

Morbidity and Mortality Among Adult Living Donors Undergoing Right Hepatic Lobectomy for Adult Recipients

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EXECUTIVE SUMMARY

Background Following the success of liver transplantation in children from living donors, many transplant centers have begun performing the procedure in adults. Living donor transplantation represents a major advance in the efforts to relieve the growing national shortage of cadaveric organs.

Donation to adults usually requires a right hepatic lobectomy, a procedure that has been associated with greater morbidity compared to the left lateral segmentectomy typically used for donation to children. A variety of complications related to right hepatic lobe donation have been described, including deaths. However, the frequency and nature of complications are incompletely understood. Thus, the purpose of this evidence report is to summarize the available evidence regarding the outcomes of donors who participated in right lobe donation for adult LDLT

Methods The primary source of evidence was the published literature identified by performing a search of the MEDLINE® database. Studies were categorized according to transplant center and author to eliminate duplicate reports. Further information was obtained from the United Network of Organ Sharing (UNOS) and from communications with representatives from some of the transplant centers with the largest experience in adult LDLT in the United States.

Results Nineteen studies met inclusion criteria. All were reports of individual patients, case series, or survey studies. Fourteen transplant centers published their experience with a total of 308 unique donors. Seven studies represented surveys of transplant centers in Europe, Japan, and the United States. These included a total of 985 donors, some of whom may also have been included in the surgical series. Details regarding donor characteristics and outcomes of interest (donor morbidity, donor mortality, and donor quality of life following right lobectomy donation surgery) were reported with variable detail. Length of follow-up was relatively short, and often not stated.

Over 771 adult-to-adult LDLT have been performed in the United States according to the UNOS registry. The number performed has increased each

year (from 139 in 1999, to 271 in 2000, and 336 in 2001). Virtually all LDLT performed currently in the United States involve right lobe donation. At least 57 of 122 transplant centers in the United States performed a minimum of one LDLT prior to October 2001. Twenty-two centers have performed at least 10 adult LDLT, accounting for 84% of all 771 reported procedures.

Protocols used by transplant centers to follow donors have not been extensively reported. Several large volume LDLT centers follow donors serially with radiographic imaging at day 7, 1 month, 3 months, 6 months, and 12 months following either donation surgery or hospital discharge. No donor outcomes are systematically collected at this time.

Donor mortality has been reported in two donors in the United States (providing an estimated mortality rate of .26%). In addition, three donors (.39% of all donors) were listed with UNOS for liver transplantation following donation hepatectomy due to the development of liver failure. One of these donors died prior to receiving a transplant. However, this donor death was previously described. One of the other donors received a cadaveric transplant and one remains on the UNOS waiting list. Published estimates of donor morbidity have ranged from 0 to 67%, depending in part upon how complications were defined. Bile leaks, prolonged ileus, and minor wound problems were the most commonly reported complications. A survey of all U.S. transplant centers reported a median complication rate of 14%; 6% of donors experienced biliary complications.

Right hepatectomy donation surgery has an impact on quality of life. The majority of donors returned to work. Some donors had prolonged time away from work, and a small percentage were unable to return to work or chose to change careers. In surveys of donors, mean recovery time was 3 to 4 months (range 1 to 12 months). Most donors surveyed would donate again and recommend donation to a potential donor contemplating LDLT. One report described lasting effects on body image during a mean follow-up of 13.7 months.

Consensus has not been reached on the optimal evaluation process of potential living donors. A step-wise evaluation to screen for medical and psychological issues is performed at most centers. Imaging studies are

obtained in potential donors without medical or psychological conditions for anatomical evaluation preoperatively. Surgical refinements in recent years have permitted the acceptance of donors with anatomic irregularities that would have precluded donation during the initial experience. Liver biopsies are performed routinely in some centers, while some centers use the biopsy selectively. Liver biopsy is particularly useful in patients with a body mass index (BMI) greater than 28 to evaluate for possible steatosis (accumulation of fat in the liver). Donor characteristics associated with lower donor morbidity rates have not been systematically evaluated. Experts currently exclude potential donors who are over age 50 and those with BMI greater than 35.

Conclusions Over 771 right lobectomies for LDLT to adult recipients have been performed in the United States as of October 2001, 58 percent of which have been reported in the medical literature (primarily in one transplant center survey) suggesting that the published experience has lagged significantly behind clinical experience. Donor mortality and morbidity have not been systematically collected or reported, although reasonable estimates of mortality and the most common types of perioperative complications can be derived from the available data. Increasing experience and refinements in surgical techniques may reduce the frequency of donor complications. The long-term consequences of right-lobe donation are unknown.

BACKGROUND

The shortage of donor organs is a major limiting factor in liver transplantation. While over 5,000 transplants are performed annually in the United States, more than 1,000 candidates die each year while on the liver transplant waiting list. Approximately 18,500 patients were awaiting liver transplantation in the United States as of December 2001 according to data from the United Network for Organ Sharing (UNOS). Living donor liver transplantation (LDLT), where a healthy volunteer donates a portion of their liver, provides one means to expand organ availability. Of 4,954 liver transplants performed in 2000, 400 (8%) were from living donors.

Living donor liver transplant to pediatric recipients has been performed in the United States since 1989. Following the success of living donation in children, many transplant centers considered donation to adult recipients as a potential solution to the growing national cadaveric organ shortage.

The adult procedure is technically different from that performed in children since the volume of donor liver needed is significantly larger in adults. Donation to adults usually requires right hepatic lobectomy while donation to children is usually limited to the smaller left lateral segment (Figure 1). Right hepatic lobectomy is currently the standard procedure in the United States.

The donor liver can be divided in a number of different ways depending on the needs of the donor and the recipient. Some programs perform a right lobectomy by removing approximately 60% of the hepatic mass, while others perform an extended right hepatectomy, removing approximately 70% of the hepatic mass, including the middle hepatic vein. Details regarding surgical techniques for adult-to-adult LDLT have been extensively reviewed elsewhere.¹⁻⁶

Donor morbidity related to right lobe donation is generally considered to be higher than for left lobe donation.⁷⁻¹⁰ As a result, morbidity and mortality rates in donors undergoing these procedures are not directly comparable.^{11, 12}

Whether right lobe donation will continue to be the standard procedure in the United States is uncertain. Recognition of the increased morbidity related to the procedure has renewed efforts to consider alternatives. A report from Japan suggested that an extended left lobe graft might be sufficient for most patients who received a right lobe graft.¹³ Furthermore, a case report suggested that small-for-size grafts (such as those provided by left lobe donation) may be sufficient when the transplant is performed using methods that divert excessive blood flow to the graft, which reduces venous congestion and permits better graft function and growth.¹⁴

The donor selection process involves multiple stages of evaluation beginning with a history and physical examination and proceeding to more invasive

procedures. Potential donors are screened for any underlying medical or psychological disease that might compromise the safety of the donor or of the donated liver lobe. Psychosocial evaluations are made to ensure that consent is informed and free of coercion. Investigation of liver function and hepatobiliary anatomy is obtained with radiographic imaging. In some cases a liver biopsy is obtained to rule-out underlying liver disease, including fatty liver. Different centers report that about 15 to 72% of potential donors are excluded for various reasons.¹⁵⁻¹⁷ The most common reasons for exclusion are incompatible blood type and steatosis on liver biopsy.¹⁵ In addition, 23% never actively pursued evaluation as a potential donor after initial inquiry.

A consensus statement issued by the Live Organ Donor Consensus Group suggests that LDLT recipients should meet listing criteria for cadaveric transplantation.¹⁸ However, interpretation of this recommendation has not been uniform. Some centers restrict recipients to those with the highest probability of a favorable outcome (2b and 3 patients on the UNOS waiting list), excluding those with multiple organ failure who are on life support or those with chronic liver failure and less than seven days life expectancy (Status 1 and Status 2a patients on the UNOS waiting list).¹⁹ Other centers offer LDLT to recipients who are clearly not candidates for cadaveric transplantation by UNOS listing criteria (such as those with certain types of liver tumors). Regardless of the differences among centers, it is generally agreed that the benefit to the recipient should justify the risk to the donor. The ethics of LDLT are still hotly debated, particularly since the risk to the donor is unclear.

Medicare policy does not presently include coverage of living liver donors. Although CMS previously investigated the safety and effectiveness of the procedure for the transplant recipient, outcomes for donors were not included in the evaluation. Coverage of left lobe donors to pediatric recipients was included in that earlier report.²⁰

The anticipated growth of adult LDLT provides a rationale for a better understanding of consequences of donors. A number of initial reports have suggested that donors may experience significant morbidity related to the procedure. A variety of complications have been described, the most

common of which were bile leaks, prolonged ileus, and minor wound problems. Donors may also experience long-term consequences on quality-of-life. Donor deaths have also been reported. Thus, the purpose of this evidence report is to summarize the available evidence regarding the outcomes of donors who participated in right lobe donation for adult LDLT.

Donor outcomes would be ideally sought from a comprehensive registry. However, unlike recipient outcomes, UNOS has not systematically collected data on donor outcomes. The American Society of Transplant Surgeons has proposed a voluntary registry, which is not yet established because long-term funding has not been identified. The European Liver Transplant Registry has tracked outcomes following liver transplantation in Europe, but does not register the morbidity and mortality of donors.²¹ The National Institutes of Health has issued a request for applications to facilitate the systematic, prospective collection of living donor outcomes data following right lobectomy to adult recipients.

METHODS

Sources of Evidence

Three sources of evidence were used for this report:

(1) The primary source of evidence was the published English-language literature. Abstracts from the 2001 annual meetings of the American Association for the Study of Liver Disease (AASLD) and the combined American Society of Transplantation (AST) and American Society of Transplant Surgeons (ASTS) meetings were also reviewed. These meetings represent the forums during which the majority of transplant-related studies are initially presented.

(2) Registry data from United Network of Organ Sharing (UNOS).

(3) Representatives from some of the major transplant programs in the United States performing LDLT.

Published Literature

The published literature regarding right lobectomy for adult-to-adult living donor liver transplantation was identified by performing a search of the MEDLINE® database. The search was restricted to articles focusing on human subjects that were published in English between January 1995 and November 2001. Search terms included: liver transplant, liver graft, hepat graft, hepat transplant, living donors, tissue donors. A search of the meeting abstract databases identified preliminary results published at the annual meetings of the AST and ASTS (May 2001), as well as the AASLD (November 2001).

Inclusion criteria

Studies were included that described any donor outcomes following right hepatic lobectomy for adult-to-adult living donor liver transplantation.

Exclusion criteria

Studies were excluded if they were: published in languages other than English, focused exclusively on children (age < 18), presented outcomes following right lobectomy that could not be discerned from outcomes following left lobectomy or other donation techniques, reviewed other sources of primary patient data or represented duplicate reports of previously-described patients.

Titles and abstracts were reviewed to identify relevant articles. The bibliographies from retrieved articles were examined to identify other potentially relevant studies. All studies were examined in duplicate and consensus was achieved for all reports that were included in this evidence report based upon the inclusion and exclusion criteria described above.

Data extraction included information on the study location, patient characteristics, donation surgery, study duration, and outcomes of interest (donor morbidity, donor mortality, donor quality of life)[Appendix I: Published Literature Data Extraction Form]. Studies were categorized according to authors and transplant center to identify duplicate reports of the same patients. Duplicate reports were included if they provided additional follow-up data; however patients were counted only once. Emphasis was placed on the largest studies, and those that reported the highest quality of information.

United Network of Organ Sharing (UNOS) Registry

Information was requested from the United Network for Organ Sharing to provide an estimate of the frequency with which living donor liver transplantation has been performed in the United States. The United Network of Organ Sharing (UNOS) under contract with the Organ Procurement and Transplantation Network (OPTN) oversees a registry that includes information on almost every cadaveric and living donor transplant recipient in the United States. Some transplant centers have electively supplied donor data as well. However, because reporting of living donor transplantation was voluntary, the information is incomplete. Furthermore, the registry contains only limited information regarding the donors. Further information about UNOS or the transplant registry can be found via the Internet at www.unos.org .

Living Donor Liver Transplantation Expert Opinions

Current experience with donor outcomes may be incompletely reflected in the published literature. Refinements in the right-lobe donor procedure that may increase its safety continue to be described. As an example, one group reported that the adoption of specific surgical methods to optimize venous outflow resulted in a much lower rate of complications than has previously been described⁷ ; no donor complications were observed in 48 right-lobe resections and transplants. Furthermore, there appears to be a learning curve for surgeons performing the procedure suggesting that donor safety has improved since the publication of the studies included in this evidence report, most of which reflected the initial experience with LDLT. On the other hand, serious donor complications (including death and the development of

post-donation liver failure) have been mentioned, but not documented in the literature or the UNOS database.

As a supplement to information provided by the literature and UNOS database, a subset of transplant surgeons and hepatologists performing LDLT was contacted to provide further insight into donor and procedure characteristics that may have a bearing on donor outcomes and provide further insight into donor adverse events [Appendix II: Expert Opinion Data Extraction Form]. Transplant surgeons and hepatologists were selected who had a large experience with LDLT and who were willing to provide information.

RESULTS

Study Characteristics

The Medline search revealed 217 abstracts of which 58 were retrieved for further analysis. Review of the bibliographies of relevant studies did not produce any additional studies. Seventeen studies were excluded because they did not contain primary data. Seven were excluded because they focused on donation to children. Three were excluded because outcomes following right lobectomy could not be discerned from outcomes following other types of surgical procedures. Five were excluded because they did not report outcomes following right lobectomy, and seven were excluded because they represented duplicate reports of previously described patients.

Nineteen studies were included in the final analysis. All were reports of individual patients, case series, or survey studies. Fourteen transplant centers published results following adult-to-adult living donor liver transplantation for 308 unique donors. Seven surveys of transplant centers in Europe, Japan, and the United States included 985 donors, some of whom may have be included in the case series

The majority of studies focused on recipient outcomes while providing only limited information regarding donor outcomes. The largest case series included 62 donors.¹³ The largest survey study included 449 right lobectomy

donors in the United States performed as of October 2000.²²

The quality of reports varied. Although most included some details regarding length of hospital stay and immediate complications, only a few described quality of life. Details about long-term outcomes were inconsistently included. Follow-up ranged from 1 to 13.7 months (Table 1a and 2a). However, most studies did not describe the follow-up period.

The following sections will review specific questions regarding living donor liver transplantation.

Question One. How many adult liver transplants have been performed in the United States from living donors? How many of these transplants have been right lobectomies?

[Literature.] A survey study of adult-to-adult living donor liver transplantation practice patterns among US transplant center reported that 449 LDLT to adults had been performed in the United States as of October 2000.²² The survey author assumed these to be right lobectomy donations, although details related to the type of donor procedure were not requested explicitly.²² Of 112 transplant centers in the United States, 86 completed surveys (77% response rate). Two hundred nineteen donors from the United States have been identified in published case series (Table 1a and 2a).

[UNOS.] The UNOS registry includes 37,357 liver transplants performed in the United States between 1990 and 2001, including 4,384 performed in 2001. UNOS reports 771 living donor liver transplants to adult recipients prior to October 2001 (Figure 2). The number performed has increased each year, from 25 performed in 1998, 139 in 1999, 271 in 2000, to 336 LDLT performed in 2001. Because data are submitted electively by transplant centers, they are not comprehensive and do not provide uniform details regarding living donors.

[Experts.] Experts were unsure of the exact number of adult-to-adult right lobectomies performed worldwide. One expert estimated that it ranged from 1000 to 2000, with approximately 50% occurring in Asia (primarily Japan, Hong Kong, and Korea).²³ The experts estimated that there have been approximately 400 to 500 performed in the United States, an underestimate given the UNOS registry. The experts state that virtually all living donor transplants performed in the United States involve right lobe donation.

While the number of transplant centers performing LDLT appears to be increasing, one expert speculated that the total number of LDLT performed annually at each transplant program in the United States might be decreasing.²⁴ When a program initiates a LDLT program, approximately one-third of patients on the waiting list opt for living donation creating a back log that diminished in size as the group undergoes the procedure. As a result, when any program starts this procedure the number of living donor transplant will be high and then decrease over time. As an example, at the Medical College of Virginia approximately 45 LDLT were performed in the first 1 to 2 years after the program was initiated.²⁴ The pace then fell to about 12 LDLT to adult recipients each year as they depleted the patients on the waiting list interested in this procedure who could find a donor. The expert believed that other centers have experienced a similar decline.

Thus, the number of LDLT that will be performed in coming years will depend upon the number of new programs beginning the procedure (apparently increasing), the output of the established programs (possibly decreasing at least in some centers), and the degree of interest in the procedure from potential donors and recipients.

[Summary] At least 771 adult-to-adult right lobe LDLT have been performed in the United States since 1997. The number performed has increased each year, from 139 in 1999, to 271 in 2000, and 336 in 2001. However, LDLT may plateau after all recipients on the waiting list for transplantation who have potential living donors undergo complete evaluation.

Question Two. How many transplant centers have performed at least one adult liver transplant from a living donor?

[Literature] A survey study of LDLT practice patterns among US transplant centers reported that 43 transplant centers had performed at least one adult-to-adult living donor liver transplantation prior to October 2000.²² Of 112 transplant centers in the United States, 86 completed surveys; thus, 50% of participating centers and at least 38% of all transplant centers have performed adult LDLT. Thirteen centers had performed at least 10 adult LDLT, accounting for 81% of all 449 reported procedures. The mean number of adult LDLT per center was 11, with a range from 1 to 71 transplants. Twenty-one centers had performed fewer than five adult LDLT. Of 43 programs not performing adult-to-adult LDLT, 22 planned to initiate programs within 12 months of the survey.

A report from the Living Donor Liver Transplantation Conference at The National Institutes of Health in December 2000 concluded that “the question of whether all U.S. transplant programs should perform this operation or if this complex procedure should be limited to only a few select centers needs to be established.”²⁵ Others have suggested that a certification process should be instituted for transplant centers that are performing or intend to perform LDLT.²⁶

[UNOS] Fifty-seven transplant centers have reported performing LDLT to adult recipients to UNOS prior to October 2001. Mean number of adult LDLT per center was 14, with a range from 1 to 99. Twenty-two centers have performed at least 10 adult LDLT, accounting for 84% of all 771 procedures. Twenty-nine centers have performed fewer than 5 LDLT.

[Experts] Five transplantation centers have experience with over 40 right lobectomies for LDLT²³ and one center has performed over 100 LDLT.²⁴

[Summary] The number of centers performing LDLT increased to a minimum of 57 as of October 2001. Twenty-two centers have performed at least 10 adult LDLT, accounting for 84% of all 771 reported procedures.

Question Three. What protocols are used by transplant centers to follow donors for adult liver transplantation after transplantation, i.e. how long and at what frequencies are donors typically followed by the transplant center?

[Literature] Protocols used by transplant centers to follow donors for adult LDLT were not well described in the medical literature. Most case reports and series report follow-up through initial hospital discharge.

[UNOS] UNOS does not collect information regarding donor follow-up.

[Experts] At one center with one of the highest volumes of LDLT in the United States, donors are followed with MRI or CT scan and serum liver studies at 7 days, 1 month, 3 months, 6 months, and 12 months following donation surgery.^{23, 27} Any evaluation beyond 12 months is on an as-needed basis. Donors are typically discharged after seven days and are reevaluated one week later.

[Summary] Protocols used by transplant centers to follow donors have not been extensively reported. In expert comments, several large volume LDLT centers follow donors serially with radiographic imaging at day 7, 1 month, 3 months, 6 months, and 12 months following either donation surgery or hospital discharge.

Question Four. What are the known morbidity and mortality rates for right lobectomy for adult-to-adult living donor liver transplantation?

- a) How many adult liver donors have experienced complications from the donor procedure?
- b) Describe the nature of the complications. Describe the follow-up of the donors.

[Literature] Donor outcomes are summarized by study in Tables 1b and 2b. The quality of reports varied. Length of follow-up was short, ranging from 1 to 13.7 months. However, most studies did not describe the follow-up period. Some reports described complications by incident rather than by patient; thus, the proportion of patients affected was often not provided.

Although most reports included some details regarding length of hospital stay and immediate complications, only a few described quality of life. No report included a definition of morbidity. Because what constitutes “morbidity” is not well codified, a “minor complication” as assessed by authors may seem very significant to donors.^{11, 28}

The most serious potential consequence of a right lobectomy is death due to intraoperative or postoperative complication. Although a right lobectomy performed in a healthy donor should carry a low risk of death, the mortality rate has not been clearly established. One adult LDLT donor death was described in the medical literature.¹¹ The donor died from sepsis during the perioperative period. A second donor death, not yet described in the medical literature, was reported in the news media January 15, 2002; the patient died three days postoperatively from aspiration after an episode of hematemesis. The hospital has been fined for negligent care, and their adult LDLT program has been suspended for six months. In a 1999 commentary, Strong stated that six persons had died as a result of liver donation²⁹ but did not specify whether the operations were performed to obtain grafts for children or adults³⁰ or if they were performed in the United States.

Mortality following right lobectomy in oncology is reported to be approximately 5%.⁸ Mortality for hepatectomy performed for nonmalignant conditions in the absence of cirrhosis or underlying liver disease is less than 1%.⁸ However, morbidity and mortality in the living donor should be less because of both the general better health of the donor compared with patients undergoing right hepatectomy for malignancy, and because of improvements in surgical techniques in recent years.

Donors are selected in part because of their good health. As a result, donor morbidity is an important outcome marker in determining the success of adult-to-adult LDLT. Morbidity associated with living donor right hepatic lobe

donation in studies that report complications ranged from 0 to 67%, with most centers reporting less than 24% (Table 2b). Bile leak, prolonged ileus, and minor wound problems were the most commonly reported complications. Other common complications include neuropraxia (nerve injury with associated paresthesias), transient pressure sores, pleural effusions, edema, and atelectasis. Overall complication rates reported in a survey of all U.S. transplant centers ranged from 0 to 100%, with a median of 14%.²² Six percent of donors experienced biliary complications. The majority of complications were addressed conservatively, such as with endoscopic placement of a biliary stent (to treat bile leaks). An occasional patient required reoperation (Table 1b and 2b). No published reports have identified liver failure as a complication following right lobectomy.

Fourteen reports provided data on the length of hospitalization after surgery (Table 1b and 2b). The average length of hospital stay was 7.3 days. There were insufficient details provided regarding any change in length of admission as a function of procedural experience (i.e. surgical learning curve) to make general conclusions. The survey of transplant centers in the United States reported a mean hospital stay of 6.4 days (range 4 to 14 days) in 449 adult-to-adult donors.²² Seven reports that included a total of 575 donors, reported a mean hospital readmission rate of 7% (Table 1b and 2b). The United States transplant center survey reported an 8% rehospitalization rate, and reported lower rates of reoperation, rehospitalization, biliary complications, and blood transfusion in higher volume centers.²²

Recovery time was described in 3 reports that included a total of 42 donors.^{11, 31, 32} Mean time to recovery was 14 weeks, ranging from 4 to 52 weeks. Of the 3 studies reporting return to pre-donation occupation, 58 of 60 donors were back at work.^{11, 32, 33} One donor was seeking job placement at the time of report.³² One donor was unable to return to work after developing chronic fatigue syndrome.¹¹ Overall, 1 of 60 donors (2%) was unable to return to pre-donation occupation following right lobectomy. Sixty-six percent of 24 of donors required a period of light-duty work for a mean of 2.8 months before returning to full-duty work.³²

Three of 19 studies included health-related quality of life as an outcome measure.^{11, 32, 34} Two centers used the Medical Outcomes Study 36-Item Short-Form (SF-36®), and one center used the Medical Outcomes Study 12-Item Short-Form (SF-12®). Surveys were administered at varying times from the donation. Thus, the stability of these quality of life determinations is unclear.

- In a study of 24 donors, 42% reported a change in body image, and 17% reported mild persistent symptoms, primarily abdominal discomfort, that they related to the donor surgery.³² All 24 donors would donate again if necessary, and 96% reported a benefit from the donor experience. The donor's relationship with the recipient was the same or better in 96% of donors, and the relationship with the donor's significant other was the same or better in 88% of donors. Mean out-of-pocket expenses incurred by donors were \$3,660.
- In another study of 14 donors using the SF-12®, no significant changes were reported in physical activity, social activity, or emotional stability.¹¹ All donors reported that they would donate again, and would recommend donation to someone in contemplation.
- A study of 30 donors reported that all living donors demonstrated significantly higher scores in general health on the SF-36 than U.S. norms.³⁴ Donors whose recipients had no complications scored significantly higher in mental health and general health compared to U.S. norms. Donors whose recipients had major complications scored significantly lower on the mental health scale than those with recipients without major complications. Thus, donor health-related quality of life following donation surgery was less for donors whose recipients experienced major complications.

[UNOS] The United Network of Organ Sharing does not systematically track morbidity of mortality of donors. However, three donors have been listed with UNOS for liver transplantation following donation hepatectomy. Of one donor listed in 1999 and two listed in 2001, one has received a

cadaveric transplant, one was removed for death prior to receiving a transplant, and one remains on the waiting list.

[Experts] Our experts were aware of two adult-to-adult donor deaths in the United States (University of North Carolina and Mt. Sinai).^{23, 27} In addition, they were aware of 3 adult-to-adult LDLT donor deaths in Europe (2 in Germany, 1 in France), mention of 1 possible donor death in Korea and 1 donor death in Argentina, and possible donors death in Hong Kong.²³ Experts were aware of donors who required cadaveric liver transplantation following donation due to the development of liver failure but were unsure of the exact number.²⁷ The experts emphasized that the published literature is largely from center surveys, and is likely to be biased toward favorable outcomes.³⁵

Although not yet described, donor complications may result from the procedures used to evaluate potential donors, particularly invasive procedures such as liver biopsy and angiography. In addition, some donors will be excluded for reasons such as unforeseen anatomical abnormalities noticed intraoperatively and thus experience morbidity related to the laparotomy and scar without having actually donated.

Long-term donor outcomes are not known. Donors may ultimately experience long-term complications that have been experienced by other groups of patients undergoing major abdominal surgery such as chronic pain and small bowel obstruction related to intestinal adhesions.

[Summary] Donor mortality in the United States is estimated to be .26% (2 deaths in a total of 771 known donations to adults). In addition, three donors (.39% of all donors) were listed with UNOS for liver transplantation following donation hepatectomy due to the development of liver failure. One of these donors died prior to receiving a transplant. However, this donor death was previously described. One of the other donors received a cadaveric transplant and one remains on the UNOS waiting list. Published donor morbidity ranged from 0 to 67%, with most centers reporting less than 24%. The different rates in part reflect variations in the definitions of donor morbidity. Bile leak, prolonged ileus, and minor wound problems were the

most commonly reported complications. Other common complications included neuropraxia (nerve injury with associated paresthesias), transient pressure sores, pleural effusions, edema, and atelectasis. The median complication rate reported in a survey of all US was 14%.²²

Right hepatectomy donation surgery affects quality of life. In surveys of donors, mean recovery time was 3 to 4 months (range 1 to 12 months). The majority of donors returned to work, although some had prolonged time away from work, and a small percentage were unable to return to work or chose to change careers. Most would donate again and recommend donation to a potential donor contemplating LDLT. One report described lasting effects on body image during a mean follow-up of 13.7 months.

Question Five. Are there identifiable donor characteristics associated with lower morbidity rates? What preoperative evaluation of living donors is necessary? Is a liver biopsy necessary in the preoperative evaluation of all living donors?

[Literature] No standard evaluation process has been identified for the preoperative evaluation of living donors. One survey of all US transplant centers reported that the median potential-donor evaluation time was 28 days (range 7 to 84).²² Minimum donor evaluation times ranged from 1 to 56 days (median 6.5 days). Approximately 45% of potential donors eventually donated (range 8 to 100%).

The donor evaluation processes described in the medical literature are summarized in Table 1a and 2a. As a general rule, the evaluation occurred in a step-wise process. In the initial evaluation, donors must be blood group (ABO) compatible and healthy, without any underlying medical condition that might compromise the safety of the donor or the health of the donated liver. Psychosocial evaluations are made to confirm informed consent and ensure that the prospective donor has adequate time to contemplate the risks of the procedure and to decline participation.^{1, 16, 36}

Screening assessments usually include a comprehensive history and physical examination. Routine chemistries, a complete blood count, and liver

enzymes and viral serologies (including evaluation for HIV and hepatitis B and C) are determined. A chest x-ray and electrocardiogram are performed. Finally, assessment of the donor anatomy for vascular and biliary variations is made using a combination of ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and arteriography. A survey of all transplant centers in the U.S. reported that 14% of programs never obtain an arteriogram, while 60% of centers obtain an arteriogram for all donors.²² Twenty-six percent of centers obtain arteriograms in selected potential donors. More extensive cardiac and pulmonary testing is performed in selected cases.

Liver biopsy is a routine part of the donor evaluation at some centers, while other programs reserve biopsy for potential donors with elevated liver enzymes or suspected steatosis (fat accumulation in the liver). The degree of steatosis has been used to correct volumetric estimates of hepatic mass estimated from imaging studies. A survey study of all U.S. transplant centers reported variable rates of liver biopsy in the routine evaluation of potential living donors.²² Fourteen percent of centers never obtained a liver biopsy, 26% obtained a liver biopsy for all donors while the remaining 60% obtained a liver biopsy only in selected cases.

No report attempted to identify donor characteristics that were associated with lower morbidity rates. However, several donor characteristics are presumed to be important for both the donor and the recipients. There is debate over the acceptability of donor livers showing steatosis; severe steatosis is generally considered to be a contraindication to donation.³⁶

Anatomic variation can also be a reason for exclusion.⁶ Graft size must be sufficient to support the metabolic demand of the donor and recipient following LDLT. As a general rule, the mass of the donor liver lobe should be no less than 0.8% to 1% of the body weight of the recipient. Some programs set a minimum donor weight at 1% of body weight, while others use 0.8%.³⁶

The donor evaluation process is not perfect. Despite extensive screening for underlying medical conditions, donors have been reported to have findings at the time of surgery that ultimately excluded the completion of donation surgery.¹¹ For example, one donor was found to have noncaseating

granulomas at the porta hepatitis after surgical incision, but prior to right lobectomy.¹¹ Although that potential donor was included, aborted donors are generally excluded from published reports of donor outcomes because they do not undergo right lobectomy.

[UNOS] UNOS does not collect data regarding the evaluation of potential living donors.

[Experts] Experts suggest that the ideal donor candidate should be young, healthy and thin. At least two centers use an age cut-off of 50 years for the donors.^{23, 27} Several centers require a liver biopsy, particularly for patients with a body mass index (BMI) greater than 28. Donors with BMI greater than 35 are not accepted. Reasons for exclusion based on anatomy are handled on an individual basis. Technical refinements of the donor procedure have permitted the acceptance of donors who were once considered to be unsuitable based upon anatomic considerations.²³ Figure 3 contains potential donor evaluation flow-charts from one major transplant center.

Acceptable indications for the recipient undergoing live donor transplantation are controversial. Some transplant centers are proceeding with live donor transplants in recipients that do not meet minimal cadaveric listing criteria because they are either not sick enough or are not thought to have disease amenable to cure with transplantation (i.e., metastatic tumors or multifocal hepatocellular carcinoma).²³ One expert expressed concern that until the true risk to the donor is fully understood, transplant programs should not be proceeding with live donor transplants in patients who would not ordinarily be transplant candidates just because they have a donor.²³

[Summary] No standardized process exists for the evaluation of potential living donors. A step-wise evaluation to screen for medical and psychological issues is performed at most centers. Imaging studies are obtained in potential donors without medical or psychological conditions for anatomical evaluation preoperatively. Liver biopsies are performed routinely in some centers, while some centers use the biopsy selectively. In a survey study, 14% of centers never obtained a liver biopsy, 26% obtained a liver biopsy for all donors, while the remaining 60% obtained a liver biopsy only in selected

cases. Liver biopsy is particularly useful in patients with a body mass index (BMI) greater than 28 to evaluate for possible steatosis. Donor characteristics associated with lower morbidity rates have not been systematically evaluated. Experts currently exclude potential donors who are over age 50 and those with BMI greater than 35. Surgical refinements in recent years have permitted the acceptance of donors with anatomic irregularities that would have precluded donation during the initial experience.

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Figure 1. Normal Liver Anatomy. The liver is routinely divided into 8 separate segments, with segments 2 to 4 making up the left lobe, and segments 5 to 8 making up the right lobe. Segment 1, often known as the caudate liver, is usually excluded in LDLT. In right lobectomy segments 5 to 8 and part of 4 are donated to an adult, while segments 2 and 3 are given to a child.

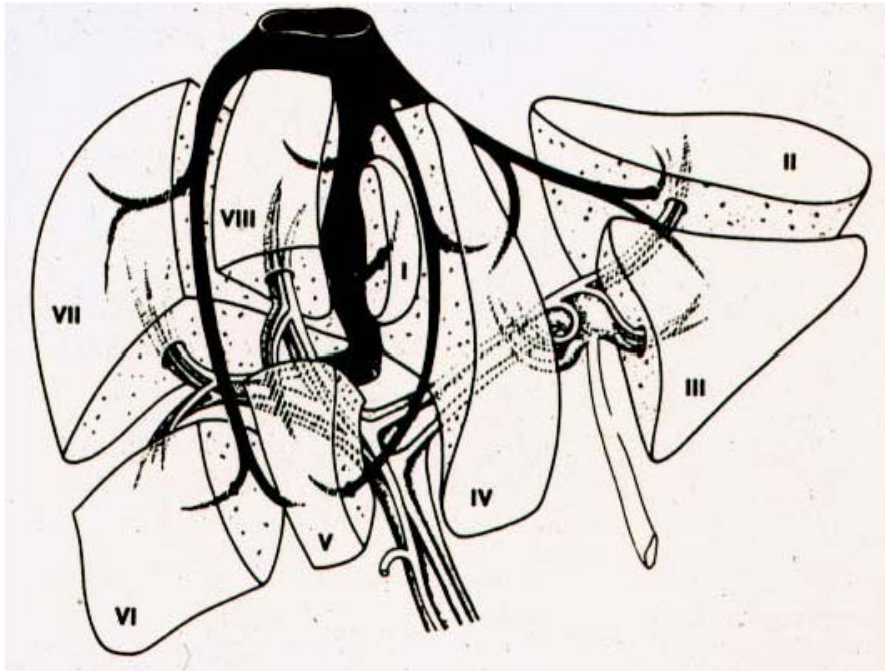
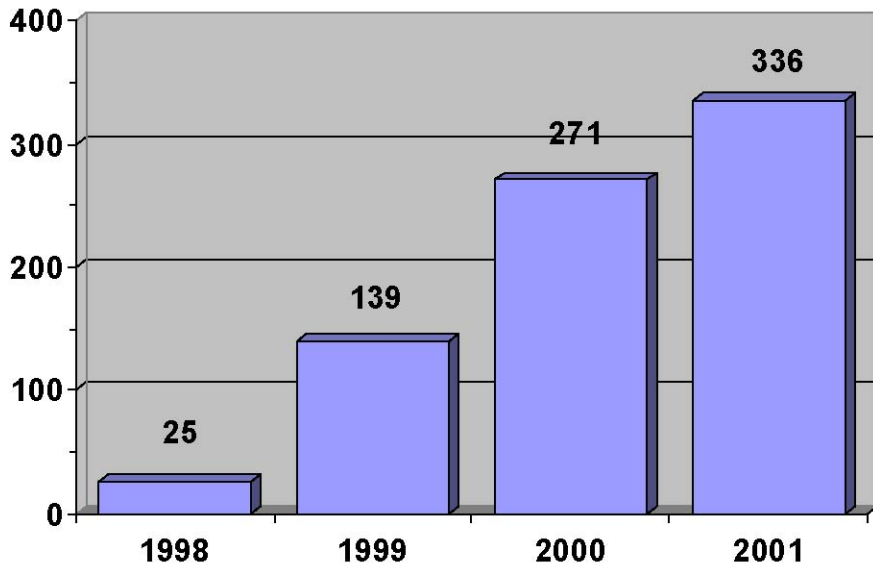


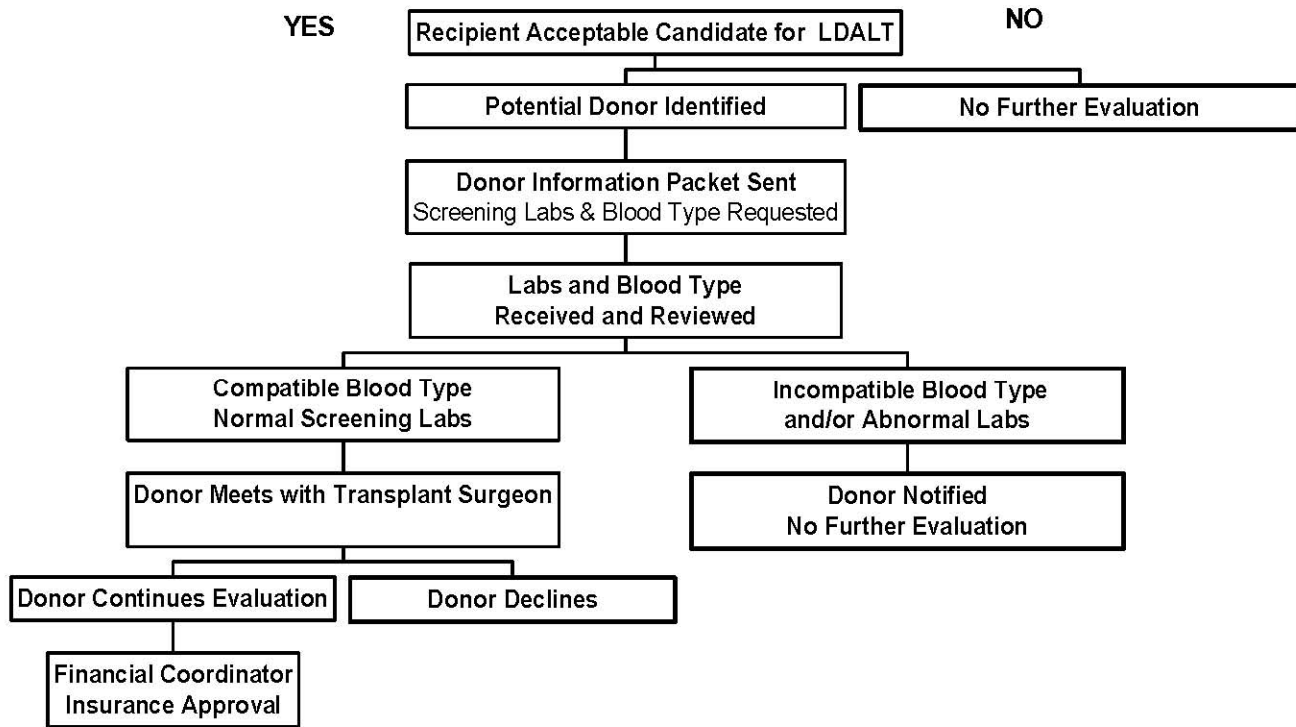
Figure 2. Number of U.S. Living Donor Adult Liver Transplants : 1998 – October, 2001*



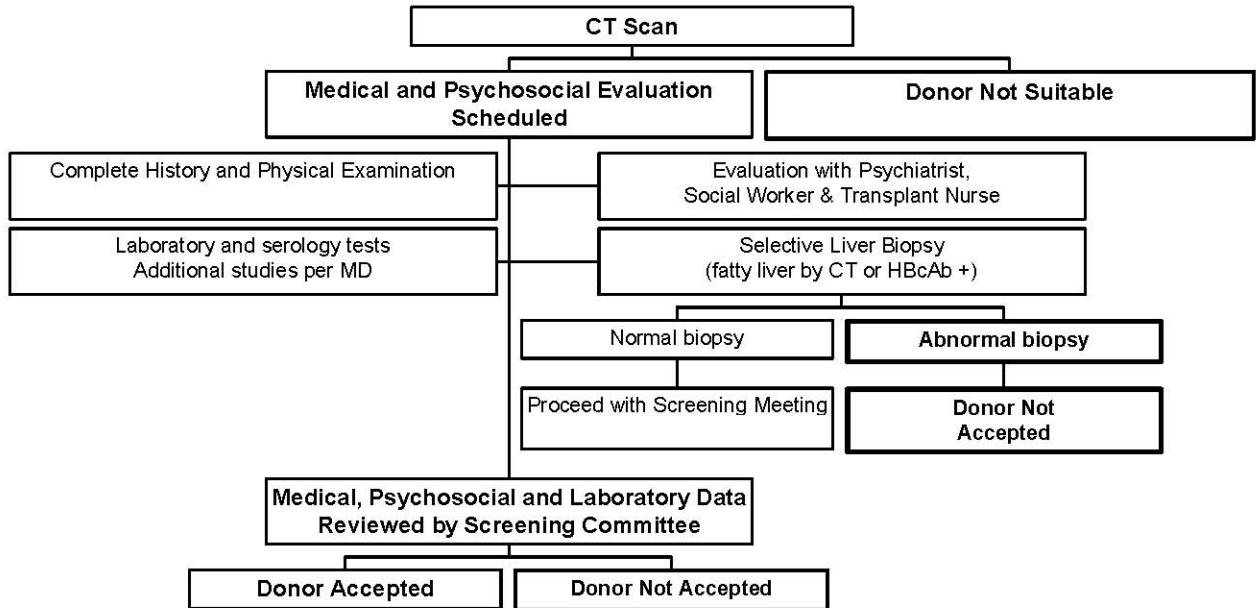
*Based on UNOS OPTN Data as of February 8, 2002

Figure 3a-c. Stepwise Evaluation of Potential Living Donors. (a) Phase I, (b) Phase II, (c) Phase III

DONOR EVALUATION FOR LDALT: PHASE I



DONOR EVALUATION: PHASE II



DONOR EVALUATION: PHASE III

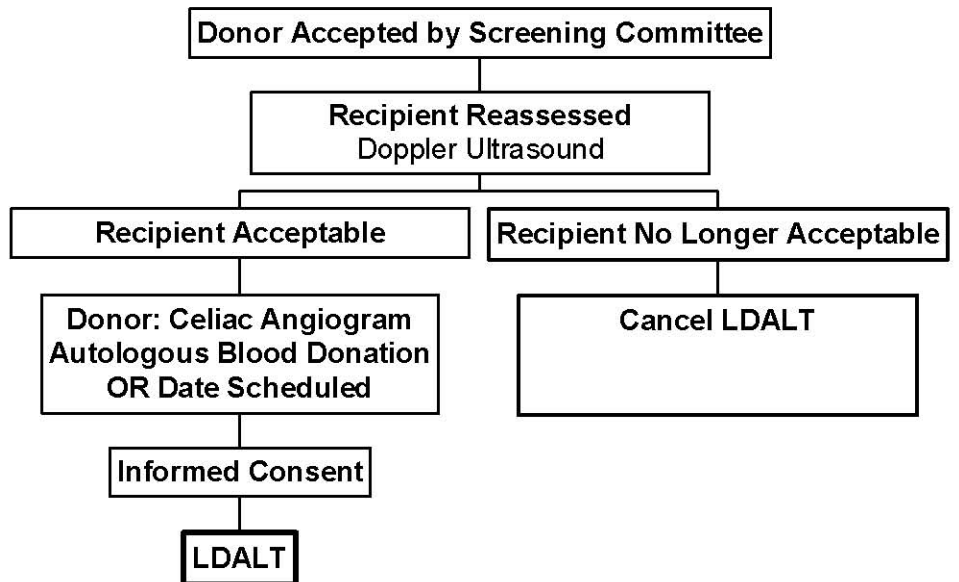


TABLE 1a. Summary of Living Donor Right Lobectomy for Liver Transplantation Case Series Study Descriptions

Author	Transplant years	Study Location	Right lobe/total LDLT	Age	Male (%)	Preoperative Testing	Mean follow-up (days)
Bak ^{32, 37} 2001	97-01	Colorado	41/41	30.8±11.2	63	Physical, psychological, social examination, laboratories, MRA, cholangiography Conventional angiography if any uncertainty liver biopsy in only 3/41	NR
Fan ^{2, 4, 33} 2000	96-99	Hong Kong	22/22	Median 35.5 (range 18-51)	NR	Psychological counseling, laboratory tests, computed tomography, hepatic arteriography routine	NR
Grewal ³ 2001	99-00	Tennessee	11/11	36.5 (mean); reported elsewhere as 48 (range 21-41)	55 (6/11)	History, physical examination, laboratory profile, counseling, MRI, MRA, MRCP and arteriography	NR
House ³⁸ 2001	00	Perth	1	24	0	History, psychosocial evaluation, laboratory tests, abdominal CT scan, angiography, ERCP, MRCP, counseling	4 weeks
Lerut ³¹ 2001	98-00	Belgium	4/6	38 (mean) range 19-53	75 (3/4)	NR	NR
Marcos ¹⁹ 2000	98-99	Virginia	40/40	37.45 (mean)	NR	History, physical and laboratory examination, MRI, MRA, cholangiography, Pulmonary function tests, EKG, Echo, stress test, liver biopsy (except for donors to status I patients if donors had no evidence of liver disease on imaging and serology)	254
Marcos ⁷ 2001	00-01	Rochester, UCSF?	48/48	33±7.2	NR	History, physical and laboratory examination, MRI, MRA, cholangiography, Pulmonary function tests, EKG, Echo, stress test, liver biopsy (except for donors to status I patients if donors had no evidence of liver disease on imaging and serology)	NR
Miller ^{34, 39, 40} 2001	98-00	New York	50/109	37.9±9.6	62.7	History and physical examination, cardiology and/or psychiatry clearances when indicated. Early cases imaging studies including angiography, CT, ERCP. Later cases mostly CT and/or MRI with hepatic volumetry and vascular reconstructions. MRI eventually replaced all preoperative imaging except for intraoperative cholangiography. Liver biopsies were performed for abnormal lipid profiles or history of significant alcohol use, body mass index more than 28, or imaging studies suggestive of steatosis	NR
Park ⁴¹ 1999	97	Korea	1/10	38	0/1	History, physical, laboratory examination, ultrasonography, CT volumetry, hepatic arteriography	NR
Pomfret ¹⁷ 2001	98-00	Mass	15/15	NR	NR	History, physical, laboratory, psychosocial examination, CT, ultrasound, celiac angiogram	NR
Sakamoto ^{6, 13, 42} 2001	94-99	Kyoto	62/62	43±11 mean, 46 median, range 21-61	58	History, physical and laboratory examination. CT	At least 30 days
Sugawara	00-01	Tokyo	6/6	39 (mean), range 23-49	67	History, physical examination, psychosocial evaluation, ABO blood typing, liver and kidney	NR

2002 ⁴³						function tests, virus serology, determination of tumor markers, and pregnancy test for women, Doppler ultrasound, CT scan, and hepatic angiography	
Williams 2001 ⁴⁴	Before 2000	London	5/5	Patient 1 42, patient 2 45, patient 3-5 NR	60	History, physical and laboratory examination. CT or MRI, angiography, MRCP	NR

TABLE 1b. Summary of Living Donor Right Lobectomy for Liver Transplantation Case Series Donor Outcomes

Author	Mortality	Morbidity (%)	Complications	Hospital stay (mean days)	Readmissions	Recovery time	Functional Outcomes
Bak 2001 ^{32, 37}	None	NR	Bile leak with reoperation (2), bile leak with external drainage (1), incisional hernia requiring surgical repair (1), transient neurapraxia (1), drain retrieval (1), hemothorax from venous access (1), idiosyncratic medication reaction causing donor lethargy that resolved on postoperative day 3 (1) 2 required nonautologous blood transfusion	6.3±1.6	NR	NR	All alive and well and have returned to predonation activity. All donors returned to work.
Fan 2000 ^{2, 4, 33}	None	5/22 22.7%	Staph aureus wound infection(1), incisional hernia(1), cholestasis(2), transient peroneal nerve palsy(1), biliary stricture (1), SBO(1)	11.5 (median); range 6-38 days (5 donors stayed longer to care from recipients and their duration is included in calculation)	1/22 for patient with SBO	NR	"All donors are well and have returned to their previous occupations" All donors returned to work.
Grewal 2001 ³	None	1/11 9%	Laparoscopic removal of a drain (1); "No adverse complications" 3 required transfusion	8.8 (mean, median 9, range 7-10)	0%	NR	"all donors are well"
House 2001 ³⁸	None	NR	Staphylococcal wound infection requiring 2 day readmission	6	100%	NR	Returned to normal full activities within 4 weeks
Lerut 2001 ³¹	None	1/4 25%	E. coli wound infection (1) – unclear if right or left lobectomy donor	11.2 mean (range 9-14)	NR	Resumed normal activities at median 3 weeks (range 2-4)	NR
Marcos 2000 ¹⁹	None	7/40 17.5%	7 minor complications: intraoperative pressure sores (3), phlebitis (1), prolonged ileus (1) atelectasis (2). No late complications. All complications occurred in first half of LDLT experience.	5.4	0%	NR	NR
Marcos 2001 ⁷	None	NR	Tube thoracostomy for pneumothorax following central catheter placement (1), presumed bile leak (1)	5.9±1.9	0%	NR	NR
Miller 2001 ^{34, 39, 40}	None	NR	Bile leak (3; none in left lobe donors) prolonged hyperbilirubinemia (1) due to an obstructed bile duct eventually resolving but left with elevated alkaline o requiring readmission (2); 2 donor operations were initiated and aborted 1 right lobe donor and 1 left	6 average stay	NR	NR	All donors are alive and well

			lobe donor required a transfusion				
Park 1999 ⁴¹	None	0%	No severe complications	NR	NR	NR	NR
Pomfret 2001 ¹⁷	None	9/15 67%	Morbidity 67%, Minor wound problems (5), temporary radial neuropraxia (2), symptomatic right pleural effusion (1). More serious complications: biloma requiring percutaneous drainage (2), pulmonary edema (1), portal vein thrombosis necessitating reoperation (1). No non-autologous transfusions	8.3±3	NR	NR	NR
Sakamoto 2001 ^{6, 13, 42}	NR	19.4%	11 surgical complications (17.7%): 10 minor self-limited bile leaks, 1 small bowel obstruction. Separated morbidity by age of donor: age <50(n=41) 22%, >=50 14.3%	15 median (range 9-115)	NR	NR	NR
Sugawara 2002 ⁴³	NR	NR	Postoperative course uneventful in all donors; no homologous blood required	14.8 mean (range 10-24)	NR	NR	All donors returned to "previous activity levels"
Williams 2001 ⁴⁴	None	NR	None; 1 aborted donation	NR	NR	NR	NR

Table 2a. Summary of Living Donor Right Lobectomy for Liver Transplantation Survey Studies.

Author	Transplantyears	Study Description	Right lobe/total LDLT	Age	Male (%)	Preoperative Testing	Mean follow-up (days)
Beavers 2001 ¹¹	98-00	Donor Survey, North Carolina	14/27	39 mean (27-50)	43	NR	390
Brown 2001 ²²	97-00	Transplant Center Survey, United States	449/449	NR	NR	Of surveyed centers, Liver biopsy is performed routinely at 26% of centers, selectively in 60%, and none in 14%. Of surveyed centers, arteriogram is performed routinely at 60% of centers, selectively in 26% of centers, and none in 14% of centers. Of surveyed centers, ERCP is performed routinely at 5% of centers, intraoperatively routinely at 35% of centers, selectively in 10% of centers, and none in 50% of centers.	>6 months in 62%
Broelsch 2000 ⁴⁵	96-00	Transplant Center Survey, Europe	111/228	NR	NR	NR	NR
Kim-Schluger 2001 ³⁴	98-00	Donor Survey, New York	30/48	40.3±9.5		NR	280±157
Todo 2000 ⁴⁶	91-99	Transplant Center Survey, Japan	82/308	NR	NR	NR	NR
Trotter 2001 ³²	97-00	Donor Survey, Colorado	24/24	33.2±11.5	58	NR	13.7 ± 8.8 months

TABLE 2b. Summary of Living Donor Right Lobectomy for Liver Transplantation Survey Study Donor Outcomes

Author	Mortality	Morbidity (%)	Complications	Hospital stay (mean days)	Returned to work (%)	Months to return to work (mean)	Readmissions	Recovery time
Beavers 2001 ¹¹	1 donor death from sepsis following donation surgery	64%	Delay in return to normal bowel function (5), abdominal pain (1), incisional pain (1), blood clot (1), pleural effusion (1), sore throat (1), brachial plexus injury (1), foot paresthesias (1), "fluid between lung and liver" (1), bile leak (1), fever/elevated white count (1). 2 donor operations initiated and aborted	9 (6-14)	93	NR	29%	18 weeks (4-52)
Brown 2001 ²²	1 (0.2%)	Median 14% (0-100)	Biliary complications 27 (6%), reoperations 20(4%)	6.4 (4-14)	NR	NR	38(8%)	NR
Broelsch 2000 ⁴⁵	Did not delineate complications between right and left lobectomy: 1 donor death from multiple postoperative complications (1/123, 0.8%)	NR	Did not delineate complications between right and left lobectomy: 14% minor complications, 17.8% major complications (22 patients experienced 25 major complications);	NR	NR	NR	NR	NR
Kim-Schluger 2001 ^{34, 39, 40}								
Todo 2000 ⁴⁶	NR	NR	Do not classify between right and left lobectomy. No donor deaths. Minor to moderate complications occurred in 20 of 215 donors: Biliary leak (11), biliary stenosis (1), wound infection (3), pulmonary complication (2), portal vein thrombosis treated surgically (1)	NR	NR	NR	NR	NR
Trotter	None	Major 4/24	Medical outcomes: survival (24), Major (4): bile leak(2), reoperation drain	6.3±1.5	96%	2.4±1.2; 16 patients	NR	3.4 months

2001 ³² 37		(15%) Minor 4/24 (15%)	retrieval(1), incisional hernia repair(1); Minor(4): GI ulcer(2),encephalopathy(1),transient neuropraxia(1); Ongoing medical treatment (1); Ongoing symptoms (17): abdominal discomfort(12), scar numbness(2), loss of appetite/nausea(2), trouble concentrating(1), poor appetite(1), weakness(4), diarrhea(1), nausea(1), back pain(1), difficulty sleeping(1) Psychosocial Outcomes: change in body image(10), scar(3), abdominal bulge(4), weight gain(2), no response(1); Relationship to recipient better(10)/worse(3)/same(18);impairment in sexual function(0);Cannot perform activity(11): afraid to drink alcohol (1), decreased ability to perform strenuous physical exertion (9), and short-term memory problems (1)			required a return to employment without full predonation duties or time for a mean time of 2.8 months		
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APPENDIX I

Published Data Extraction Form

Author: _____ Citation: _____

Inclusion criteria (check if article reports the following): Exclusion criteria (check if article reports the following):

Outcomes for adult donors of right hepatic lobes Pediatric recipients

Report in English Review article without inclusion of primary data

Published between 1996 and 2001 Results do not separate right lobectomy from left lobectomy donors

No outcomes of interest reported in results

Duplicate report. Includes citation:

Location of Transplant Center: Age of Donors:
Years of transplants reported: Sex of Donors:
No. of right lobe donors to adults included in report: Length of Study follow-up:
No. of left lobe donors to adults included in report: Right lobectomy procedure:
Total number of living donors included in the report: Study design:

MORTALITY (check one) MORBIDITY (if reported – as described by authors)
No mortality reported Author reported complication rate:
Mortality not stated in report Length of hospital stay:
Mortality reported (provide details) Length of recovery:
Need for hospital readmission:

QUALITY OF LIFE (if reported – as described by authors)
% donors able to return to predonation occupation:
Length of time until return to work:
HRQOL scores:

AUTHORS CONCLUSIONS REGARDING LIVING DONORS:

APPENDIX II

Expert Opinion Data Collection Form

1. Sources of data regarding donor outcomes other than the published literature:
2. Sources of data regarding the number of living donor transplants performed, the number of centers performing living donor transplant and the number of donor transplants that have been performed:
3. Any donor deaths following right lobectomy donation surgery:
4. Any donors that have required listing for emergent liver transplantation following right lobectomy:

5. Protocols that have been used by transplant centers to follow donors for adult liver transplantation after transplantation:

6. Any other pieces of information that might be useful:

APPENDIX III

Living Donor Liver Transplantation Expert Opinions

We gratefully acknowledge the contributions of our experts.

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