

Title: Perioperative Management of Adult Living Donor Liver Transplantation: Part 1 – Recipients

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Abstract:

Living donor liver transplantation was first developed to mitigate the limited access to deceased donor organs in Asia in the 1990s. This alternative liver transplantation option has become an established and widely practiced transplantation method for adult patients suffering from end-stage liver disease. It has successfully addressed the shortage of deceased donors. The Society for the Advancement of Transplant Anesthesia and the Korean Society of Transplant Anesthesia jointly reviewed published studies on the perioperative management of live donor liver transplant recipients. The review aims to offer transplant anesthesiologists and critical care physicians a comprehensive overview of the perioperative management of adult live liver transplantation recipients. We feature the status, outcomes, surgical procedure, portal venous decompression, anesthetic management, prevention of acute kidney injury, avoidance of blood transfusion, monitoring and therapeutic strategies of hemodynamic derangements, and Enhanced Recovery After Surgery protocols for liver transplant recipients.

Keywords: review, liver transplantation, recipients, living donor liver transplantation, anesthesia, SATA, KSTA

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Introduction

Liver transplantation (LT) has become the ultimate treatment for end-stage liver disease (ESLD), acute fulminant liver failure, liver-based metabolic disorders, and liver malignancies. Improvement in surgical techniques and immunosuppression management have led to the acceptance of LT as a standard surgical procedure. However, its broader application has been hampered by the shortage of deceased donor liver grafts. This has, in turn, encouraged the development of living donor liver transplantation (LDLT) (1). The advent of adult-to-adult LDLT has significantly impacted graft supply, thus reducing the burden on the waitlist.

Current Status and Outcomes

LDLT is the most common form of LT performed in most Asian countries. Notably, in South Korea, LDLT cases outnumber deceased donor LT (DDLT) cases, with an ongoing gradual increase in annual LDLT cases, which were counted for 75% (1200 cases) of the entire liver transplantation cases in 2019. In the US, LDLT recipients were only a tiny fraction [442 (5.3%)] of the 8,345 adult patients (≥ 18 years) who received LT in 2019, although the number of LDLTs, in general, grew by 31% since the year prior (2).

Outcomes after LDLT remain under heavy scrutiny given donor risks and technical complexity. Though it was shown that the recipient outcome after LDLT was superior to the combined outcomes of the patients remaining on the DDLT waitlist and the patients who received DDLT (3), a direct comparison of LDLT to DDLT outcomes is less straightforward (3,4). Currently, in the US, long-term outcomes of LDLT recipients are similar, if not better, than those of deceased donor LT recipients; LDLT graft failure occurs in 5.9% at six months, 7.1% at one year, 13.8% at three years, 23.7% at five years, and 32.1% at ten years. LDLT recipient survival demonstrates patterns similar to those of DDLT recipients, with 5.3%

mortality at six months, 7.4% at one year, 13.1% at three years, 19.7% at five years, and 39.5% at ten years (2).

Clinical Features of LDLT Recipients and Evaluation

Several studies have reported that LDLT recipients are younger, healthier, and have lower MELD scores than DDLT recipients (1,5). This is not unsurprising, as DDLT patients are offered organs based on their higher MELD scores and increased time spent on the waitlist, often worsening general health. The apparent advantage of LDLT is planning the procedure before the recipient's health deteriorates. LDLT recipients are more likely to have less portal hypertension, less metabolic liver failure, and better ability to tolerate a smaller graft (1).

The basic tenants of pre-LDLT recipient evaluation are shared with those for DDLT recipients, including physical examination, laboratory tests, evaluation of medical comorbidities, social conditions, and psychiatric evaluations. The initial step for LDLT is to identify the potentially suitable donor candidate. Upon identifying potential LDLT donors, the donor candidate should undergo detailed anatomical evaluations to assess the liver volume and predict the volume of the remnant liver. The appropriate size graft type (the left lateral lobe, the left lobe, or the right lobe) and recipient matching (age, body size, MELD) are essential. If a donor graft is too small for the recipient, the graft is often unable to handle the recipient's portal blood flow, leading to hepatocellular dysfunction and an inability to provide for the recipient's required metabolic needs. This so-called "small for size syndrome" (SFSS) may ultimately result in graft failure, necessitating retransplantation (6). Currently, the remnant liver volume $>30\%$ of the normal liver volume is recommended for the LDLT donor to minimize the potential of the post-operative liver failure (7), and the graft to body weight ratio >0.8 is essential to assure post LT metabolic needs of the LDLT recipient and a

better mid-term outcome (8). All-in-one protocols using multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) have simplified the donor evaluation process (9,10). The use of a three-dimensional volumetric assessment of liver volume has become a great adjunct (11). The decision to balance the recipient benefit with the donor risk should be made in a multidisciplinary transplant committee at an LDLT center, based on the center-specific guideline.

Essentials of the LDLT Recipient Surgical Procedure

Even though right-lobe LDLT (with or without the middle hepatic vein) is one of the most complicated and technically demanding procedures compared to the left lateral lobe LDLT or the left lobe LDLT, it has become the most common choice for adult LDLT due to the larger liver graft volume (12,13). In general, DDLT can be performed using two different techniques: the classic technique, with vena cava replacement, or the piggyback technique, with preservation of the recipient vena cava. In LDLT, preservation of the recipient vena cava is mandatory. In preparation for LDLT implantation, the recipient's hepatectomy differs from that for a DDLT, carefully considering the shorter vessels and bile duct accompanying the donor's liver lobe segment. Hence, meticulous hilar dissection in the recipient, paying particular attention to preserving the appropriate length of the hepatic arteries (right and left), portal vein, hepatic vein, and bile duct, is necessary. Graft implantation starts with a wide anastomosis of the right hepatic vein cuff of the graft to the recipient's caval opening. To optimize outflow from the allograft, a patch venoplasty of the liver graft right hepatic vein is secured and anastomosed either to the recipient's hepatic veins or to a surgically created opening in the vena cava. All significant sized venous tributaries of the middle hepatic vein (segment 5 and 8 veins) and any accessory right hepatic veins should be preserved and connected via interposition vascular grafts to the recipient's hepatic veins or vena cava

(**Figures 1 and 2**). After the hepatic vein anastomosis is completed, portal vein anastomosis is performed. Correct orientation and length are verified to avoid portal vein redundancy and kinking. Once the portal vein anastomosis is completed, vascular clamps are removed, and the graft is reperfused. Once hemostasis is achieved, hepatic arterial anastomosis is performed. A recipient hepatic artery of appropriate length and caliber is selected and anastomosed to the donor's hepatic artery. The last anastomosis performed is the biliary outflow. This can be performed using a duct-to-duct or Roux-en-Y hepaticojejunostomy (14). Grafts with insufficient functional hepatic mass can develop SFSS; because of this risk, portal venous decompression is emphasized, as described below.

Intraoperative Portal Venous Decompression

Portal decompression can be an important component of LT, especially for the recipients with portal hypertension, since high portal flow is thought to impair liver regeneration and potentially complicate postoperative recovery (15). The splanchnic circulation maintains circulating blood volume; by decompressing the portal system, blood can be shifted to the central circulation, which results in less venous congestion and potentially less blood loss during the dissection of the diseased liver to the completion of hepatectomy (15,16). This can also result in increased systemic circulation and potentially preserve renal function. Both pharmacologic and surgical methods are used to decompress the portal system during LT.

Pharmacological Methods

Current pharmacological agents for portal venous decompression include octreotide, vasopressin, and terlipressin. Octreotide is a somatostatin analog that causes splanchnic vasoconstriction, which decreases the splanchnic blood flow and, subsequently, portal venous

flow. It is primarily used to treat esophageal variceal bleeding and hepatorenal syndrome. There is debate regarding the effects of octreotide on portal pressure and renal blood flow. Escorsell et al. demonstrated that portal pressure rapidly decreased after a bolus dose of octreotide, but this effect was short-lived (17). They also demonstrated that octreotide infusion had no significant effect on portal pressure. Busani et al. demonstrated that octreotide infusion combined with esmolol infusion decreased portal vein flow in LDLT recipients (6). Sahmeddini et al. performed a randomized controlled trial to evaluate the effect of octreotide in combination with norepinephrine on postoperative renal function in patients undergoing DDLT (18). They found that mean arterial pressure (MAP) and urine output were more significant in the patients who received octreotide and norepinephrine than in those who did not but found no significant difference in postoperative creatinine. They concluded that octreotide might help improve the vasoconstrictor effects of norepinephrine to maintain better MAP (18). Byram et al. were unable to show a significant reduction in the need for intraoperative PRBC transfusion in their retrospective review (16).

Vasopressin and its long-acting synthetic analog, terlipressin, are splanchnic arteriolar vasoconstrictors, and their end effects on portal flow are thought to be similar to those of octreotide. Both agents are used for bleeding varices and hepatorenal syndrome. Like octreotide, their effects on portal venous pressure and renal function in LT patients are mixed. Wagener et al. reported that a low dose infusion of vasopressin (three to six units/hour) decreased portal vein blood flow and pressure in the native diseased liver (19). Mukhtar et al. found reduced portal pressures, less vasopressor requirement, less colloid use, and better renal function in patients who received terlipressin infusion during LDLT (20). Karaaslan et al. observed no significant difference in intraoperative vasopressor requirements or blood product transfusion in LDLT recipients who received terlipressin infusion (21). They also noted no significant difference in postoperative complications or renal function. A meta-

analysis of randomized controlled trials investigating the effects of perioperative terlipressin in LDLT by Won et al. found no significant difference in intraoperative hemodynamics or postoperative serum creatinine levels (22). The only randomized, double-blind, controlled trial investigating the benefits of perioperative terlipressin in LDLT was published by Reddy et al., who demonstrated no difference in estimated blood loss, transfusion requirements, vasopressor requirements, intraoperative portal pressure, and urine output (23).

Interestingly, they did find higher lactate levels in patients who received terlipressin. Terlipressin is currently not FDA-approved for use in the US due to associated adverse effects such as bradycardia, hypertension, ischemic skin changes, bowel ischemia, and ischemic heart disease. These adverse effects are similar to those reported for vasopressin.

Debate surrounds the benefits of each of these methods. This is likely due to each transplant center's preference and the absence of more extensive randomized controlled trials.

Surgical Methods

Surgical methods for portal decompression include venovenous bypass (VVB) and portocaval/portosystemic shunts.

VVB is a technique that involves using an extracorporeal circulation system that redirects venous blood of the portal and femoral veins to the heart via venous access of the upper body (24). VVB was thought to improve hemodynamic stability, decrease blood loss, and prolong a tolerable anhepatic time (25). Sun et al. found that the use of VVB was associated with a lower incidence of post-transplant acute kidney injury (AKI) (26). However, some argued there was a lack of evidence of these benefits (27,28), and the advent of the piggyback method reduced the needs. Some VVB related complications in adult DDLT recipients were reported, including air embolism, low flow status, arrhythmia, hemo-mediastinum, hemothorax, vascular injury, blood clots, and pulmonary embolism (29).

Alternatively, surgical portocaval/portosystemic shunts can be temporarily created intraoperatively between the portal vein and the inferior vena cava. Upon the placement of a liver graft, the shunt is removed. The shunts can be left in place if there is a concern for SFSS (30). Shunts are associated with improved hemodynamic stability, less blood transfusion, and less postoperative renal dysfunction (31). Nacif et al. described that intraoperative temporary portosystemic shunt was associated with decreased length of hospital stay, and a permanent portocaval shunt was associated with increased one-year graft and patient survival rates (32). The benefit of portosystemic shunts over VVB is that shunts can be placed even if there is portal vein thrombosis, which often prohibits the use of VVB (33).

Essentials of Anesthetic Management of LDLT Recipients

General Principle

Anesthetic management of LDLT recipients closely mirrors that of DDLT recipients. The main difference, which has a profound effect on surgical technique and therefore on required anesthesia support, is the LDLT graft's reduced liver mass and altered anatomy. Prominent vascular and biliary structures have been dissected out for anastomosis with corresponding structures on the recipient's end, but these anastomoses are technically tenuous. The pathophysiological changes in ESLD are associated with several alterations in blood flow dynamics and hemostasis that put the graft at risk for potential failure. During graft transplantation, the surgical team has two major concerns: a hypercoagulable state that can lead to hepatic artery thrombosis (HAT) and/or portal vein thrombosis (PVT), and proper blood flow to the new graft after reperfusion. Blood coagulation depends on a delicate balance of pro- and anti-thrombotic processes. When this equilibrium is upset in favor of thrombosis, the risk of HAT or PVT and subsequent graft failure increase (34). Inadequate or stagnant flow accentuates this problem. On the other hand, excessive flow via the hepatic

artery and/or portal vein into a small graft may cause SFSS (35). While surgical technique, including the practice of portal flow modulation, can alleviate some of these problems, anesthesiologists can do their part by regularly monitoring the coagulation status of the blood, ensuring that splanchnic flow and hemodynamic stability are maintained.

Anesthetic Maintenance of Choice

Various volatile and intravenous anesthetic agents are considered safe for recipients during LDLT (36-39). However, the impact of each anesthetic on liver blood flow, oxygen delivery, and hepatic function should be considered. Currently, volatile anesthetics are reported to decrease total hepatic blood flow due to decreased cardiac output and impose various compromising effects on hepatic oxygen supply (40). However, among these agents, isoflurane increases flow velocity in hepatic sinusoids and preserves microvascular blood flow better than halothane or enflurane (41). Desflurane is known to have similar effects on hepatic blood flow and function compared with isoflurane (42), and patients with ESRD undergoing non-LT surgery receiving both desflurane and isoflurane are reported to show minimal changes in perioperative liver function test results (43). Sevoflurane is reported to maintain hepatic arterial blood flow, hepatic O₂ delivery, and O₂ delivery-to-consumption ratio similar to or superior to isoflurane (44).

On the other hand, propofol-based total intravenous anesthesia has been suggested to protect against ischemia-reperfusion injury in significant organs, including the liver, possibly through its antioxidant properties (45,46). However, data are mixed, with some clinical studies demonstrating that propofol has a protective effect against ischemia-reperfusion injury, leading to better graft outcomes when compared with desflurane anesthesia in LT recipients (47). In contrast, other anesthetics do not demonstrate such a benefit (48). Dexmedetomidine is an emerging drug with highly selective α -2 adrenoceptor activity that

includes sedative, analgesic, anxiolytic, sympatholytic, opioid-sparing, and respiratory-preserving features (49); these unique properties are potentially beneficial in decreasing the incidence of postoperative delirium and opioid consumption in LDLT recipients. However, there is a lack of evidence regarding the effects of intraoperative dexmedetomidine infusion on postoperative outcomes in LDLT recipients who may have large variability in the pharmacokinetics of dexmedetomidine (50).

Intraoperative Fluid of Choice

Although fluid administration in LDLT is critical for organ perfusion, there is insufficient evidence regarding the choice of optimal crystalloid solutions. Lactate in lactated ringer's solution (LR) could increase the lactate load to a newly perfused liver graft. In pediatric LDLT patients, a propensity-score matched analysis comparing LR and normal saline for intraoperative volume replacement showed that the LR group had a higher 90-day mortality rate (11.5% vs. 0.0%) and higher rates of early allograft dysfunction and primary nonfunction (19.7% and 11.5% vs. 3.3% and 0.0%, respectively) over the normal saline group (51). In a study involving adult LDLT donors, LR was associated with hepatic dysfunction compared with Plasma-Lyte (52). Attalla et al. showed that compared to LR, Plasma-Lyte decreased the liver's metabolic load and improved hepatic energy status in patients with hepatic insufficiency (53). Therefore, using non-lactate-containing crystalloid solutions (*i.e.*, Plasma-Lyte) is advisable.

The potential side effects of synthetic colloids are the risk of AKI and coagulation derangement. Although two small randomized controlled studies showed no adverse effect of hydroxyethyl starches (HES) 130/0.4 on the renal function when compared to albumin 5% (54) and gelatin 4% (55), both studies were conducted on small-sized samples of patients with relatively normal renal function, requiring cautious interpretation regarding whether

HES 130/0.4 is as safe as albumin in patients with renal impairment. Regarding the effect of HES on blood loss, no randomized controlled study has directly compared the effect of colloids on blood loss as a primary outcome in LDLT. The above studies reported no differences regarding coagulation profile and/or intraoperative transfusion requirement among patients receiving HES 130/0.4, albumin 5% (54), or gelatin 4% (55).

Acute Kidney Injury Prevention

The incidence of AKI after LDLT has been reported to be 35.2% - 61.8% using KDIGO criteria (56-58). Studies have shown that graft type (LDLT vs. DDLT) does not significantly impact the risk of developing postoperative AKI (59), and both methods share common risk factors that can lead to poor graft and reduced patient survival (60,61). Identifying modifiable risk factors for AKI is essential for improving patient outcomes. A meta-analysis involving 28,844 patients from 67 studies detected 27 modifiable risk factors classified as related to the recipient, donor, or surgical and postoperative factors (62). Hemodynamic instability variables are the most significant, including intraoperative hypotension (odds ratio [OR] 5.58), major bleeding (OR 2.90), vasopressor use (OR 2.08), large red blood cell transfusion (OR 3.12), and postreperfusion syndrome (OR 1.69) (62). Anesthetic management should mitigate these interrelated modifiable risk factors. Terlipressin, a synthetic vasopressin analog (15), has been tested for its ability to prevent postoperative AKI in the LDLT setting. A study by Mukhtar et al., wherein patients with high portal pressure of >20 mmHg received a bolus dose of terlipressin (1 mg over 30 minutes) during surgery followed by continuous infusion of 2 mcg/kg/h for 48 hours, revealed that postoperative creatinine and cystatin C values were significantly lower with terlipressin infusion compared with placebo (20). Reddy et al. also reported a significantly lower incidence of AKI after LDLT with terlipressin infusion compared with placebo (27% vs.

60%, $P=0.04$) (23). Conversely, a randomized controlled study involving 50 patients undergoing LDLT failed to demonstrate terlipressin's benefit (1–4 mcg/kg/h for five days starting at the beginning of surgery) (44% vs. 48% for the terlipressin and placebo groups, respectively, $P=0.777$) (63). Due to inconsistent randomized controlled study results, routine use of terlipressin is not recommended to prevent AKI occurrence after LDLT. Terlipressin infusion should be restricted to patients at high risk for AKI until more evidence is available (64). Terlipressin is currently not FDA-approved for use in the US.

Intraoperative Hemodynamic Changes

While graft reperfusion marks the most acute period of hemodynamic instability, hemodynamic derangements can occur in all stages of LDLT due to insensible losses, hemorrhage, thrombosis, and myocardial dysfunction. Attention to heart rate, blood pressure, pulse pressure variation, pulmonary arterial pressure, cardiac output, and volume status on transesophageal echocardiogram (TEE) is necessary to manage acute changes.

Immediately after graft reperfusion, hypotension is expected secondary to hyperkalemia, myocardial dysfunction, or arrhythmia, and in severe cases, post-reperfusion syndrome (PRS). PRS is defined as a decrease in MAP of $>30\%$ from baseline for at least one minute within the first five minutes after reperfusion (65). PRS is thought to occur due to the release of accumulated vasoactive and inflammatory mediators and micro-emboli from the graft into the recipient's circulation when the portal vein is unclamped (66). The prevalence of PRS in LDLT is similar to that in DDLT (upwards of 34% of cases); it is also associated with higher MELD scores (67).

Surgical and anesthetic factors may play a role in the development of PRS. The choice of preservative solution used to cool the liver graft and prevent cellular edema, acidosis, and cell death may influence hemodynamic derangement after reperfusion (68).

University of Wisconsin (UW) solution is high potassium (125 mmol/L) and high viscosity fluid designed to mimic the intracellular environment to minimize potassium release from liver cells during storage. It remains the standard for optimal graft and patient survival DDLT (68). Histidine-tryptophan-ketoglutarate (HTK) solution mimics the extracellular environment with low potassium (10 mmol/L) and lower viscosity (68). UW solution must be thoroughly flushed from the graft before reperfusion to prevent hyperkalemia, while HTK does not need to be flushed; therefore, shorter warm ischemic time is a theoretical advantage of HTK (69-72). Studies comparing UW and HTK for LDLT revealed that both solutions were equally safe, with no difference in adverse events, intraoperative complications, blood transfusion, graft function, or mortality (69-71). LDLT reperfusion with non-flushed HTK was associated with a more significant decrease in MAP and a significantly higher incidence of PRS compared to UW or flushed HTK solutions. After reperfusion between the solutions, there was no difference in patient temperature, acid-base status, or potassium concentration (72). Compared to flushing HTK from the liver graft before anastomosis, not flushing before reperfusion in LDLT was associated with more frequent PRS, more episodes of severe hypotension (MAP < 60 mmHg within five minutes of reperfusion), and more frequent requirement of norepinephrine infusion (66). Anesthetic management can mitigate the severity of PRS. Hyperkalemia can be prophylactically managed with calcium, insulin/glucose, sodium bicarbonate, and furosemide administration. In cases requiring a large volume of PRBC transfusion, prewashing the banked blood with a cell-salvage device can decrease potassium load while preserving hematocrit (73,74). Pre-reperfusion prophylactic treatment with ephedrine was associated with a decreased incidence of PRS (43.2% vs. 35%, p=0.006) in one small retrospective study (75).

Catastrophic cardiopulmonary collapse is a risk at any stage of transplantation. Intraoperative cardiac arrest (ICA) occurs less frequently in LDLT than in DDLT (1-2.4% vs.

3-3.6%) (76,77). ICA most commonly occurs secondary to PRS, hyperkalemia, and bleeding at reperfusion. However, ICA during dissection and the anhepatic phase may also occur due to hemorrhage, intracardiac thrombus (ICT), or pulmonary thromboembolism (PTE) (76,78). In a large, multicenter, retrospective review, LDLT was a risk factor associated with ICA (OR 2.13; 95% CI [1.16-3.89]; P=0.014) (77). Though the association between LDLT and ICA was based on small sample size (396 patients), outcomes from LDLT patients with ICA were promising, with a lower intraoperative mortality rate than DDLT patients (0.5% vs. 1.1%) (77).

ICT and PTE occur most commonly after reperfusion but can occur at any stage of transplantation (79). ICT can occur in patients with low MELD scores (MELD <20) and has been associated with both hyperfibrinolysis and fibrinolytic shut down (less than physiologic fibrinolysis) on viscoelastic testing (79,80). ICT and PTE may present as cardiac arrest or severe hypotension with a concurrent increase in pulmonary arterial pressure and central venous pressure (81). TEE in LDLT may aid in the early diagnosis of ICT/PTE with evidence of right ventricular dilation and failure and new or worsening severe tricuspid regurgitation, sometimes with thrombus visible in the cardiac chambers (81-84). Early diagnosis of ICT/PTE allows for prompt and targeted treatment with inotropic medications, pulmonary vasodilators, heparin, and thrombolytics (85).

Reduction of Allogeneic Blood Transfusion

A retrospective study on 635 LDLT patients performed between 1995 and 2002 at a single institution showed that the average blood loss during LT was 136 ml/kg (86). An A2ALL study, however, reported that transfusion requirements in LDLT were lower than those in DDLT (median four vs. six units, p<0.001) (87). Less severe ESLD in the LDLT recipients is likely related to the reduced blood transfusion requirements (88). Still, massive

blood loss can occur in LDLT and is associated with poorer outcomes (86,89). Hepatocellular carcinoma and preoperative blood transfusion are reported risk factors for significant blood loss (90).

There are several anesthetic strategies to reduce intraoperative blood loss during LDLT, including low central venous pressure management during the pre-anhepatic phase (91) and portal decompression using surgical or pharmacological methods described previously. The finding that blood markers of portal hypertension, including von Willebrand factor and soluble CD163, are associated with significant blood loss (92) may support the theoretical benefit of the latter strategy. Cell salvage is a viable technique to avoid allogeneic transfusion. Some investigators advocated the safety of this technique during LT in patients with hepatocellular carcinoma (6) based on findings showing an extremely low tumor recurrence rate (93,94).

Point-of-care coagulation monitoring devices have been widely used to avoid excessive allogeneic blood transfusion in LT. These viscoelastic tests (VETs) provide objective measures of global coagulation status at the bedside and allow clinicians to perform goal-directed coagulation management. VET parameters also assist clinicians in identifying patients at higher risk for thromboembolic complications during LT (95). While studies have shown the benefits of VET in reducing transfusion requirements (96), data on its impact on long-term outcomes in LT is limited. A recent survey by SATA reported increased use of prophylactic anticoagulants during the perioperative period of LT, and VETs would likely prove helpful in managing therapeutic anticoagulation (97).

Pain Management

Surgical pain management for LT recipients remains underappreciated. Unlike LDLT donors, multimodal pain regimens and fast-track recovery programs for LDLT recipients have not been widely implemented.

Preoperatively, LT candidates often present with chronic pain (50-80% of cirrhosis patients take opioids), anxiety, depression, and psychosocial issues (98). Given the non-emergent nature of LDLTs, the multidisciplinary transplant care team has an opportunity to optimize these recipients' conditions and facilitate their understanding of post-LDLT recovery processes. This is critical for the successful management of perioperative pain (98).

Intraoperatively, opioid-sparing protocols have been implemented using ketamine, lidocaine, magnesium, dexmedetomidine, midazolam, and steroids (98). The timing and duration of these medications must be carefully considered as they relate to liver function and the potential for over-sedation. Coagulopathy limits the use of neuraxial anesthesia techniques; however, thoracic epidural analgesia (TEA) anesthesia was successfully used in selected LT recipients with normal coagulation status. Hausken et al. reported that patients in a TEA group (n=327) had less pain compared to a non-TEA group (n=358), with a mean numeric pain rating scale score of 1.4 versus 1.8 at postoperative days 0-5 ($P = 0.008$). No difference was found in opioid use at discharge or one year (99). Preoperative or pre-emergence transversus abdominis plane or quadratus lumborum blocks may be applied, and the surgical team can perform local wound infiltration with local anesthetics.

Post-operatively, multidisciplinary pain management is essential, using multimodal pain management to decrease opioid consumption, including acetaminophen and nonsteroidal anti-inflammatory agents (100). A post-discharge plan for pain control must be arranged with close follow-up. Patients prescribed opioids before transplant are at risk for chronic postsurgical pain. A single institutional retrospective study on 322 DDLT recipients from 2008 to 2016 revealed that 61 patients (18.9%) who were prescribed opioids before LT had

increased postoperative opioid requirements and increased incidence of chronic postsurgical pain (CPSP) compared to the control group of 261. They found that CPSP was a significant risk factor for patient mortality after transplantation ($p = 0.038$, HR 1.26) (101).

Enhanced Recovery After Surgery for Liver Transplant Recipients

Enhanced Recovery After Surgery (ERAS) protocols have revolutionized surgical care in various surgical specialties and led to reduced surgical stress, in-hospital stay length, and morbidity. Recently, the successful application of ERAS programs for LT recipients has been reported (102). The ideal LT ERAS protocol includes general anesthesia with short-acting agents (induction with propofol, rocuronium and fentanyl; maintenance with sevoflurane, remifentanyl, and rocuronium) to reduce the postoperative sedative effect; a goal-directed fluid therapy with balanced saline solution (Plasma-Lyte-A/Ionolyte) to avoid excessive fluid administration and maintain a relative hypovolemia; a restrictive PRBC transfusion policy (for hemoglobin <7 g/dl or central venous oxygen saturation $<70\%$); routine preoperative whole blood hemo-extraction, in which units are reinfused during the biliary reconstruction; routine use of a cell-saver; maintaining a MAP of 65 mmHg with preload optimization guided by both a pulse index continuous cardiac output monitor and administration of pressors, including norepinephrine, phenylephrine, and/or terlipressin; VET-guided coagulation management; and the use of sugammadex as the primary reversal agent of choice, as sugammadex is associated with a lower incidence of major pulmonary complications (103).

The primary goal of this ERAS protocol is early extubation. Early extubation after LT is possible using standard criteria (102) in the operating room. It is safe (104) and known to improve survival (105), with an added cost-savings benefit (106) and a marked reduction in the need for mechanical ventilation (107). Patients with hemodynamic stability without the

need for prolonged ventilatory support and lacking clinical evidence of bleeding, graft dysfunction, or vascular problems can be safely transferred to a post-anesthesia care unit (PACU) and later to a surgical ward bypassing the ICU (108). This practice requires the availability of a 24/7-staffed PACU and an initial 1:1 nurse-to-patient ratio in the surgical ward for the first 12 to 24 hours after the LDLT procedure and integration of the critical care team into the ERAS program. Known factors related to ICU admission include old age, elevated MELD score, transfusion needs, and surgical time (108).

Although the initial resource mobilization is required, ERAS protocol can be implemented to manage LDLT recipients. A quasi-experimental study suggested the potential cost saving with such a fast-tracking protocol in LT without compromising patient welfare (109).

Special Issues in LDLT

LDLT has some aspects that create special considerations and applications not pertinent to DDLT. With LDLT, there is more control over the timing of the surgery, and there is usually an opportunity to pick the best anatomical match. Additionally, patients with lower MELD scores have access to organs they otherwise might not have in an allocation system that prioritizes higher MELD. The potential for the significant risk undertaken by the donor may alter the risk assessment such that sicker recipients may not be deemed appropriate candidates. One practical application of LDLT is in lower MELD patients with chronic diseases that may progress. When the patient's MELD is high enough to undergo LT, their severe chronic condition will exclude them from LT. This is of particular interest in cardiovascular disease. Patients with moderate aortic or mitral valve stenosis and lower MELD scores can have an LDLT safely then undergo cardiac surgery when their valvular disease progresses (110). Additionally, LDLT allows for optimal timing of combined procedures such as coronary artery bypass surgery with LDLT or staged procedures such as

LDLT after transcatheter aortic valve insertion (111,112). Likewise, there is concern surrounding LDLT in patients with cirrhosis secondary to alcoholism due to potential for relapse, but these patients' short- and long-term outcomes have been good (113-115).

Given the potential for mortality and significant morbidity for the LDLT donor, the appropriateness of LDLT is controversial for high-risk and high MELD patients such as those with fulminant hepatic failure (FHF) in which the right lobe is almost exclusively necessary. Such an urgent LDLT for an FHF recipient may carry the risk of suboptimal outcomes, and informed donor consent might need to be obtained urgently, which may present the risk of coercion. Despite such concerns, there have been case reports demonstrating good outcomes with LDLT for FHF, including pregnancy (116,117). With careful donor and recipient selection, LDLT provides a safe and effective treatment for complex patients who might not otherwise be suitable transplant candidates (1,118).

LDLT may offer the only chance of a cure for patients with hepatocellular carcinoma (HCC) who may not be amenable to receiving a timely DDLT. This could be due to the geosocial lack of deceased donations in Asian countries. In the US, this condition happens to patients whose tumor stage prevents allocation exception points and, therefore, could not access DDLT (119). Although some studies suggested poorer oncological outcome in LDLT than DDLT in patients with HCC within the University of California-San Francisco criteria (120), other studies support the usage of LDLT (121,122).

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Figure Legends

Figure 1

Right lobe graft bench preparation: Patch venoplasty that includes the right hepatic vein (A) and two inferior accessory right hepatic veins (B). Also shown, outflow reconstruction of segments V and VIII with cadaveric vein graft (C).

Figure 2

Right lobe graft after implantation: A. Right hepatic vein anastomosed end-to-side to the recipient vena cava. B. Outflow reconstruction of segments V and VIII with cadaveric vein graft anastomosed to the recipient's left hepatic vein.

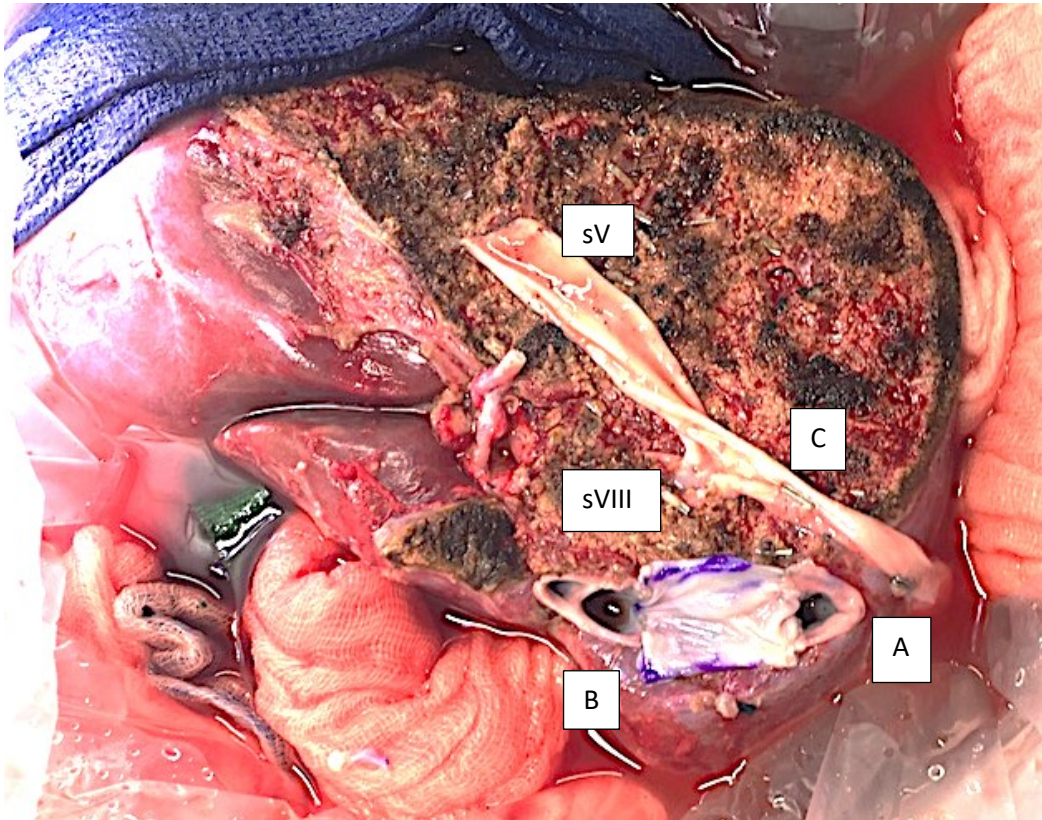


Figure 1

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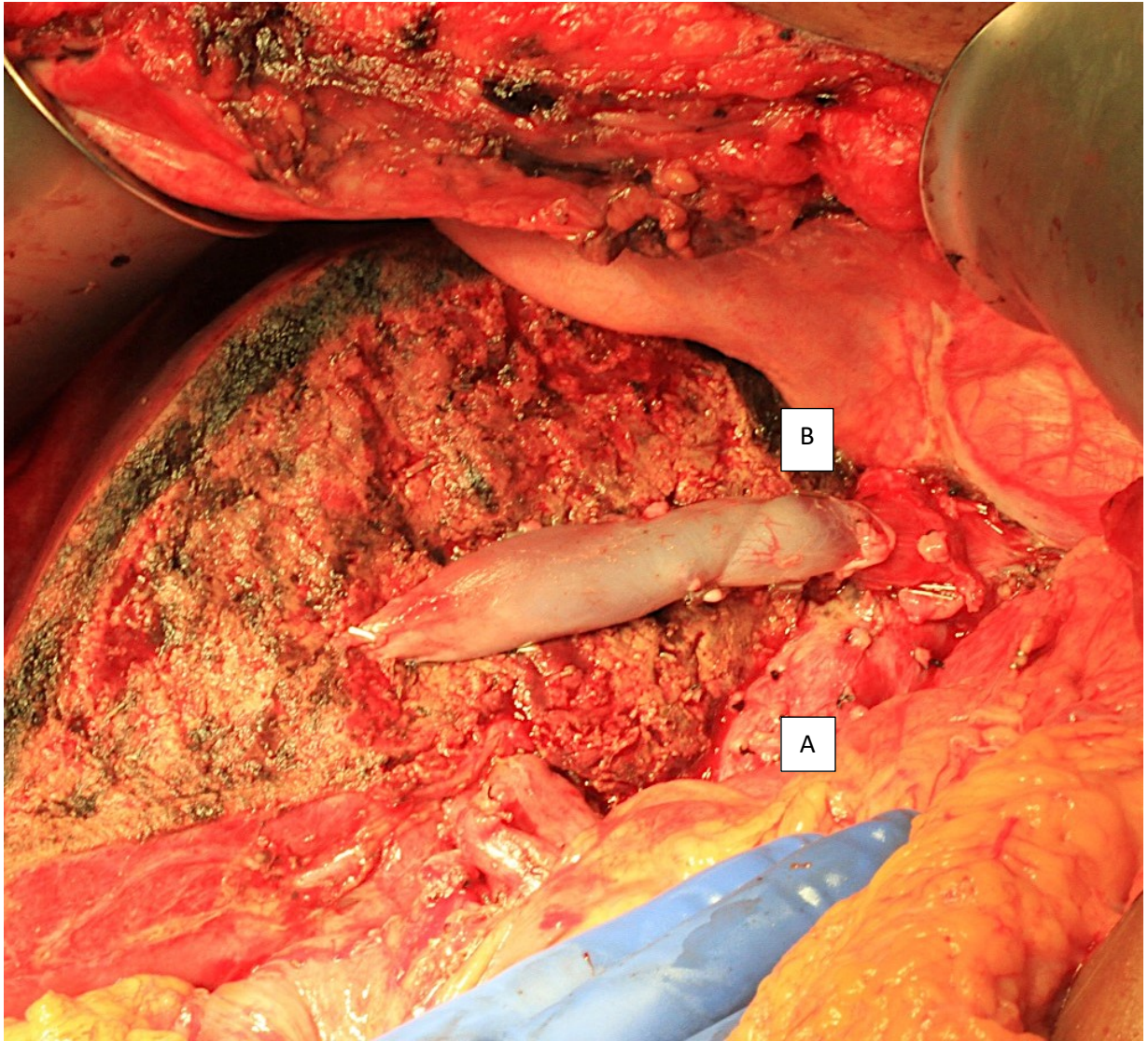


Figure 2

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