Living Donor Liver Transplantation When Deceased Donor Is Not Possible or Timely: Case Examples and Ethical Perspectives

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This article analyzes the ethical soundness of living donor liver transplantation (LDLT) in situations where the transplant team does not consider deceased donor liver transplantation (DDLT) a clinical or timely option. Given that patients with end-stage liver disease have a high risk of death without LDLT, the option of LDLT becomes compelling and may save lives.

We present 3 representative cases from our center that raise concerns over social behavior, limited time constraints for decision making, and high potential for disease recurrence that render DDLT an unlikely option. Thereafter, we discuss ethical issues for each patient, which predominantly pertain to compromises to the living donor informed consent process and the feasibility of LDLT. We conclude with recommendations regarding whether LDLT is an acceptable ethical option for those patients, which may inform clinical practice in the broader transplant community.

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Deceased donors remain the primary source of organs for patients wait-listed for liver transplantation (LT). Most transplant centers initially evaluate patients' eligibility for transplantation in general and then decide on the best treatment option: deceased donor liver transplantation (DDLT) or living donor liver transplantation (LDLT), the latter of which is only performed in a subset of centers. The number of LDLTs has not significantly increased over time in the United States due to issues with local surgical expertise, programmatic decisions, and risks to healthy living donors.1

Although most living donor hepatectomy complications are mild in nature, the serious rare complications become highly publicized, reduce interest in living donation, and thus limit further expansion of LDLT.2 Despite these risks, given the organ shortage, LDLT may be a clinically comparable alternative to DDLT that enables patients to receive LT significantly earlier and reduces the number of deceased organs needed by candidates on the DDLT waiting list.3,4 The most optimal situation is when LDLT confers a favorable ratio of benefits (lifesaving for the recipient) to risks (donor hepatectomy).5

Another enduring challenge that transplant clinicians face is determining whether LDLT is an ethically appropriate alternative when DDLT has been clinically ruled out or needed acutely. This article delineates the ethical considerations of 3 actual cases at our institution for which DDLT was not considered an optimal or timely option but when LDLT could have been plausible with adequate donor informed consent. These clinical
scenarios have not been analyzed or characterized previously from an ethical perspective and are important to consider because of increasing interest in certain LDLT situations.\(^6\) After each case presentation, we discuss key ethical issues and conclude with recommendations as to whether LDLT is an acceptable ethical option.

**Case 1: LDLT in a Patient With Alcoholic Hepatitis**

A 43-year-old female with a history of alcohol abuse presented with several weeks of progressive jaundice, malaise, and increased abdominal girth. She had been a social drinker since her 20s, previously consuming 2 drinks per day, though at that time she consumed 7–8 drinks daily in response to her divorce. Because of jaundice and liver dysfunction, she was told to discontinue drinking by her primary care physician 2 months earlier; however, she did not follow these recommendations. Her laboratory values were notable for white blood cell count of 20.1 K/μL, sodium of 129 mEq/L, creatinine of 0.63 mg/dL, aspartate aminotransferase (AST) of 125 U/L, alanine aminotransferase (ALT) of 43 U/L, total bilirubin (TB) of 22.3 mg/dL, and international normalized ratio of 2.4. Her Maddrey score was 82, and she was started on prednisolone for severe alcoholic hepatitis. Her Lille score at day 7 of treatment was 0.60, indicating that she was a steroid nonresponder. She had a strong family support system that included her biological parents and sister, and she voiced a strong commitment to maintaining posttransplant sobriety and attending treatment programs. Although the center evaluated her performed transplantations in select patients for alcoholic hepatitis, she did not meet the DDLT eligibility criteria given her continued alcohol use despite medical advice and knowledge of liver disease. Given her lack of improvement and poor prognosis without transplant, the family asked about the LDLT option, and her sister volunteered to be a living donor.

Case 1 highlights ethical challenges regarding the option of LDLT for a patient who was declined for DDLT, even at a center that performed DDLT for select patients with alcoholic hepatitis, as described elsewhere.\(^7,8\) The central reason that most patients with alcoholic hepatitis are excluded from DDLT is because the high risk of relapse after transplantation outweighs the public health consideration of diverting a deceased donor liver away from other wait-list candidates. However, LDLT in this context refocuses the risk away from another wait-listed candidate not receiving that liver (if DDLT were done) toward a living liver donor. Additionally, early LT through LDLT could be lifesaving compared with nontransplant options in which mortality rates are extremely high.\(^7,8\) Even though LDLT does not affect the chances of other wait-listed patients getting organs, the feasibility and ethical soundness of LDLT in these circumstances are not straightforward. Table 1 outlines the key ethical issues.

This case raises ethical challenges regarding living donor informed consent, which is critical to respecting the living donor’s autonomy.\(^9\) Organ Procurement and Transplant Network Policy 14.3 outlines informed consent requirements for living donors. Living liver donors may be under internal and external pressure to donate given the severity of their loved one’s illness and the high risk of mortality without LT.\(^11\) Both donors and recipients must be well informed of the risks, including the morbidity and mortality rates of donors and the benefits to themselves and each other during the informed consent process to ensure that they can provide meaningful informed consent.

However, potential living donors may desire information about the recipient’s disease, disease etiology, and risk of relapse in the LT recipient population as part of their decision-making and mutual consent process. Yet the Health Insurance Portability and Accountability Act secures recipient confidentiality, even at the cost of undermining the potential living donor’s informed consent. Interviews with living liver donors have demonstrated that although donors perceive adequate disclosure of risks and benefits, their comprehension of the recipient’s liver disease is commonly inadequate.\(^12\)

We argue that LDLT in this case is medically and ethically acceptable as long as the informed consent process is adequately performed for the living donor, which involves disclosure to the living donor of both the donor and recipient risks. Disclosure of the recipients’ risks of relapse may be controversial. However, given that the LDLT procedure risks a healthy person’s life and quality of life, we recommend that the donor be informed of the recipient’s underlying liver disease, the general risk of relapse, and the potential complications to the graft to determine whether the LDLT is sensible in light of their values. At a minimum, the transplant team could disclose risk information pertaining to the likelihood of graft failure based on the diagnosis.
Therefore, open and direct communication between the donor and recipient about the recipients’ underlying disease and her posttransplant commitment to sobriety may help the living donor make the most informed decision about donating. Transplant centers should develop noncoercive strategies to encourage recipients to engage in open communication with donors about their diagnosis. Such communication is important for ensuring that both sides are knowledgeable of simultaneous risks before proceeding.\(^{13}\)

## Case 2: LDLT in a Patient Under a Time-Sensitive Situation

A 25-year-old female with no past medical history presented with a 2-week history of fatigue, jaundice, and confusion. Her laboratory values were notable for ALT of 1438 U/L, TB of 16 mg/dL, international normalized ratio of 2.7, and creatinine of 0.6 mg/dL. Serological workup showed anti-nuclear antibody 1:360 and anti-smooth muscle antibody 1:160. A liver biopsy revealed interface hepatitis with plasma cell infiltration and 80% necrosis. She was deemed to have acute liver failure (ALF) from autoimmune hepatitis and was listed as status 1A. Her family asked about LDLT given the acuity and mortality of her disease and the concern for waiting for a DDLT. Her parents and sibling were willing to donate but were not suitable candidates secondary to anatomical variants. The parents reached out to distant relatives and approached a healthy 30-year-old second cousin. His interactions with the patient had been limited, mainly at intermittent family gatherings. The cousin was found to be anatomically compatible and a viable living donor candidate.

Case 2 describes a patient with ALF, a severe clinical condition defined as new rapid deterioration of liver function.\(^{14,15}\) This type of liver failure is a potentially fatal condition if emergent LT is not performed.\(^{16}\) Spontaneous recovery is expected in only 10%-40% of patients with ALF, whereas the survival rates after LT are >80%.\(^{17}\)

This case highlights the uncertainties over whether LDLT is an appropriate alternative for this patient. Although a deceased donor liver may become available at any time, the family’s concern about the patient’s rapidly deteriorating status drove the search for a
potential living donor. Although patients with ALF are assigned the highest priority for DDLT, the mortality rate during the waiting period is exceedingly high.\textsuperscript{[17,18]} In emergent situations, a full evaluation of the living donor can be expedited but may be associated with shortcomings due to the expedited process.\textsuperscript{[18]}

The patient’s urgent situation presented time constraints for decision making and may have potentially jeopardized the living donor’s ability to provide informed consent. A lack of sufficient time can limit information disclosure to the potential living donor about the risks, benefits, alternatives, and procedures for the donor and recipient. The donor’s decision can have life or death consequences for the recipient, and the time constraints of an expedited process may leave little time to deliberate. Donors may not have the opportunity to partake in a cooling-off period, which impedes time for processing the information and reflecting on their decision. Such circumstances can jeopardize a donor’s ability to make a voluntary, adequately informed decision.\textsuperscript{[0,19]} The Toronto transplant team reported that their evaluation of potential donors could be feasibly performed within a short time period (18–72 hours).\textsuperscript{[3]} They included a psychologist in their donor evaluation process to attenuate potential undue influences on the donor. Others point out that the urgent context introduces greater opportunities for errors by the transplant team in evaluating the potential donor’s risks.\textsuperscript{[19]} Moreover, research of liver donors in India found that emergency donation was significantly associated with reduced quality of life after donation.\textsuperscript{[20]}

In such a time-constrained circumstance, we question the quality of a potential donor’s decision-making process. Living liver donors are commonly motivated to donate primarily to help a loved one survive.\textsuperscript{[10]} In this case, the donor and recipient were distant relatives, so it was unlikely that they had an emotional relationship. Research has found that LT clinicians find it more acceptable to justify the donation when donors have emotional relationships with recipients because of motivations to donate (eg, to help improve the recipient’s health) and potential benefits to the donor (eg, seeing the recipient get better and/or retaining the family unit) are recognizable.\textsuperscript{[21]} Thus, the time pressures could be attenuated or deemed less of an issue. Yet, it is unclear what this distant familial donor’s motivation may be, if the benefits from donating outweigh the risks to both the donor and recipient, and how the relationship may influence the decision-making process. We believe that the nature of distant donor-recipient relationships merits careful attention to the motivation of the donor and the potential benefits donors gain by donating.

Clinicians should strive to obtain a comprehensive and detailed informed consent, but this becomes even more important when the donor is a distant relative, particularly in an acute setting like in this case. Although debate about the feasibility of accepting distant relative donors does arise in clinical practice, there is little evidence to help navigate this predicament. Fewer studies on DDLT have been performed in the United States compared with Asia. Additionally, sick patients with ALF typically rise to the top of the United Network for Organ Sharing waiting list and receive DDLT before discussions about DDLT even commence. However, Asian countries, in which deceased donors are scarce, provide a useful model for how informed consent can be practiced in acute decision-making contexts.\textsuperscript{[22]} Emergent DDLT may not be feasible for all patients given that patients may become too sick to consider DDLT as an option before the donor evaluation process finishes.\textsuperscript{[19]}

We recommend that transplant teams develop efficient donor evaluation procedures to ensure that shared decision making occurs. The fundamental ethical principles of nonmaleficence and autonomy require that donors are not unnecessarily harmed; thus, being adequately informed is key, even if this delays DDLT in the acute setting. An ethics consultation service may help to expedite this process. Future research should assess the bare minimum of information that donors would require for informed consent, perceptions of expedited consent processes, and strategies to mitigate perceptions of undue influence to donate in these circumstances.

**Case 3: DDLT in a Patient With Hepatocellular Carcinoma Outside of Milan Criteria**

\textit{A 55-year-old male with hepatitis C cirrhosis was recently found to have a 10-cm hepatocellular carcinoma (HCC) without portal vein invasion on magnetic resonance imaging. Alpha fetoprotein (AFP) was 5000 ng/mL. Further workup revealed no spread of the tumor outside of the liver. He underwent 2 cycles of chemoembolization, and on follow-up, he was found}
to have a decrease in tumor size to 8 cm and an AFP of 800 ng/mL. He was listed for transplant. However, his Model for End-Stage Liver Disease score was only 17, and he was not eligible for exception points. He had good functional status and no other complications of cirrhosis. Given the low likelihood of receiving a DDLT unless his liver disease progressed, the idea of LDLT was broached. He had a close friend who was interested in donating.

Case 3 illustrates a patient whose clinical condition is outside of the established cutoffs for DDLT in the United States. The Milan criteria established that DDLT is a viable option for HCC when transplantation is restricted to patients with a single lesion ≤5 cm or up to 3 separate lesions each ≤3 cm. Patients transplanted within this criterion have low recurrence rates and excellent survival rates after transplantation. For patients within the Milan criteria, LDLT confers comparable patient and graft outcomes and reduces long DDLT wait times.

Although the Milan criteria have provided excellent outcomes after transplant, it has been criticized as being overly restrictive for patients with larger lesions. To accommodate such patients, the University of California, San Francisco (UCSF), developed broader criteria. These criteria include HCC with 1 nodule ≤6.5 cm in diameter or 2-3 nodules with individual diameters ≤4.5 cm and a total tumor diameter ≤8 cm. Studies document an improvement in patient outcomes without increases in mortality or disease recurrence rates when patients undergo DDLT within these criteria.

Similarly, LDLT may have similar outcomes in patients beyond Milan criteria, although the risk to the donor must also be considered in this expanded indication for transplantation. Currently, there is no consensus about an acceptable HCC recurrence risk when considering this patient population for transplantation. The risk of recurrence is a factor in determining whether living donation should be an option. Other comparable situations, such as LDLT for liver metastases from colorectal cancer, raise similar ethical issues in which recurrence rates are high but may provide better survival in select patients than denying transplantation.

The lack of consensus invariably makes decision making for LDLT in this patient population challenging. The recipient, the transplant team, and the potential donor must all determine their willingness to accept the risks of adverse events to the recipient (eg, graft failure and HCC recurrence) in light of the risk of donor complications. Donors commonly experience psychological distress when their recipient’s graft fails or if the recipient dies. Accordingly, information about the recipient’s higher risks of recurrence and death should be disclosed to the potential donor as part of the informed consent process. Transplant teams might not respect a potential donor’s autonomy if the recipient’s risk of recurrence is too high or if the prognosis is too poor. Despite the clinical risks to donors, some donors may persist in pursuing donation, and a donor-centered approach to decision making would require that transplant teams seriously consider donors’ preferences and proceed with LDLT after a thorough informed consent process.

Patients outside of both Milan and UCSF criteria, such as this case, commonly experience recurrence of HCC if transplanted, which usually leads to decreased survival. When considering LDLT in this population, the benefit to recipients is low if the disease quickly recurs, and thus, the benefits do not appear to outweigh the medical and surgical risks to the donor. However, if the donor is informed of the risks of HCC recurrence (akin to case 1, which focused on alcohol-use relapse) and understands the operative risks, denying donation may be difficult. Indeed, the cutoff between acceptable and excessive risk is somewhat arbitrary. Ultimately, the transplant team must respect the principle of nonmaleficence to the donor by preventing donations that could ultimately do more harm to the donor than are justified for the benefit provided to the recipient. In the absence of clinical consensus, case study research of how transplant teams weigh the advantages and disadvantages of LDLT in similar scenarios could help to build an ethical framework for determining whether to proceed with LDLT.

**Conclusion**

The cases present a composite of ethical dilemmas routinely seen at transplant centers when DDLT is not an option and LDLT is alternatively considered. Each unique clinical scenario compromised the living donor’s informed consent in different ways. We recommend that transplant teams carefully prepare policies in advance for enabling an efficient and effective informed consent process that protects donors’ autonomy and informs donors of recipient risks and vice versa. Future
research should assess donors’ intentions across these scenarios and decision-making factors to guide the development of consent procedures. Mindfulness of the ethical considerations herein may help transplant teams provide more donor-centered care.

REFERENCES