Review Article

# Current Status of Liver Transplantation

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**Abstract**

Liver transplantation (LTx) is the treatment of choice for patients with end-stage liver disease (ESLD). Improvement in outcomes (allograft and patient survival) has led to widespread use of LTx worldwide. However, new problems that include severe organ shortage, recurrence of primary disease, opportunistic infections, and development of *de novo* malignancies are the major problems affecting further implementation of LTx.

**Keywords:** Indications, immunosuppression, liver transplantation, outcomes, results

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## Brief history of liver transplantation (LTx)

The first successful liver transplantation (LTx) was performed in the United States by Thomas Starzl in Denver, Colorado in 1967.[1] With increasing numbers of patients on the waiting list, transplantation of partial liver grafts from living donors has evolved to increase the donor pool. Strong et al. performed the first successful living-donor liver transplantation (LDLT) in 1989, when they implanted a left lateral liver segment into a pediatric patient.[2] The first LTx was performed in Iran at Shiraz University in 1992.[3] Since then, more than 1000 cases have undergone LTx with acceptable results. There has been gradual, yet slow development of new programs in Tehran, Mashhad, and Kerman in Iran.

## Indications and contraindications for LTx

Patients with end-stage liver disease (ESLD) should be considered for LTx if they can survive perioperatively and comply with the extensive multidisciplinary workup. As shown in Tables 1 and 2, the indications for LTx in adults and children differ. The main indication for adult LTx in the US is hepatitis C virus (HCV), which counts for 60% of LTx in American adults.

Lack of patient compliance, poor psychological support, absence of sobriety, active drug abuse, advanced cardiovascular or pulmonary diseases, uncontrolled sepsis, irreversible multiple organ failure, AIDS, and active cancer are contraindications for LTx.

## Liver allocations in the United States

Before 2002, liver allocation was based on Child's Score (CS). Nevertheless, CS was not a good tool to measure disease severity in patients waiting for LTx because it could not differentiate between patients with progressively abnormal laboratory values. Additionally, the clinical parameters of the CS are based on subjective measures such as ascites or encephalopathy, which are influenced by clinical interpretation. Also, this allocation has led to increased mortality on the list as CS was not predictive of a patient's disease severity and the chances of dying without LTx. Therefore, in 2002, model of end stage liver disease (MELD) was developed based on three objective criteria that included bilirubin, creatinine, and international normalized ratio (INR) levels and implemented in the US. Changes to the organ allocation policy in 2002 reduced the number of adult patients on the LTx waiting list, decreased wait list mortality, and increased the number of patients who received simultaneous liver-kidney transplantations (SLK).[4] Because of the huge heterogeneity among centers in the size of the waiting list and organ availability, as well as large distances and numbers of centers, the model for organ allocation in the US was set to be patient-based rather than center-based. In this model, patient-specific criteria were developed to prioritize patients; thereby, donors would be allocated to patients, not centers or physicians. This scoring system correlated well with the mortality of those who suffered from liver disease. Since implementation of MELD, the wait list mortality has declined. The disadvantage of this system is the complexity of calculation and the existence of certain conditions in which there is a low MELD score despite the high priority in certain patients who need LTx (i.e., those with hepatocellular carcinoma or metabolic diseases). These patients have currently been listed with exceptional MELD scores after approval by regional committees.

Increased public awareness, improved efficiency of the donation process, greater expectations for transplantation, expansion of the living donor pool, and the development of standardized donor management protocols have led to unprecedented rates of organ procurement and transplantation. Despite attempts by the Organ Donation and Transplant Collaborative and the marked increase in the number of deceased donors early in the effort, the number of deceased donors rose modestly. Our study has shown a decrease in the number of living donors since 2004 in addition to the decrease in donation after brain death (DBD) since 2006. Although the number of deceased donors per million population (pmp) increased from 22.9 pmp in era 1 to 26.3 in era 2, there was a significant change in donor characteristics. For years, Spain has maintained the highest rate of deceased organ donation worldwide. The rate increased from 14.3 donors pmp in 1989 to 33–35 donors pmp in recent years. This was the result of the creation of a national transplant organization in 1989 and development of a coordinated network of highly motivated in-hospital medical doctors placed in charge of the donation process, and detection and management of donors.

The decline in live donors could be due to loss of income while

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**Table 1.** Indication for liver transplantation (LTx) in adults.

| |
|---|
| **Liver cirrhosis caused by viruses such as HBV, HCV, HDV** |
| **Alchoholic cirrhosis** |
| **Cryptogenic cirrhosis** |
| **Cholestatic liver disorders** |
| Primary sclerosing cholangitis |
| Primary biliary cirrhosis |
| Secondary sclerosing cholangitis |
| **Metabolic/genetic disorders** |
| α-1 antitrypsin deficiency |
| Wilson disease |
| Hemochromatosis |
| Familial amyloidotic polyneuropathy |
| **Fulminant hepatic failure: Acetaminophen, toxins, mushroom** |
| **Malignancy** |
| Hepatocellular carcinoma |
| Hepatoblastoma |
| Hemangio endothelioma |
| Hilar cholagiocarcinoma |
| Liver metastases of neuroendocrine tumors |
| **Others** |
| Severe liver trauma |
| Budd-Chiari syndrome |

**Table 2.** Indications for liver transplantation (LTx) in children.

| |
|---|
| **Biliary artesia** |
| **Alagille syndrome** |
| **α-1 antitrypsin deficiency** |
| **Wilson disease** |
| **Crigler-Najjar syndrome** |
| **Metabolic/genetic disorders** |
| Tyrosinemia type I |
| Gylcogenosis type III, IV |
| Urea cycle defects |
| Neonatal hemochromatosis |
| Congenital hepatic fibrosis |
| Cystic fibrosis |
| **Fulminant hepatits** |
| **Hepatoblastoma** |

off work after the procedure, potential future insurability issues, and expenses that may not be covered by insurance. The decline in liver live donation could be due to donor death or implication of the MELD system. The decline in DBD donors can be attributed to increases in the number and percentage of marginal donors and donation after cardiac death (DCD). The observed increase in DCD also explains, in part, the fewer number of organs per donor that are recovered and transplanted. For DCD livers, there is a high rate of biliary strictures that have been attributed to the period of warm ischemia that occurs between withdrawal of donor life support and organ preservation. This leads to a reduction in graft survival and an increase in the need for retransplantation. On the other hand, marginal liver allografts have been shown to be associated with increased hospital costs.[4]

## Types of LTx

The majority of livers are procured from deceased donors. Nevertheless, the increasing number of patients dying on the waiting list due to the shortage of livers has prompted the transplant community to use more organ resources. Their effort to expand the donor pool has provided alternative ways of organ supply, including using live donors, split-LTx, and utilization of expanded criteria donors (ECD). The ideal, general donor criteria include donor age ≤ 50 years, normal liver values, hemodynamic stability, and no systemic infections or cancers. Nonetheless, the increasing number of patients who need a suitable organ and the current organ shortage has pushed the transplant community to utilize ECD livers. The definition of ECD liver allograft is not universal and somewhat center-based. An ECD liver might be considered but not limited to the following: donor age > 65 years, steatosis > 30% of the graft volume, peak donor serum sodium level > 155 mEq/L, use of high dose or multiple vasopressor agents, prolonged intensive care unit stay, and long cold ischemia time (> 12 hr).[5–7]

### *Living-donor liver transplantation (LDLT)*

Living-donor liver transplantation (LDLT) is an established treatment for ESLD. In Asian countries, approximately 90% of donor organs for LTx are obtained from live donors, as the deceased donor rate is low due to social and religious factors. The US has the highest rate of donation worldwide after Spain. The peak of adult LDLT was in 2001, but the sudden death of a living donor postoperatively in New York led to a continual decline in the numbers of LDLT in the US.[4]

LDLT has some well-documented advantages, including the use of a graft from a healthy donor with minimal ischemic time, the ability to schedule surgery electively, a reduced risk of the recipient dying on the waiting list, and it allows for the recipient to be medically stabilized. Disadvantages of LDLT are the higher rate of surgical complications for both the donor and recipient and a potential risk of small-for-size syndrome. LDLT carries inherent risks for the healthy donor. Therefore, careful selection of the donor and recipient is crucial to minimize risks and complications, and to obtain an acceptable outcome.[7–10]

Initially donors undergo psychosocial evaluation to assure there is no coercion. Next, donors are evaluated by clinical examination and serologic testing for liver disease, renal disease, viral hepatitis, and human immunodeficiency virus (HIV). The second stage is comprised of diagnostic studies to evaluate the vascular and biliary anatomy of the donor. Several options for preoperative imaging are available and include non-invasive modalities such as multi-phase

computed tomography, duplex ultrasonography, and magnetic resonance imaging. The third phase can consist of a percutaneous liver biopsy. Many centers perform liver biopsies either routinely or selectively.

The ideal candidates for LDLT are usually those patients who are not extremely sick from ESLD and typically have MELD scores < 20. One of the most difficult problems to tackle in the expansion of LDLT to adults is graft size to avoid small-for-size syndrome (SFSS). This is manifested as the constellation of persistent ascites, coagulopathy, prolonged cholestasis, and poor bile production in the absence of a technical cause.

The pathophysiology of SFSS is not well described but might be related to allograft size, portal hyperperfusion or venous outflow obstruction. The graft-to-recipient weight ratio (GRWR) should be at least 0.8%.

The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) is a consortium of liver transplant centers in the United States that have a primary goal of comparing outcomes of adult-to-adult LDLT versus deceased donor liver transplantation (DDLT). In its first detailed report on 385 cases, 90-day graft survival was 87%, with a one-year graft survival of 81%. The outcomes were characterized by frequent biliary complications (30% early, 11% late) and a 13% graft failure because of vascular complications, primary non-function (PNF), and sepsis. Marcos et al. have compared the outcomes after adult-to-adult LDLT to those who underwent DDLT, using nationwide databases. The one- and three-year patient survival rates after LDLT (89.1% and 80.3%) were similar to those after DDLT (85.7% and 77.7%). Graft survival rates at one [79.3% (LDLT) and 70.1% (DDLT)] and three [80.7% (LDLT) and 71.1% (DDLT)] years were also similar. However, the severity of illness was substantially lower in LDLT recipients compared to DDLT recipients.[10]

It has been suggested that HCV replication might be increased in reduced-size LDLT grafts, but the data is controversial. The major concern in adult-to-adult LDLT is the adequacy of the graft size. Although harvesting a larger graft carries a higher risk for the donor, a residual liver volume of 30% can be tolerated by the donor in the absence of steatosis and right-lobe grafts have become standard for adult LDLT.[8–10]

To minimize donor risk, use of the left lobe has been popularized in the US and Asia. Although single center data has shown comparable outcomes using the right versus the left lower lobe, analysis of the US experience has revealed lower allograft and patient survival when using left lobes due to the high rate of complications and need for retransplantation.[11]

***Split-liver transplantation (SLT)***

Split-liver transplantation (SLT) is two allografts that have been created from a single deceased donor liver allograft. This technique has been developed to address organ shortages. However, the technical and logistic issues in both donors and recipients prevent its worldwide usage. SLT accounts for only 4% of LTx in the US. While splitting was originally performed as an ex vivo bench procedure, *in situ* liver splitting was introduced to decrease cold ischemic time (CIT) and prevent blood loss after reperfusion. It had been feared that prolonged surgical time and increased blood loss associated with *in situ* splitting of the livers might negatively affect the function of other solid organs procured from the same donor. However, in stable donors *in situ* splitting can be accomplished without significant negative effects on the remaining organs.

Left-lateral-segment (LLS) or left-split grafts have mainly been transplanted into children and right split or right trisegment (RTS) grafts into adults, both with excellent outcomes. Rogiers et al. reported the results of 100 livers split *in situ* which resulted in 190 grafts for transplantation. LLS grafts were transplanted into the pediatric recipients and RTS grafts were transplanted into older children and adults. Patient and graft survivals equaled those of 1086 recipients who received whole livers from deceased donors.[12,13]

## Immunosuppression

Immunosuppressive therapy includes induction and maintenance therapy. The induction agents are added to the standard immunosuppressive agents to prevent or reduce the incidence of early rejection rates following LTx.[14] Induction therapy consists of anti-CD25-receptor antibodies (basiliximab, daclizumab), an anti-CD52 monoclonal antibody (alemtuzumab), or depleting polyclonal antibodies (thymoglobulin or ATG). The standard immunosuppressive regimen is a triple therapy regimen that consists of calcineurin inhibitors (CNI; cyclosporine or tracrolimus), steroids, and MMF. CNI are the cornerstone of the immunosuppressive regimen in most liver transplant centers. Nevertheless, therapy with CNIs is associated with adverse effects such as nephrotoxicity, neurotoxicity, hypertension, hyperkalemia, and hyperlipidimia. Corticosteroids are considered to be a fixed part of initial and maintenance treatment for LTx patients. Because of the dose-dependent side effects that include osteoporosis, diabetes, Cushing syndrome, hypertension, and hyperlipidemia, as well as steroid promotion of viral replication (HBV, HCV), tapering and discontinuation of the therapy

**Table 3.** Commonly used immunosuppressive agents in liver transplantation (LTx) and their target pathways.

| Immunosuppressive agent | Mechanism of action |
|---|---|
| **Maintenance immunosuppression** | |
| ***Corticosteroids*** | Inhibits cytokine transcription by antigen presenting cell, Selective lysis of immature cortical thymocytes |
| ***Calcineurin inhibitors (CNI)***: | Inhibits signal 2 transduction via T-cell receptor |
| (Cyclosporine and tacrolimus**)** | |
| ***mTOR* inhibitors:*** | Inhibits signal 3 transduction via IL-2 receptor |
| (Sirolimus, rapamycin, everolimus) | |
| ***Azathioprine*** | Inhibits purine and DNA synthesis |
| ***Mycophenolic acid*** | Inhibits purine and DNA synthesis |
| **Induction immunosuppression** | |
| Antithymocyte globulin (ATG**)** | Causes depletion and receptor modulation in T-cells |
| ***Anti IL-2 alpha chain receptor antibodies:*** | Inhibits T-cell proliferation to IL-2 |
| (Basiliximab, daclizumab**)** | |
| Anti-CD52 monoclonal antibodies | Causes depletion of thymocytes, T-cells, B-cells (not plasma cells) and monocytes |
| *Mammalian target of rapamycin | |

**Table 4.** Surgical complications following liver transplantation (LTx).

| Complication (incidence) | Treatment |
|---|---|
| **Hepatic artery thrombosis (HAT; 4%–6%)** | |
| Early (within seven days) | Retransplantation |
| Late | Biliary drainage, ERCP |
| **Portal vein thrombosis (PVT; 1%–3%)** | Thrombectomy |
| **Hepatic vein/IVC thrombosis (1%)** | Thrombectomy |
| **Biliary complications (15%–25%)** | |
| Bile leak | Drainage, revision |
| Bile duct stricture | ERCP*/stenting, operative revision |
| **Intra-abdominal abscess (5%)** | Drainage |
| *ERCP: Endoscopic retrograde cholangiopancreatography | |

have been recommended during six months post-transplantation. The adverse effects of MMF include bone marrow suppression, gastrointestinal symptoms, and slight increase of the incidence of lymphoproliferative diseases, as well as opportunistic infections. Table 2 shows common immunosuppressive agents used in LTx.

## Postoperative complications

Postoperative complications can be divided into surgical (Table 4 and medical complications. The surgical complications after LTx are further categorized as vascular, biliary, and other complications. [15–17]

The incidence of early (with seven days after LTx) hepatic artery thrombosis (HAT) is 4%–6%, and necessitates retransplantation as damage to the bile duct is severe enough to cause a lack of collateral flow. Arterial complications include anastomosis bleeding and acute or chronic stenosis/occlusion due to thrombosis, steal syndrome, and aneurysm. Early HAT arterial occlusion and thrombosis are the result of technical defects and preservation injuries, respectively. Late occlusion may be caused by preexistent stenosis. Late HAT can be asymptomatic (due to collateral flow) or presents as biliary complications such biloma, leak or strictures.

Portal vein thrombosis (PVT) is a rare event, occurring in 1%–3% of transplantations. PVT requires re-exploration and thrombectomy to salvage the allograft. Hepatic vein/IVC thrombosis results from technical problems or recurrence of underlying disease such as Budd-Chiari syndrome. The allograft can be salvaged by repeat surgery and thrombectomy.[15]

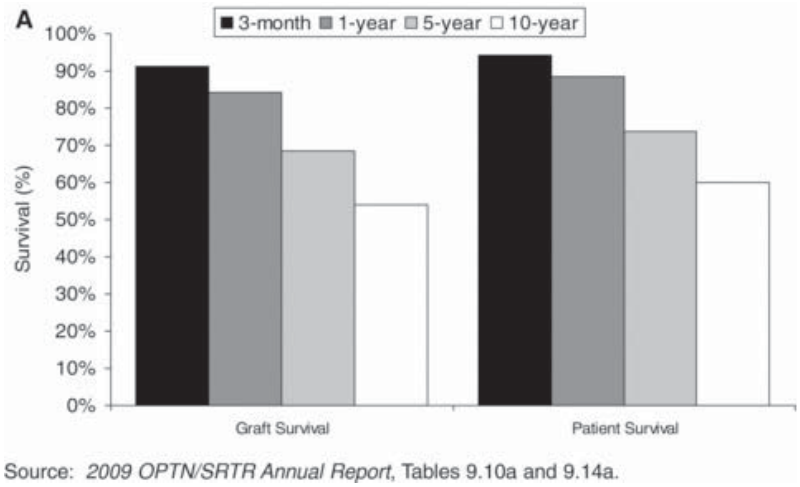
Bile duct reconstruction has been labeled the 'Achilles' heel' of LTx.[16,17] Despite progress in surgical techniques, organ preservation and immunosuppressive management, biliary complications still frequently occur after LTx and have a high risk of significant mortality and morbidity. Anastomotic problems have been the major reason for biliary complications despite various innovations for biliary reconstruction that have been achieved for whole organ LTx. Biliary reconstruction in LDLT using partial liver grafts is still a matter of debate. In the past, Roux-en-Y choledochojejunostomy (RYCJ) was the standard technique for biliary reconstruction as the majority of LDLT recipients had biliary atresia. Recent reports on biliary complications have shown an incidence of 12% to 28% after RYCJ in LDLT recipients. The disadvantages of this technique are the comparatively long operative time, possibly higher risk of contamination as a result of spillage of enteric contents, the non-physiologic nature of the re-established bilioenteric, and the frequent inability to access the anastomosis endoscopically during the post-operative period. In contrast, duct to duct choledochocholedochostomy (DDCC) reconstruction is the technique of choice for biliary anastomosis in whole organ LTx. When the duct-to-duct (DD) technique can be used for LDLT, an extraintestinal anastomosis can be avoided, the continuity is more physiological than that of RYCJ, and preservation of the sphincter function of the lower bile duct may reduce the risk of enteric reflux into the biliary tract. [17]

Medical complications include infection (pneumonia, urinary tract infections, cholangitis and intra-abdominal abscesses).[18] The causes of early infection during the first month after LTx are exacerbated pre-transplant infection in the recipient as a result of immunosuppression, infection in the allograft, and similar infections that would occur in non-immunosuppressed patients undergoing comparable surgeries such as wound, pulmonary, biliary, and urinary tract infections, which account for more than 95% of the infections. Infections in the first six months following LTx include the residual effects of technical problems and earlier infections, infection with immunomodulating viruses (CMV, EBV, HBV, HCV, and HIV), and opportunistic infections. Infections more than six months post-LTx result from community-acquired respiratory viral infections (80%), recurrent chronic infection with HBV or HCV, and opportunistic infections in patients with poor allograft function and excessive immunosuppression.

Primary non-function (PNF) can be multifactorial and is observed in 3%–4% of cases.[19] PNF is described as graft failure within ten days which necessitates retransplantation. Nevertheless, according to the proposed United Network for Organ Sharing Criteria, PNF is defined as signs of graft non-function that include AST $\geq$ 5000 U/L along with either INR $\geq$ 3.0 or the presence of acidosis within ten days post-transplant. Donor factors related to PNF are extended donor criteria such as age, steatosis, hypernatremia, high-dose multiple inotropic therapy, prolonged intensive care, and non-heart-beating donor. The procurement criteria are prolonged cold ischemia time.

## Follow-up

All patients are routinely followed at least weekly for the first month after LTx. Initial follow ups include blood tests and duplex ultrasound of the transplanted organ to monitor for patency of vasculature, rejection and infection. If rejection is suspected, a liver biopsy should be performed. Today, HCV recurrence is an important, yet unresolved problem after LTx. LTx recipients are at higher risk than the general population for malignancy due to immunosuppression. There are no specific guidelines for screening. The most common neoplasms are skin cancer and post-transplant lymphoproliferative disease (PTLD) Cancers, cardiovascular, infectious, and recurrent diseases are the most common causes of patient death over the long term.




Source: *2009 OPTN/SRTR Annual Report*, Tables 9.10a and 9.14a.

**Figure 1.** Short-term and long-term results of liver transplantation in United States.

## Outcomes after LTx

Several factors relevant to post-transplant outcomes following LTx can be classified as donor, recipient, operative, and postoperative factors. The following donor parameters are predictors of poor outcome: advanced age, high BMI, cause of brain death (particularly stroke), length of hospitalization, use of pressors, liver function, sodium level, reduced/split grafts, steatosis, and cold ischemia time. The recipient parameters include urgent status, renal dysfunction, age, ventilation requirement, and HCV. Operative factors are the amount of blood loss and blood product administration, the lack of immediate bile production, low urine output, CIT > 12 hr and warm ischemia time > 35 min. Finally, postoperative indicators are parameters such as elevated ALT and AST, serum bilirubin, serum creatinine, and prothrombin time.

Liver transplant survival has increased over the past decade. According to Figure 1, those who have received a liver from a deceased donor had the following unadjusted graft survival rates: three-month (91.2%), one-year (84.3%), five-year (68.4%), and ten-year (54.1%); unadjusted patient survival rates were as follows: three-month (94.3%), one-year (88.4%), five-year (73.8%), and ten-year (60.0%).[20]

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