patient state at time \( t \in T \).

Patient state could, for example, consist of patient health and patient waiting time, both of which are used to prioritize patients for transplantation. A simplified patient-state definition may consist of only the Model for End-Stage Liver Disease (MELD) score, which is used to determine the medical urgency of an ESLD patient (Malinchoc et al. 2000, UNOS 2005, Wiesner et al. 2001). UNOS uses a modified version of the original MELD formula that restricts the range of MELD scores to be integer values between 6 and 40, where MELD is a decreasing function of patient health. UNOS uses MELD scores to prioritize patients for transplantation (UNOS 2005). We assume that there exists a complete ordering of the patient states.

\( S_H \): patient-state space, i.e., \( S_H = \{1, \ldots, H+1\} \), where \( H+1 \) represents death.

\( l_t \): quality of the cadaveric liver offered to the patient at time \( t \in T \). We assume that there exists a complete ordering of the liver qualities.

\( S_L \): organ-state space, i.e., \( S_L = \{1, \ldots, L+1\} \), where \( L+1 \) represents the case that no liver is offered.

\( s_t = (h_t, l_t) \): state of the process at time \( t \in T \).

\( S \): state space, i.e., \( S = S_H \otimes S_L \).

\( L_D \): living-donor liver quality. The quality of the living-donor liver is assumed to be stationary.

\( a^*(s) \): optimal action in state \( s \), i.e., \( a^*(s) \in \{T_C, T_{LD}, W\} \), where \( T_C \) represents accepting the cadaveric offer, and thereby quitting the process; \( T_{LD} \) represents accepting the living-donor liver, and thereby quitting the process; and \( W \) represents waiting for one more period.

\( r(h, l, T_C) \): total expected discounted posttransplant reward if the patient accepts the cadaveric liver described by \( l \) while in state \( h \). We define \( r(h, l, T_C) = 0 \) when \( h = H+1 \) or \( l = L+1 \). Note that \( r(h, l, T_C) \) is also a function of the patient type, e.g., gender and blood type. However, because we assume that these factors are fixed, we suppress this dependency for notational convenience.

\( r(h, l_{LD}, T_{LD}) \): total expected discounted posttransplant reward that the patient accrues when she is transplanted with the living donor in state \( h \). We define \( r(H+1, l_{LD}, T_{LD}) = 0 \).

\( \rho(h) \): penalty (disutility) associated with using the living donor when the patient is in state \( h \) at the time of transplantation. We assume that the penalty function is in units of total expected discounted post-transplant reward, and depends on the patient state because the disutility function of a very sick patient might be different than that of a very healthy patient. Note that this penalty is incurred by the recipient, not by the donor. We define \( \rho(H+1) = 0 \).

\( r'(h, l_{LD}, T_{LD}) \): net total expected discounted post-transplant reward that the patient accrues when she is transplanted with the living donor and she is in state \( h \) at the time of the transplantation, i.e.,

\[ r'(h, l_{LD}, T_{LD}) \equiv r(h, l_{LD}, T_{LD}) - \rho(h) \]

\( r(h, W) \): expected intermediate reward accrued in the current time period when the patient state is \( h \) and she chooses to wait. We define \( r(H+1, W) = 0 \).

\( \mathcal{H}(h' \mid h) \): probability that the patient will be in state \( h' \) at time \( t+1 \) given that she is in state \( h \) at time \( t \) and a liver is not transplanted at time \( t \). We define \( \mathcal{H}(H+1 \mid H+1) = 1 \), i.e., the death state is absorbing.

\( \mathcal{L}(l \mid h) \): probability that the patient will receive a liver offer \( l \) at time \( t+1 \) given that she is in state \( h \) at time \( t \). We define \( \mathcal{L}(L+1 \mid H+1) = 1 \), i.e., the patient does not receive any organ offers after she dies.

\( \mathcal{P} \): transition probability matrix, \( \mathcal{P} = \{ [\mathcal{P}(h' \mid h)] \} \), \( h, h' \in S_H \).

\( \mathcal{P}(l \mid h) \): organ arrival probability matrix, \( \mathcal{P} = \{ [\mathcal{P}(l \mid h)] \} \), \( l \in S_L \) and \( h \in S_H \).

\( V(h, l) \): maximum total expected discounted reward that the patient can attain when her current state is \( h \) and the quality of the current liver offered is \( l \).

The above definitions imply that the probability of receiving a cadaveric liver of type \( l \) at time \( t+1 \) depends only on the patient state at time \( t \) and is independent of the type of cadaveric liver offered at time \( t \). Because patients often need to be retransplanted due to posttransplant complications (Deshpande et al. 2001; Icoz et al. 2003; Rosen et al. 2003a, b; Thuluvath and Yoo 2004; Yao et al. 2004; Yu et al. 2004), we incorporate the possibility of, and the reward associated with, retransplantation into \( r(h, l, T_C) \) and \( r(h, l_{LD}, T_{LD}) \). We provide a detailed discussion about incorporating retransplantation into the reward function in Alagoz et al. (2007). Both \( r(h, l, T_C) \) and \( r(h, l_{LD}, T_{LD}) \) also include the possibility of death during transplantation. Note that although we assume a complete ordering of cadaveric liver types, we do not assume a complete ordering between the cadaveric livers and the living-donor liver, i.e., for a given liver type \( l \), it might be the case that \( r(h, l, T_C) \geq r'(h, l_{LD}, T_{LD}) \) for some \( h \in S_H \) and \( r(h', l, T_C) < r'(h', l_{LD}, T_{LD}) \) for some \( h' \neq h \), \( h' \in S_H \). This possibility exists because of the fact that, by definition, the disutility function may cause the life expectancy for a living-donor transplant recipient to decrease in health-at-transplant at a different rate than does life expectancy for a cadaveric donor transplant recipient.

According to the MDP model, the decision maker can take one of three actions in state \( (h, l) \), namely,
“transplant cadaveric liver $l_i$,” “transplant living-donor liver $l_{LD}$,” or “wait for one more decision epoch.” If the patient chooses the “transplant the cadaveric liver” action in state $(h, l)$, she receives a reward of $r(h, l, T_C)$, quits the process, and moves to the absorbing state “posttransplant” with probability one. Similarly, if the patient chooses “transplant the living-donor liver” in state $(h, l)$, she receives a reward of $r'(h, l_{LD}, T_{LD})$, quits the process, and moves to absorbing state “posttransplant” with probability one. If the patient chooses to “wait” in state $(h, l)$, then she receives an intermediate reward of $r(h, W)$ and moves to state $(h', l') \in S$ with probability $\mathbb{P}(h', l' | h)$. The optimal solution to this problem, which we call the living-and-cadaveric-donor model (LCDM), can be obtained by solving the following set of recursive equations (Puterman 1994):

$$V(h, l) = \max \left\{ r(h, l_{LD}, T_{LD}), r(h, l, T_C), r(h, W) + \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' | h)V(h', l') \right\},$$

$$h = 1, \ldots, H + 1, \quad l = 1, \ldots, L + 1.$$  \hspace{1cm} (1)

### 3. Structural Properties

In this section, we derive some structural properties of the LCDM. The following assumptions are common to all results in this section:

**Assumption 1.** The function $r(h, l, T_C)$ is positive and nonincreasing in both $h$ and $l$. That is, as the patient deteriorates and/or the liver quality drops, her postcadaveric-transplant reward does not increase.

**Assumption 2.** The function $r(h, W)$ is positive and nonincreasing in $h$. That is, as the patient deteriorates, her intermediate reward does not increase.

**Assumption 3.** The functions $r(h, l_{LD}, T_{LD})$ and $r'(h, l_{LD}, T_{LD})$ are positive and nonincreasing in $h$. That is, as the patient deteriorates, her (net) postliving-donor-transplant reward does not increase.

**Theorem 1.** $V(h, l)$ is monotonically nonincreasing in $l, l \in S_L \forall h \in S_H$.

**Definition 1.** An at-most-two-region liver-based policy (AM2RL) for a particular health state $h$ is of the following form: When the patient is in health state $h$, “accept” the cadaveric organ if and only if the offered organ is of types $1, 2, \ldots, i(h)$, for some liver type $i(h)$, called the AM2RL control limit. Furthermore, if $a^*(h, i(h) + 1) = W$, then $a^*(h, l) = W$ holds for $l = i(h) + 2, \ldots, L + 1$, and if $a^*(h, i(h) + 1) = T_{LD}$, then $a^*(h, l) = T_{LD}$ holds for $l = i(h) + 2, \ldots, L + 1$.

An example for the AM2RL policy is presented in Figure 2(c). An AM2RL policy is an example of a control-limit policy in which there exists a threshold cadaveric liver type for each health state such that if the patient receives a cadaveric liver offer with a higher quality, she will use that organ for transplantation, otherwise she will either continue to wait or use the living-donor organ for transplantation.
THEOREM 2. There exists an optimal AM2RL policy.

Observe that by setting \( r'(h, l_{LD}, T_{LD}) = 0 \ \forall \ h \in S_h \), i.e., the patient has no available living donor, we obtain Theorem 3 from Alagoz et al. (2007), which establishes sufficient conditions for a control-limit policy in the cadaveric-only case. While Assumptions 1, 2, and 3 suffice to guarantee the monotonicity of \( V(h, l) \) in \( l \), we need additional assumptions to prove the monotonicity of \( V(h, l) \) in \( h \). Next, we present a condition that is used by many researchers (Barlow and Proschan 1965; Derman 1962, 1963a, b; Pierskalla and Voelker 1976) to ensure the existence of structured policies.

DEFINITION 2 (Barlow and Proschan 1965). (A) A discrete distribution \( \{p_i\}_{i=0}^\infty \) is IFR (increasing failure rate) if \( p_i / \sum_{k=0}^\infty p_i \) is nondecreasing in \( k = 0, 1, 2, \ldots \).

(b) A \( n \times n \) stochastic matrix \( P \) is said to be IFR if its rows are in increasing stochastic order, that is,

\[
b(i) = \sum_{j=m}^{n} P(j \mid i) \]

is nondecreasing in \( i \) for all \( m = 1, \ldots, n \).

Intuitively, this definition implies that the sicker the patient, the more probable that the patient will become even sicker. Alagoz (2004) shows that transition matrices estimated from clinical data describing the natural history of ESLD nearly satisfy the IFR assumption.

PROPOSITION 1. Let \( \mathcal{L} \) be an IFR matrix and

\[
\frac{\mathcal{L}(l \mid h + 1)}{\mathcal{L}(l \mid h)} < \frac{r(h, l, T_C)}{r(h + 1, l, T_C)}
\]

for \( h = 1, \ldots, H - 1 \) and \( l = 1, \ldots, L \). (3)

Then, \( V(h, l) \) is nonincreasing in \( h \).

Condition (3) implies that for any given liver type, as the patient deteriorates, the increase in the probability of receiving an offer must be smaller than the reduction in the benefit of total expected discounted posttransplant reward. Observe that the conditions of this proposition are identical to those of Theorem 2 in Alagoz et al. (2007).

DEFINITION 3. An at-most-three-region (AM3R) policy satisfies the following two conditions: For a given liver type \( l \), there exists a health state \( j(l) \) such that the optimal policy is to choose the “wait” action if and only if the observed health state is one of the states \( 1, 2, \ldots, j(l) \). Furthermore, there exists an AM2RL policy for each health state \( h \).

An example for the AM3R policy is presented in Figure 2(c). Note that the vertical line dividing the “wait” and “transplant the living donor liver” policies in Figure 2(c) is a characteristic of an AM3R-type policy. An AM3R policy can be explained intuitively as follows: There exists a patient healthiness threshold above which the patient should accept high-quality cadaveric offers or wait. Below this healthiness level, the patient should accept the living-donor organ unless the current cadaveric offer has a greater reward when compared to the living-donor reward less the disutility associated with using the living-donor liver.

The following theorem, the main result of this section, gives a set of intuitive conditions that ensure the existence of an optimal AM3R policy.

THEOREM 3. Let \( \mathcal{H} \) be an IFR matrix, suppose \( \mathcal{L} \) satisfies (3),

\[
\sum_{k=j}^{H} \mathcal{H}(k \mid h) \leq \sum_{k=j}^{H} \mathcal{H}(k \mid h + 1)
\]

for \( h = 1, \ldots, H, j = h + 1, \ldots, H \). (4)

and

\[
\max \left\{ \max_{(h,l)} \left\{ \frac{r(h,l,T_C) - r(h + 1, l, T_C)}{r(h + 1, l, T_C)} \right\}, \frac{r'(h,l_{LD},T_{LD}) - r'(h + 1, l_{LD}, T_{LD})}{r'(h + 1, l_{LD}, T_{LD})} \right\} \leq \lambda \mathcal{H}(H + 1 \mid h + 1) - \mathcal{H}(H + 1 \mid h)
\]

for \( h = 1, \ldots, H - 1 \). (5)

Then, there exists an optimal AM3R policy.

Condition (4) and Definition 2 have similar interpretations, but (4) is neither a consequence of, nor sufficient to establish Definition 2. Condition (5) on the reward functions has an intuitive explanation, namely, that as the patient deteriorates, the reduction in the benefit of waiting is greater than the reduction in the benefit of performing the transplant. Observe that if we remove \( r'(h,l_{LD},T_{LD}) \ \forall \ h \in S_h \), i.e., the patient is only considering cadaveric livers, then we obtain Theorem 4 from Alagoz et al. (2007), which establishes sufficient conditions for a control-limit policy in the cadaveric-only case. Similarly, we obtain Theorem 3 from Alagoz et al. (2004), which establishes sufficient conditions for a control-limit policy in the living-donor-only case, by setting \( \rho(h) = 0 \ \forall \ h \in S_h \) and removing \( r(h,l,T_C) \ \forall \ h \in S_h, \ \forall l \in S_l \) from (5).

Proposition 2 compares the optimal policies of two identical patients who have different disutility functions. This result establishes conditions under which Patient 1 has a higher disutility of using the living donor than Patient 2 and their disutility functions are perfectly linearly related. Then, the set of states in which the “transplant the living-donor liver” action is optimal is a subset of the set of states that Patient 2 chooses to “transplant the living-donor liver.”

PROPOSITION 2. Let \( \Pi_1 \) and \( \Pi_2 \) be two problem instances that have identical \( \mathcal{P}, r(h,W), r(h,l_{LD},T_{LD}) \), and
\(r(h, l_{LD}, T_{LD})\). Let \(V_1(h, l)\) and \(V_2(h, l)\) be the optimal value functions and \(\rho_1(h)\) and \(\rho_2(h)\) be the disutility functions of \(\Pi_1\) and \(\Pi_2\), respectively, where \(\rho_1(h) \geq \rho_2(h)\) for \(h \in S_H\).

Then, the following hold:

(a) \(V_1(h, l) \leq V_2(h, l)\) for \(h \in S_H\) and \(l \in S_L\).

(b) Let

\[
\rho_1(h) = \rho_1 r(h, l_{LD}, T_{LD})
\]

and

\[
\rho_2(h) = \rho_2 r(h, l_{LD}, T_{LD}),
\]

where \(\rho_2 = \alpha \rho_1\) and \(0 \leq \rho_1, \alpha \leq 1\), so that \(\rho_1\) and \(\rho_2\) are perfectly linearly related. Also let \(a_1'(h, l)\) and \(a_2'(h, l)\) be the optimal actions of \(\Pi_1\) and \(\Pi_2\) for state \((h, l)\), respectively. If \(a_1'(h, l) = T_{LD}\), then \(a_2'(h, l) = T_{LD}\) must also hold.

Proposition 3 compares the optimal policies of two identical patients who have different living donors. This result establishes conditions under which if Patient 1 has a lower-quality living-donor liver than Patient 2 and their net posttransplant reward functions are perfectly linearly related, then the set of states in which the “transplant the living-donor liver” action is optimal for Patient 1 is a subset of the set of states that Patient 2 chooses to “transplant the living-donor liver.”

**Proposition 3.** Let \(\Pi_1\) and \(\Pi_2\) be two problem instances that have identical \(\mathcal{P}, r(h, W), r(h, l_{LD}, T_{LD}), \) and \(\rho(h)\). Let \(V_1(h, l)\) and \(V_2(h, l)\) be the optimal value functions and \(r_1(h, l_{LD}, T_{LD})\) and \(r_2(h, l_{LD}, T_{LD})\) be the posttransplant reward functions of \(\Pi_1\) and \(\Pi_2\), respectively. Let \(r_1(h, l_{LD}, T_{LD}) \leq r_2(h, l_{LD}, T_{LD})\) for \(h \in S_H\). Then, the following hold:

(a) \(V_1(h, l) \leq V_2(h, l)\) for \(h \in S_H\) and \(l \in S_L\).

(b) Let \(a_1'(h, l)\) and \(a_2'(h, l)\) be the optimal actions of \(\Pi_1\) and \(\Pi_2\) for state \((h, l)\), respectively. Let \(r_2(h, l_{LD}, T_{LD}) = (1 + \alpha) r_1(h, l_{LD}, T_{LD})\) for all \(h \in S_H\). Then, \(a_2'(h, l) = T_{LD}\) implies that \(a_1'(h, l) = T_{LD}\).

Proposition 4 compares the optimal policies for two identical patients, one of whom (Patient 2) is an available living donor, while the other one (Patient 1) does not. The result shows that the set of states in which the “transplant the cadaveric liver” action is optimal for Patient 2 is a subset of the set of states that Patient 1 chooses to “transplant the cadaveric liver.” This result can be observed in Figure 2. Namely, for each health state, the AM2RL limits of LCDM (Figure 2(c)) are smaller than or equal to those of the cadaveric-donor-only model (Figure 2(b)).

**Proposition 4.** Let \(\Pi_1\) and \(\Pi_2\) be two problem instances that have identical \(\mathcal{P}, r(h, W), r(h, l_{LD}, T_{LD}), \) and \(\rho(h)\). Let \(V_1(h, l)\) and \(V_2(h, l)\) be the optimal value functions and \(r_1(h, l_{LD}, T_{LD}) = 0\) for all \(h \in S_H\) and \(l \in S_L\) and \(r_1(h, l_{LD}, T_{LD})\) be the posttransplant reward functions of \(\Pi_1\) and \(\Pi_2\), respectively. Also let \(a_1'(h, l)\) and \(a_2'(h, l)\) be the optimal actions of \(\Pi_1\) and \(\Pi_2\) for state \((h, l)\), respectively. Then, \(a_2'(h, l) = T_{LD}\) implies that \(a_1'(h, l) = T_C\).

Proposition 5 compares the optimal policies for two identical patients, one of which (Patient 2) is listed on the waiting list, while the other one (Patient 1) is not. The result shows that Patient 2 will choose to delay the “transplant the living-donor liver” action until at sicker health states than Patient 1. This result can be observed in Figure 2. Namely, the patient listed on the waiting list (Figure 2(c)) chooses the “transplant the living-donor liver” action at a MELD score of 28 or higher, while the other patient (Figure 2(a)) chooses the “transplant the living-donor liver” action at a MELD score of 14 or higher.

**Proposition 5.** Let \(\Pi_1\) and \(\Pi_2\) be two problem instances that have identical \(\mathcal{P}, r(h, W), r(h, l_{LD}, T_{LD}), \) and \(\rho(h)\). Let \(V_1(h, l)\) and \(V_2(h, l)\) be the optimal value functions and \(r_1(h, l_{LD}, T_{LD}) = 0\) for all \(h \in S_H\) and \(l \in S_L\) and \(r_1(h, l_{LD}, T_{LD})\) be the posttransplant reward functions of \(\Pi_1\) and \(\Pi_2\), respectively. Also let \(a_1'(h, l)\) and \(a_2'(h, l)\) be the optimal actions of \(\Pi_1\) and \(\Pi_2\) for state \((h, l)\), respectively. Then, \(a_2'(h, l) = T_{LD}\) implies that \(a_1'(h, l) = T_C\).

### 4. Computational Results

In this section, we solve several instances of the LCDM using clinical data. The estimation of the parameters is described in §4.1. We provide numerical examples in §4.2.

#### 4.1. Parameter Estimation

We use three data sources. The first (UNOS1) is a publicly available data set from UNOS that covers 28,717 patients listed for their first liver transplant between 1990 and 1996 and contains data through 1999. This data set is used to estimate \(r(h, l_{LD}, T_{LD})\) and \(r(h, l_{LD}, T_{LD})\). The second data set (UNOS2), also from UNOS, includes data from February 27, 2002 to May 31, 2003. This data set includes information for 25,810 patients waiting for liver transplantation such as region, MELD score, age, blood type, gender, race, and disease type. The UNOS2 data set also includes information on the cadaveric organ offers such as the patients to whom each organ was offered, the date of the offers, and the donor’s gender, cause of death, age, and region. This data set is used to estimate \(P\). The third data set (UPMC) is provided by the private database of The Thomas E. Starzl Transplantation Institute at the University of Pittsburgh Medical Center (UPMC), one of the largest liver transplant centers in the world. The UPMC database includes information about 3,009 ESLD patients who joined the waiting list between 1991 and 2000. For each patient, the UPMC data set contains demographic and clinical data, including the disease type, the results of all laboratory testing done at UPMC, the location of the patient at the time of laboratory testing, whether death occurred before transplantation, and indication.
of the existence of various clinical covariates. This data set is used to estimate $\mathcal{H}$.

We use MELD scores to represent health states and aggregate MELD scores into groups of two due to the sparsity of data. Using the UPMC data set and aggregate MELD scores into groups of two due to data set is used to estimate of the existence of various clinical covariates. This

to Alagoz (2004) and Alagoz et al. (2005b), we estimate the $\mathcal{H}$ matrix for each disease group separately because the progression of liver disease is highly disease dependent (Dienstag and Isselbacher 2001, Podolsky and Isselbacher 2001).

We discretize liver types based on age (seven categories), race (two categories), and gender match (two categories), which yields a total of 28 liver types. Because of the sparsity of the data, we further aggregate these liver types into 14 types, where the cadaveric liver types are ordered in decreasing quality, i.e., Cadaveric Liver Type 1 represents the best cadaveric organ quality and Cadaveric Liver Type 14 represents the worst cadaveric organ quality. Furthermore, Cadaveric Liver Type 15 represents the “no offer” case.

To compute $\mathcal{D}$, we first compute the total number of days that each patient waits at each MELD score. Then, we calculate the total number of days on which a liver is offered by recipient MELD score. We then compute the organ arrival probability by dividing the first quantity by the second quantity. Because $\mathcal{D}$ depends highly on geographical factors, we estimate 11 regional $\mathcal{D}$s as well as a national $\mathcal{D}$ using UNOS2.

Possible definitions for the reward function include total discounted expected life days and total discounted quality-adjusted life days (QALD) of the patient, a common measure in medical decision-making research. The QALD measure is based on a patient-assigned quality score between zero and one to each health state (Gold et al. 1996). Because we are unaware of any existing data on quality-adjusted rewards for MELD scores, we use total discounted life expectancy in days rather than total discounted QALD for the reward function in our computational tests. We use UNOS1 and the Cox proportional hazards model (Cox 1972) of Roberts et al. (2004) and Valenta (2002) to estimate the expected posttransplant life days of the patient given her MELD score at the time of transplant and liver quality.

Because we are unaware of any studies that quantify the disutility of living-donor liver transplants, we define $\rho(h)$ as a linear function of $r(h, I_{LD}, T_{LD})$, i.e., $\rho(h) = \rho_0 \cdot r(h, I_{LD}, T_{LD})$, in which case $r(h, I_{LD}, T_{LD}) = (1 - \rho_0) \cdot r(h, I_{LD}, T_{LD})$. This definition implies that the sicker the patient, the smaller the disutility associated with accepting the living-donor liver.

More details on these parameter estimation techniques are given in Alagoz (2004) and Alagoz et al. (2007).

### Table 1: Living-Donor Characteristics

<table>
<thead>
<tr>
<th>Living-donor Organ number</th>
<th>Age</th>
<th>Sex</th>
<th>Blood type</th>
<th>Donor white(^a)</th>
<th>CMVGR(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Female</td>
<td>A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>Female</td>
<td>A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>Female</td>
<td>A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>Male</td>
<td>A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>Male</td>
<td>A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>Male</td>
<td>A</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\)Indicates whether the donor is white or not. \(^b\)Indicates whether the donor has cytomegalovirus (CMVGR) or not.

#### 4.2. Numerical Examples

Consider a 60-year-old female patient with primary biliary cirrhosis who has blood type A. We use a 0.99 annual discount rate (daily $\lambda = 0.999972$) and $\rho_0 = 0.1$. Figure 2(c) shows the optimal policy when the only living-donor liver available to this patient is Organ 2, whose donor characteristics are given in Table 1. As can be seen from the figure, as the patient gets sicker, the “transplant cadaveric liver” action is optimal for more cadaveric liver types and the “wait” action is optimal only in healthier states. This policy is an example of the AM3R policy described in §3. We tested a total of 240 instances and all optimal policies were of the AM3R type.

Figure 2 compares the optimal policy for the LCDM with the optimal policies for the living-donor-only model described in Alagoz et al. (2004) and cadaveric-donor-only model described in Alagoz et al. (2007) when the annual discount rate is 0.99 ($\lambda = 0.999972$) and $\rho_0 = 0.1$. As shown by Theorem 3, the patient becomes more selective in accepting the cadaveric liver offers for the LCDM. Note that the optimal policy obtained by the living-donor-only model is a vertical line in this figure because a patient not listed on the waiting list is indifferent among various cadaveric liver offers. As proved by Proposition 5, the “transplant the living-donor liver” action occurs in sicker health states for the LCDM than for the living-donor-only model. Similarly, the “transplant the cadaveric-donor liver” action occurs in sicker health states for the LCDM than for the cadaveric-donor-only model, which is proved by Proposition 4.

We now consider a group of identical 30-year-old female patients with Hepatitis C with different disutility functions. As expected, the disutility function $\rho(h)$ significantly affects the optimal policy. Figure 3 shows the optimal policies for various values of $\rho_0$ when these patients have a living donor of Type 2. Patients with higher disutility functions have a fewer number of states in which it is optimal to “transplant the living-donor liver,” which is proved by Proposition 2.

Different living-donor livers may result in different optimal policies. Figure 4 shows the optimal policies
Figure 3  
Transplant-Wait Decisions for Different Disutility Functions

(a) $\rho_0 = 0$

(b) $\rho_0 = 0.05$

(c) $\rho_0 = 0.10$

(d) $\rho_0 = 0.20$

(e) $\rho_0 = 0.25$

(f) $\rho_0 = 0.50$
for the same patient and disutility function and various living-donor livers when $\rho_0 = 0.1$ and the annual discount rate equals 0.99. The organ types that are used in Figure 4 are defined in Table 1. Note that living-donor livers are ordered in decreasing quality, i.e., Living-Donor Organ 1 is the best organ and Living-Donor Organ 6 is the worst organ. As can be seen from the figure, as the quality of the living-donor organ drops, the number of states in which it is optimal to “transplant the living-donor liver” decreases, which is proved by Proposition 3. This result is intuitive because as the quality of the living donor drops,
the patient benefits less from the living-donor transplantation. As a result, the patient is less selective when considering the cadaveric liver offers.

As can be seen from Figure 4, when the patient has Living-Donor Organ 3, the optimal policy suggests the following: She should accept a cadaveric liver offer that is of Liver Type 10 when her MELD score is 32 or 36, and she should decline the same liver type in favor of the living-donor liver when her MELD score is 34. This result may appear counterintuitive; however, recall that the current form of the disutility function does not ensure the existence of a complete ordering between living-donor and cadaveric liver types. For this particular example, the transplantation of the living-donor liver results in a smaller net total expected discounted reward than the Cadaveric Liver Type 10 transplant when the patient’s MELD score is 32 or 36. On the other hand, the living-donor liver transplantation results in a larger net total expected discounted reward than the Cadaveric Liver Type 10 transplant when the patient’s MELD score is 34.

The location of the patient also affects the optimal policies. We consider two identical 72-year old female patients with acute liver diseases. Figure 5 shows the optimal policies for Patients A and B who are listed in Region A and Region B, respectively. In general, patients listed in Region B are more likely to receive more frequent and better quality organs than patients listed in Region A. As presented in Figure 5, because the threshold for $T_{LD}$ for Patient A is lower than that for Patient B, Patient A will be more likely to use her living donor than Patient B.

5. Conclusions and Future Work
This paper considers the most general model to date of the decision problem faced by ESLD patients: Should such a patient accept a cadaveric liver offer, the living-donor liver, or wait? We extend the studies by Alagoz et al. (2004, 2007) by considering the simultaneous availability of cadaveric and living-donor livers for an ESLD patient.

We use a discrete-time, infinite-horizon MDP model to solve this problem, in which the objective of the decision maker is to maximize the patient’s total expected discounted reward. We derive structural properties of the MDP model, including conditions that guarantee the existence of a newly defined AM3R policy. An AM3R policy can be explained intuitively as follows: There exists a patient healthiness threshold above which the patient should accept high-quality cadaveric offers or wait. Below this healthiness level, the patient should accept the living-donor organ unless the current cadaveric offer has a greater reward when compared to the living-donor reward less the disutility associated with using the living-donor liver.

We show that under reasonable conditions, the optimal value function is monotonic in patient health and cadaveric liver quality. The conditions used to establish the structural results in this paper are sufficient but not necessary to establish the structural results in Alagoz et al. (2004, 2007). We also perform sensitivity analysis on the living-donor disutility function.

We also compare the optimal policies of a patient (Patient A) with access to both cadaveric and living-donor livers to a similar patient who only has access to a living-donor liver (Patient B) and show that Patient B should use her living-donor liver earlier than Patient A. Similarly, we compare the optimal policies of Patient A to a similar patient who only has access to cadaveric livers (Patient C) and show that Patient C should accept lower-quality cadaveric livers than Patient A.
In all of our computational tests, although the sufficient conditions in Theorem 3 are not strictly satisfied, the optimal policy is of AM3R type. Our computational tests also show that the disutility function associated with transplanting the living-donor liver significantly affects the optimal policy. In general, patients with higher disutility functions have fewer states in which it is optimal to “transplant the living-donor liver.” The AM2RL control limits are not necessarily monotonic in patient health because there is not necessarily a complete ordering of liver quality between the living-donor and cadaveric livers.

The policy implications of our work are twofold. First, our results offer guidelines for individual patients and their surgeons as to how they should structure their acceptance policies regarding living-donor and cadaveric organ offers. Second, although we offer these guidelines within the confines of the current allocation policy, our results may inform allocation-policy redesign in two ways. On one hand, individual adoption of acceptance policies like those presented here would alter the performance of the current allocation policy (by making more efficient use of organs and/or encouraging more living donors to come forward by quantifying their value) which could beg allocation-policy level changes. On the other hand, from a pure allocation-policy design perspective, the insights that our model could provide into how patients should respond to organ offers under different allocation mechanisms would clearly enhance any such analyses.

This paper defines the disutility associated with living-donor liver transplantation as a function of patient health because the disutility function of a very sick patient might be different than that of a very healthy patient. Note that we only consider a disutility function that decreases as the patient gets sicker, but we could also examine a disutility function that increases as the patient gets sicker. Furthermore, a more complete definition of the disutility function might depend on the age of the patient at the time of transplant, which may require a more complicated decision model with expanded state space. Some of our results in this paper may not hold using such a disutility function. Future research may consider these and more complex disutility functions.

Lastly, a similar model could also be used to address the problem of accepting/declining kidneys where both living-donor and cadaveric organ transplantations are possible.

Acknowledgments
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Appendix. Proofs of the Results
Proof of Theorem 1. The proof of Theorem 1 can be achieved using the same steps in the proof of Theorem 6.1 in Alagoz (2004) and is omitted.

Proof of Theorem 2. Before proving Theorem 2, we state two lemmas whose proofs are obvious and are omitted.

Lemma 1. For a given health state $h$, if $a^*(h, l) = T_{LD}$, then $a^*(h, l') = T_{LD}$ for $l' > l$.

Lemma 2. For a given health state $h$, if $a^*(h, l) = W$, then $a^*(h, l') = W$ for $l' > l$.

We first show that $a^*(h, l + 1) = T_C$ implies $a^*(h, l) = T_C$, $∀ h ∈ S_H$. If $a^*(h, l + 1) = T_C$ for a given $h ∈ S_H$, then it is obvious that $r(h, l, T_C) ≥ r(h, l + 1, T_C) ≥ r(h, T_{LD}, T_{LD})$. The following are also true about the optimality equations:

$$V(h, l + 1) = r(h, l + 1, T_C) ≥ r(h, W) + \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' | h)V(h', l') \quad (6)$$

and

$$V(h, l) = \max \{r(h, l, T_C), r(h, W) + \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' | h)V(h', l')\}. \quad (7)$$

Because the second components of (6) and (7) are identical, as a result of Assumption 1 we can write the following:

$$r(h, l, T_C) ≥ r(h, l + 1, T_C) ≥ r(h, W) + \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' | h)V(h', l'),$$

which is equivalent to $a^*(h, l) = T_C$.

Now, suppose that $a^*(h, l) = T_C$ for $l = 1, \ldots, l^*$ and $a^*(h, l^* + 1) ≠ T_C$. As a result of Lemma 1 and Lemma 2, the optimal action will be either $W$ or $T_{LD}$ for $l > l^*$, from which the result follows.

Proof of Proposition 1. The proof of this proposition can be achieved using the same steps in the proof of Theorem 6.2 in Alagoz (2004) and is omitted.

Proof of Theorem 3. Note that Theorem 2 applies under the conditions of Theorem 3. Therefore, if we show that for any $l$, $a^*(h, l) = W$ implies $a^*(h - 1, l) = W$, then the result follows.

Note also that the monotonicity results in Theorem 1 and Proposition 1 hold. Now assume that for a given $l$ and $h$, $a^*(h, l) = W$ but $a^*(h - 1, l)$ is uniquely either $T_{LD}$ or $T_C$. The proof of Proposition 2 follows.
Then, there are two cases:

Case 1. \( a^*(h - 1, l) = T_{LD} \).

Because \( \mathcal{R} \) is IFR, condition (5.8) in Alagoz (2004) is satisfied, and condition (5) implies condition (5.9) in Alagoz (2004), the proof of Theorem 5.3 in Alagoz (2004) applies. As a result, \( a^*(h - 1, l) \) must also be \( W \), from which the result follows.

Case 2. \( a^*(h - 1, l) = T_C \).

Because \( \mathcal{R} \) is IFR and conditions (4) and (5) are satisfied, the proof of Theorem 6.4 in Alagoz (2004) applies. As a result, \( a^*(h - 1, l) \) must also be \( W \), from which the result follows.

Proof of Proposition 2. (a) Suppose that we solve the two problems simultaneously using the value iteration algorithm. We first show that starting with a value of zero for all states in both problems, at the end of each iteration of the algorithm, the value function of \( \Pi_2 \) will be greater than or equal to the value function of \( \Pi_1 \) for each state. Let \( V_j(h, l) \) be the value function of the state \((h, l)\) of problem \( j \) at the end of iteration \( j \). Starting with zero for both problems, it is obvious that \( V_1(h, l) = \max \{ r(h, l, T_{LD}) - \rho_1(h), r(h, l, T_C), r(h, l, W) \} \leq \max \{ r(h, l, T_{LD}) - \rho_2(h), r(h, l, T_C), r(h, W) \} = V_2(h, l) \) for \( h \in S_H \) and \( l \in S_S \) because \( \rho_1(h) \geq \rho_2(h) \). Therefore, the result holds for the base case.

Now, assume that \( V_1^{j+1}(h, l) \leq V_2^{j+1}(h, l), (h, l) \in S \) holds for iterations \( j = 2, \ldots, n \). Then, we want to show that \( V_1^{n+1}(h, l) \leq V_2^{n+1}(h, l), (h, l) \in S \). If for any state \((h, l) \in S \), \( V_1^{n+1}(h, l) = r(h, l, T_{LD}) - \rho_1(h) \), then the result immediately follows because \( V_2^{n+1}(h, l) \geq r(h, l, T_{LD}) - \rho_2(h) \geq r(h, l, T_{LD}) - \rho_1(h) \). Similarly, if for any state \((h, l) \in S \), \( V_1^{n+1}(h, l) = r(h, l, T_C) \), then the result immediately follows because \( V_2^{n+1}(h, l) \geq r(h, l, T_C) \). Otherwise, the application of the value iteration algorithm results in the following:

\[
V_1^{n+1}(h, l) = r(h, W) + \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' \mid h)V_1^n(h', l')
\]

and

\[
V_2^{n+1}(h, l) \geq r(h, W) + \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' \mid h)V_2^n(h', l'),
\]

from which we obtain the following:

\[
V_2^{n+1}(h, l) - V_1^{n+1}(h, l) \geq \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' \mid h)[V_2^n(h', l') - V_1^n(h', l')]
\]

or

\[
\geq \lambda \sum_{h'} \sum_{l'} \mathbb{P}(h', l' \mid h)[V_2^n(h', l') - V_1^n(h', l')] = 0,
\]

(8)

where (8) follows from the induction assumption and the nonnegativity of the transition probability matrix. Because the value function for \( \Pi_2 \) is always greater than or equal to that of \( \Pi_1 \) at each iteration of the value iteration algorithm, the optimal value function of \( \Pi_2 \) will always be greater than or equal to that of \( \Pi_1 \), from which the result follows.

(b) If we show that \( r_2'(h, l_{LD}, T_{LD}) = r_2(h, l_{LD}, T_{LD})(1 + \alpha') \) for some \( \alpha' \geq 0 \), then the proof of part (a) of Theorem 5.4 in Alagoz (2004) applies to this situation and the result follows. The definition of \( r_2'(h, l_{LD}, T_{LD}) \) implies that

\[
r_2'(h, l_{LD}, T_{LD}) = r(h, l_{LD}, T_{LD})(1 - \rho_2)
\]

or

\[
r_2'(h, l_{LD}, T_{LD}) = r(h, l_{LD}, T_{LD})(1 - \alpha'\rho_2).
\]

where (9) follows because \( 1 - \alpha\rho_2 \leq 1 - \rho_2 \geq 1 - \alpha'\rho_2 \geq 1 \) by the definition of \( \alpha' \).

Proof of Proposition 3. Because this theorem implies \( \alpha > 0 \), the proof of this theorem is similar to the proof of part (a) of Proposition 2 and is omitted.

Proof of Proposition 4. Note that part (a) of Proposition 3 holds, and therefore \( V_1(h, l) \leq V_2(h, l) \) for all \((h, l) \in S \).

Suppose that the reverse is true, i.e., for some state \((h, l) \), \( a_1^*(h, l) = T_C \) but \( a_2^*(h, l) \) is uniquely \( W \). Note that \( a_2^*(h, l) \) cannot be uniquely \( T_{LD} \) because \( r(h, l_{LD}, T_{LD}) = 0 \leq r(h, W) \). This implies that

\[
V_1(h, l) = r(h, l, T_C) < r(h, W)
\]

\[
+ \lambda \sum_h \sum_{l'} \mathbb{P}(h', l' \mid h)V_1(h', l')
\]

and

\[
V_2(h, l) = r(h, l, T_C) \leq r(h, W)
\]

\[
+ \lambda \sum_h \sum_{l'} \mathbb{P}(h', l' \mid h)V_2(h', l').
\]

Inequality (10) implies that

\[
V_1(h, l) = r(h, l, T_C) < r(h, W)
\]

\[
+ \lambda \sum_h \sum_{l'} \mathbb{P}(h', l' \mid h)V_2(h', l')
\]

because \( V_1(h', l') \leq V_2(h', l') \). It is obvious that there is a contradiction between (11) and (12), from which the result follows.

Proof of Proposition 5. The proof of this proposition is similar to the proof of Proposition 4 and is omitted.

References


