Progression of living liver donation worldwide

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Purpose of review
Living donor liver transplantation (LDLT) has developed into a well tolerated and viable option when deceased donor transplantation is not available. Transplant and advanced hepatobiliary surgeons from around the world have performed living donor hepatectomies consistently for decades with acceptable donor outcomes. However, optimizing the preoperative workup, donor selection, operative technique, and perioperative care will improve these outcomes. This manuscript reviews recent worldwide literature for the living liver donor.

Recent findings
Overall, younger living donors produce better recipient outcomes but with careful selection donor over 55 years old may be used safely. Magnetic resonance is becoming the imaging of choice for living donor preoperative planning and its ability to predict steatosis may make predonation liver biopsy unnecessary. Programs with experience in LDLT and laparoscopic liver resection are making significant progress toward consistent use of the laparoscopic approach to living donor hepatectomy. Biliary, pulmonary, and infectious complications are the predictable complications with more serious complications and donor death being very rare. In a majority of cases, the donor's health-related quality of life and psychological well being are preserved.

Summary
These recent findings will allow us to better care for the living liver donor and enable LDLT continued progress.

Keywords
laparoscopic donor hepatectomy, living donor liver transplantation, living liver donor, living liver donor age, living liver donor quality of life

INTRODUCTION

The first human liver transplants performed at the University of Colorado Hospital in 1963 by Starzl [1] created an opportunity for tremendous progress over the next 2 to 3 decades. Significant improvements in organ preservation and immunosuppression made liver transplantation a viable and effective treatment of end-stage liver disease. However, because of the shortage of donor organs, not all patients with an indication are able to benefit from liver transplantation. Having the ability but not the means to cure these patients led surgeons and hepatologists to consider the precarious option of using partial liver grafts from living donors.

WORLDWIDE PROGRESSION OF LIVING DONOR LIVER TRANSPLANT

Although living liver donation was initially considered the late 1960's [2], the first real attempt at living donor liver transplant (LDLT) did not occur until 1988 when Raia *et al.* [3] used an adult left lateral segment graft in a young girl with biliary atresia. Around the same time Strong *et al.* [4] were able to successfully transplant a left lateral segment graft from a mother to her son. With the growing interest across the world, the group at the University of Chicago addressed the ethical considerations and described their success with adult-to-child LDLT [5,6]. Over the next few years, attempts continued throughout Western Europe but significant progress was achieved in Eastern Asia where religious and

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KEY POINTS

- LDLT is a well tolerated and viable option when a deceased donor transplant is not an option.
- Better recipient outcomes are seen with younger living donors and with carefully selected older donors.
- MR is replacing CT as the imaging of choice for living donor preoperative evaluation and planning.
- Programs with experience in LDLT and LLR are making significant progress toward consistent use of the laparoscopic approach to living donor hepatectomy.
- Biliary, pulmonary, and infectious complications are the predictable complications with more serious complications and donor death being very rare.
- The living liver donor's postoperative health-related quality of life and psychological well being are preserved.

cultural beliefs did not allow deceased donation to significantly contribute to the donor pool [7–11].

The continued progress in adult-to-child LDLT set the stage for expanding the use of living donor grafts in adult recipients. The majority of patients with end-stage liver disease and other indications for liver transplantation are adults. The large donor gap in Asia continued to motivate those with advanced technical skills in hepatobiliary surgery to come forward as pioneers in adult-to-adult LDLT. Attempts to use left lobe grafts produced mixed results [12,13]. The ability to consistently use the left lobe has been limited by the size ratios of the donor and recipient. In order for the graft to provide enough hepatic function, the recipient typically needs to be the same size or smaller than the donor. Recognizing that using right lobe grafts would allow a much more broad application of LDLT, Lo *et al.* [14] at the Queen Mary Hospital in Hong Kong were able to safely take a graft with segments 5–8 and the middle hepatic vein and successfully transplant it into a larger recipient with fulminant hepatic failure. Over the next decade, this team successfully performed hundreds of right lobe LDLTs and firmly established this procedure as a well tolerated and viable treatment for end-stage liver disease.

Within the next year, the first adult-to-adult right lobe LDLTs were performed in the United States and Europe with similar success [15,16]. Subsequently, the right lobe became the preferred choice around the world for adult-to-adult LDLT. Over the next 4 years the number of LDLTs within the United States increased dramatically with 92 transplants performed in 1998 to 522 in 2001. The number of centers offering LDLT increased from 24 to 65 in that same time period [17]. Over the next decade the numbers decreased to approximately 250 cases per year (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#). This was likely because of a combination of the implementation of model for end-stage liver disease (MELD) for deceased donor liver allocation in the United States and a highly publicized donor death in early 2002 [18–20]. Some experts have considered the increased use of extended criteria donors (increased age, donation after cardiac death, steatosis, and hepatitis B and C grafts) has contributed to the decline by contributing to the donor pool and thereby easing the need for considering LDLT. It is also possible that the waitlist had a backlog of potential recipients that was used when LDLT was first utilized, thus leaving only newly evaluated recipients as candidates over the last 2 decades. The institution of the MELD score for improved allocation of deceased donor grafts to the sickest patients significantly decreased waitlist mortality [21,22]. From 1998 through 2007 approximately 2360 LDLTs were performed in the United States [23]. Over the last decade the amount of LDLTs increased with 367 performed in 2017 (https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#).

Recognizing that with properly selected donors and recipients, LDLT had the potential to be an effective treatment for end-stage liver disease, the National Institute of Health sponsored a prospective multicenter study group, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) in 2004. This group included nine high-volume centers in the United States charged with two principle aims: determine whether it was more beneficial for a liver transplant recipient candidate to pursue LDLT or wait for a deceased donor liver transplant (DDLT) and to study the impact of liver donation on the health of the donor and quality of life [23]. These efforts demonstrated that in high-volume centers survival rates of LDLT recipients are similar to DDLT recipients, waitlist mortality is reduced, and that outcomes and complication rates improve with experience [24,25]. Posttransplant mortality, graft failure, and retransplantation rates significantly improve after a center has performed 20 cases or more [23,26,27]. This same learning curve was observed on the donor side of the procedure [28]. As deceased donor organ allocation continues to change throughout world, the role of LDLT and the living liver donor will continue to evolve. This manuscript reviews recent published literature regarding selection, evaluation, techniques, and outcomes of the living liver donor.

DONOR AGE

Donor age remains an important factor determining outcomes after transplantation. Although this is established in the DDLT setting, evidence of the significance in predicting recipient outcomes in the LDLT setting has also been presented. Donor age cutoffs vary between centers and focus primarily on donor safety, with most centers avoiding donors older than 50–55 years. Tokodai *et al.* [29] reported worse short term and long-term graft recipient outcomes with older donors (58 years vs. 32 years). Similarly, Kubota *et al.* [30▪] showed improved survival after LDLT with younger donors (20–29 years old), independent of the age of the recipients. Recently, Kim *et al.* [31▪] demonstrated that donor age was a modifiable variable. When compared with younger donors they showed that equivalent outcomes after LDLT were possible when carefully selected donors older than 55 years are appropriately matched with stable, slim recipients.

PREOPERATIVE IMAGING

With continuing improvements in MRI technology, magnetic resonance (MR) is increasingly replacing computed tomography (CT) for hepatobiliary imaging. Advantages of MR over CT include the lack of ionizing radiation and allergic reactions to iodinated contrast. Although most centers still use a combination of CT and MR for donor vascular and biliary evaluation, new MR techniques are increasingly seen as replacing the need for CT imaging. Yamashita *et al.* [32] reported good visualization of hepatic vein tributaries with noncontrast MR. Jhaveri *et al.* [33] reviewed the use of MRI as a sole imaging modality for donors. Although MR provided excellent delineation of portal and hepatic venous system, arterial imaging was hampered by the inability to delineate segment 4 artery.

Assessment of donor liver steatosis is an important part of donor evaluation. Donor steatosis increases the risk of posttransplant graft dysfunction and also increases donor risk by delaying recovery and increasing the risk of complications. Liver biopsy is considered the gold standard for evaluation of steatosis [34]. However, its limitations include the invasive nature of the procedure and the risk of missing representative areas of liver when steatosis is patchy. Most centers use noninvasive screening techniques such as CT (liver attenuation index), ultrasound, and elastography or MR to rule out donors with significant steatosis. Recent studies have reported the feasibility of using MR techniques such as MR spectroscopy and MR proton density fat fraction as primary and stand-alone methods for steatosis assessment [35,36]. MR techniques have been reported to be superior to CT in steatosis prediction [37]. A recent meta-analysis reported high accuracy of MR techniques in predicting clinically significant steatosis with an area under the curve of 0.96 [38▪]. With widespread availability of these evolving techniques, the need for a liver biopsy to assess steatosis should reduce significantly.

MINIMALLY INVASIVE DONOR HEPATECTOMY

Advances in minimal access techniques and increasing experience have led to increasing popularity of laparoscopic liver resection (LLR). Laparoscopic left lateral segmentectomy was considered standard practice during the first consensus meeting on LLR back in 2009 and has now become the standard of care in many centers [39]. Extension of this technique to right sided hepatectomies is now increasingly being accepted, though it is still considered as an innovative procedure [40]. Improving donor safety and reduction of morbidity remain the lynchpins of LDLT and applying LLR to living liver donation is a logical progression. Wound complications related to open donor hepatectomy remain a source of considerable morbidity [41]. The cosmetic effect of a large incision can also be a deterrent for young potential donors.

Well tolerated laparoscopic donor hepatectomy has the potential to increase the donor pool and speedup the postoperative recovery. In the setting of LDLT, distinct donor and recipient concerns affect the implementation of laparoscopic donor hepatectomy. Donor issues include the safety of LLR, need for unplanned conversion, impact of prolonged surgery, effect of the pneumoperitoneum on liver regeneration, and the risk of late biliary complications. Recipient concerns include the risk of graft injuries during LLR, increased graft retrieval time, and the risk of more difficult vascular and biliary anastomoses. As a technical exercise, laparoscopic donor hepatectomy is probably more straightforward than hepatectomy for tumors as the donors are usually young and fit, the liver is healthy, and the hepatic anatomy has been delineated in detail even before the first port is placed.

Though slow to start, laparoscopic left lateral segmentectomy donation for pediatric transplantation is being increasingly considered in many centers with experience in LDLT and LLR [42]. The smaller transection area, distance from large veins during transection, and a fairly standard biliovascular anatomy in left lateral segmentectomy donation make it an ideal procedure for centers attempting to start laparoscopic donor hepatectomy. The laparoscopic approach for left lateral segmentectomy donors is recommended as the

Table 1. Minimally invasive living donor hepatectomy experience

Authors	Year	Technique
Cherqui *et al.* [47]	2002	First case reports of two laparoscopic donor left lateral segmentectomies
Koffron *et al.* [48]	2006	First case report and technical description of a laparoscopic hand-assisted right lobe donor hepatectomy
Samstein *et al.* [44]	2013	Case reports and technical description of two pure laparoscopic left lobe donor hepatectomies
Troisi *et al.* [49]	2013	Case reports and technical description of four pure laparoscopic left lobe donor hepatectomies
Soubrane *et al.* [50]	2013	Case report and technical description of a pure laparoscopic right lobe donor hepatectomy
Rotellar *et al.* [51]	2013	Case report and technical description of a pure laparoscopic right lobe donor hepatectomy
Kim *et al.* [46]	2017	Case reports and technical description of three pure laparoscopic right lobe donor hepatectomies
Suh *et al.* [52▪▪]	2017	55 pure laparoscopic right lobe donor hepatectomies

standard of care in the recent consensus conference [43]. Comparative analysis has shown similar donor and recipient outcomes with open and laparoscopic left lateral segmentectomy donation with the laparoscopic group experiencing less postoperative pain and earlier return to work. Laparoscopic left hepatectomy is the natural next stage in the learning process and again its safety in terms of donor and recipient outcomes has been confirmed [44].

Laparoscopic right lobe donor hepatectomy is a more major undertaking. Given that the donors already have a narrow margin of safety in terms of remnant liver volume, any break in safety during the procedure can have serious implications to donor safety and graft quality. Development of laparoscopic right lobe donor hepatectomy has hence been much slower and tentative, even in highly experienced centers [45,46] (Table 1). It is still a developing technique and only surgeons and centers with a large experience in both LDLT and LLR should attempt these procedures. Suh *et al.* [52▪▪] recently reported the largest series of 55 cases of pure right laparoscopic donor hepatectomy. The authors reported longer operating times and a higher frequency of multiple bile ducts compared with their historical open cohort, but similar donor outcomes.

Newer techniques such as indocyanine green fluoroscopy and use of 3d laparoscopy have the potential to improve real-time visualization to enable precise vascular dissection and well tolerated division of the donor right hepatic duct. With increasing experience, reports of successful laparoscopic donor hepatectomies in donors with variant anatomy are also being reported [53,54]. Ultimately, the choice of technique would be determined by the surgeon's experience, preference, and outlook, but the expectation is that with increasing experience, right LDH has the potential to replace the open procedure similar to laparoscopic donor nephrectomy. The use of robotic surgery in donor hepatectomy has also been reported with its benefits of multiaxial maneuvering, and more precise dissection [55].

DONOR CLINICAL OUTCOMES

The ability to reduce wait time mortality continues to be the real advantage of LDLT but short-term and long-term morbidity to the donor is the trade-off. Findings from the A2ALL study group and other single center studies describe a 38–44% complication rate for right lobe donors, typically occurring in the first postoperative year with almost half presenting while the donors are still in the hospital [56–58]. The most common significant complications include bile leak, pleural effusion, and infection. Serious complications resulting in residual disability, liver failure, or death were very rare with each being about 1 or 2% [56]. Recently, there have been a number of single and multicenter reports exploring living donor outcomes from Asia. Reports from high-volume centers in Korea, [59] Japan, China, [60] India, [61] Pakistan, [62] and Turkey [63] continue to demonstrate the safety of the donor operation. Although a quarter to a third of all donors have at least one postoperative complication, major morbidity (greater than or equal to Clavien grade 3) ranged from 2–10% [64] (Table 2).

Table 2. Living liver donor postoperative complications incidence within 1 year

Any complication	13.6–46.4%
Biliary	1.5–19.1%
Infection	13%
Pleural effusion	11%
Hernia	5%
Ileus	3–3.5%
Re-exploration	2–3%
Neuropraxia	3%
Bowel obstruction	1%

Adapted with permission [28,56,65,66▪▪,67].

In the largest review, Rossler *et al.* [66▪▪] reported outcomes after donor hepatectomy in a cohort of 5202 right and left liver donors from 12 high-volume centers over a 10-year period. They reported an overall complication rate of 12% though the rate varied widely between centers from 3.5 to 62.5%. Major complications (greater than Clavien grade 2) were reported in 3.8% donors. Biliary and cardiopulmonary complications, intraabdominal bleeding, and collections were the top four types of major complications. Only one donor mortality was reported from this study. This survey reported a significantly higher incidence of overall and major complications after right hepatectomy vs. left. Interestingly, the authors found a strong correlation between center volume and donor morbidity with the incidence of overall complications and major complications 3–4 times lower in centers performing over 100 donor hepatectomies, highlighting the learning curve involved in this operation. The two most recent donor deaths in the United States occurred in centers that were among the most experienced at the time. Even with the most experienced surgeon in a high-volume center, the perioperative risk of death in a living donor hepatic lobectomy will never be zero.

DONOR QUALITY OF LIFE AND PSYCHOLOGICAL WELL BEING OUTCOMES

The studies to date allow us to describe the short-term and long-term morbidity and mortality risks to the living liver donor. However, insight into the long-term effects of donation on perceived quality of life and psychological well being remain limited [68–71]. Serial evaluation of the A2ALL cohort with validated surveys provided pre and postdonation health-related quality of life (HRQOL) data on 374 donors. With up to 11 years of follow-up, donation does not appear to negatively affect long-term HRQOL [72]. Following the anticipated decrease in the initial postoperative period, these donors reported emotional and physical well being scores that returned to baseline and remained above the normative general population. Although this is very reassuring, donors with a lower educational status were more likely to report a significantly lower HRQOL. Death of a recipient predicted low HRQOL reporting in the associated donor. This analysis indicated there are subpopulations that require better predonation communication and extra surveillance postdonation.

Further evaluation of the A2ALL cohort found similar results when specifically surveying psychological well being postdonation [73▪▪]. Low rates of major depressive, alcohol abuse, and anxiety syndromes were found with an overall psychological well being reporting at or better than the normative general population. Over 95% of donors reported they would make the decision to donate again with only 11% expressing regret at some time point in follow-up. Although these findings are reassuring, donors whose recipients died were eight times more likely to regret donating. A third of these donors reported guilt and nearly a quarter felt responsible after their recipient died. The authors from both studies agree that these donors should be monitored and offered any needed social and psychological support.

CONCLUSION

LDLT has developed into a well tolerated and viable option when deceased donor transplantation option is not available. Transplant and advanced hepatobiliary surgeons from around the world have performed living donor hepatectomies consistently for decades with acceptable donor outcomes. Better recipient outcomes are seen with younger living donors and with carefully selected older donors. MR is increasingly replacing CT as the imaging of choice for living donor preoperative planning. The ability to predict steatosis is improving and may make predonation liver biopsy and the associated risks unnecessary. Programs with experience in LDLT and LLR are making significant progress toward consistent use of the laparoscopic approach to living donor hepatectomy. Developing a well tolerated minimally invasive operation with decreased morbidity may increase the donor pool. Biliary, pulmonary, and infectious complications are the predictable complications with more serious complications and donor death being very rare. Understanding the psychological effects on the living liver donor is necessary to manage expectations and consent appropriately. In a majority of cases, the donor's HRQOL and psychological well being are preserved. However, if the associated recipient does not survive transplantation, then the donor requires focused support. These recent findings will allow us to better care for the living liver donor and enable LDLT continued progress.

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Conflicts of interest

There are no conflicts of interest.

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This study is the largest, prospective, multicenter evaluation of the psychological outcomes of living liver donors. It identified predictors of positive psychological well-being as well as donor who will require closer psychological monitoring. The findings have significant implications for preoperative living liver donor evaluation, the consent process, and long-term follow-up.