Review Article

Liver Transplantation

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ABSTRACT

Great progress has been made in the field of liver transplantation in the last 50 years. From being an experimental therapy to a well-recognized surgical modality, liver transplantation has come a long way. It is now the only treatment option and potential cure for thousands of patients with a wide range of acute and chronic liver diseases. This paper details the basic tenets of liver transplantation, the differences between cadaveric and living donor liver transplantation, the outcomes and its current status.

Historical background :

In 1955, Welch was the first to describe scientifically the liver transplantation as a treatment modality for chronic liver diseases. In 1958, Francis Moore described the first orthotopic liver transplantation in dogs. Starzl *et al* performed the First liver transplantation in humans on 1st March 1963; this was done in a 3 year old boy with biliary atresia who died during the surgery because of uncontrolled & massive bleeding[1]. After several equally unsuccessful attempts, Starzl succeeded in performing the first successful liver transplantation in 1967 in a patient with advanced hepatocellular cancer who survived for 18 months with preserved liver function and died due to the disease recurrence[2].

During the successive years, major breakthroughs happened such as introduction of the brain-dead criteria in 1968, realization that rejection is one of the major cause of graft loss and associated mortality and the introduction of new immunosuppressive medication cyclosporine in 1979 by Sir Roy Calne. In 1983, the National Institutes of Health (NIH) declared that liver transplantation was a valid therapy for End-stage liver disease (ESLD) and, a few years subsequently, the United Network for Organ Sharing (UNOS) was founded. In 1989, Starzl *et al* reported the 1 to 5 year survival of 1,179 liver transplant recipients (73% and 64%, respectively). Finally, in 1990 Tacrolimus was first used as a immunosuppressive agent for liver transplant recipients and became the mainstay of therapy to prevent rejection after liver transplant.

The first successful living donor liver transplant from an adult to child was performed in 1989 by Strong *et al* in Australia. The first adult to adult left lobe transplantation was done by Makuuchi in 1993 in Japan and Fan et al conducted the first right lobe transplantation in 1996. These efforts resulted in a rapid increase in the number of transplantations in Asia, Europe, North and South America after 1997.

Indian government passed the Transplantation of Human Organs Act (THOA) in 1994 and the first deceased donor liver transplantation (DDLT) as well as the first successful Living donor liver transplantation (LDLT) in India were performed in 1998[3]. Northern India, especially Delhi, was the seat of growth of LDLT from 2001 and southern India, especially Chennai and Hyderabad, played a key role in establishing DDLT in the country[4]. The total number of LTs performed in India to date is close to 7500; approximately 80% are LDLT, and the remaining are DDLT. The total number of LT centers in India stands at approximately 30[5].

Disease Pattern :

The liver disease burden in India is quite large with 22.2 deaths per 100,000 population attributed to cirrhosis by the Global Health Observatory data from the World Health Organization (WHO)[6]. The etiology of chronic liver disease is however quite different from the western population with alcohol being the most common cause in adults followed by

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viral hepatitis. In recent years, the incidence of Nonalcoholic steatohepatitis (NASH) has also increased. This is attributable to an ever-increasing diabetic & obese population with metabolic syndrome. The etiology of Acute Liver Failure is also different from that in the Western population with hepatitis E being the most common cause. Biliary atresia is the most common etiology among children requiring transplantation followed by metabolic liver disease (especially Wilson's disease).

Liver transplantation should be considered for any patient in whom anticipated overall survival exceeds life expectancy of the underlying disease or where a significant increase in quality of life can be achieved[7].

An overview of some of the conditions requiring LT as a curative procedure is given in ***(Table 1)***[8].

Table 1 : **Indications for Liver Transplantation**

Viral
- Hepatitis C
- Hepatitis B

Autoimmune liver disease

Alcohol-related liver disease

Inherited/metabolic liver diseases
- Hemochromatosis
- α1-Antitrypsin deficiency
- Wilson's disease
- Nonalcoholic fatty liver disease
- Tyrosinemia
- Type IV glycogen storage disease
- Neonatal hemochromatosis
- Amyloidosis
- Hyperoxaluria

Urea cycle defects
- Amino acid defects

Cholestatic liver disease
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Biliary atresia
- Alagille syndrome
- Progressive familial intrahepatic cholestasis
- Cystic fibrosis
- Bile duct loss

Malignancy
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Fibrolamellar carcinoma
- Epithelioid hemangioendothelioma
- Hepatoblastoma
- Metastatic neuroendocrine tumor

Polycystic liver disease

Vascular disorder
- Budd-Chiari syndrome

Fulminant hepatic failure
- Hepatitis A/E
- Acetaminophen poisoning

Contraindications for Liver Transplant :

Absolute contraindications for liver transplantation includes life-limiting medical conditions such as advanced cardiovascular, pulmonary, or neurologic disorders. Uncontrolled systemic infections, which exclude patient survival under immunosuppression, and AIDS-defining symptoms in HIV patients are absolute contraindications; however, the possibility of doing LT in these situations must be assessed in each individual patient.

For alcoholic patients, abstinence from alcohol and drug abuse for a minimum of 6 months is required in most of the DDLT programs all over the world. However, this mandatory duration of abstinence is a matter of debate because the 6-month threshold has shown to be insufficient for predicting long-term graft and patient survival.

Relative contraindications may be psychosocial conditions resulting in poor compliance, advanced age, and severe hepatopulmonary or hepatorenal syndrome that may not be cured or improved after liver transplantation, as well as severe obesity or severe malnutrition. Here, the indication must be assessed individually for each patient.

Liver transplantation for Malignancy :

Liver transplantation for malignancy is the most radical intervention, although long term oncological outcomes under continuous immunosuppression remain a challenge.

Mazzaferro *et al*. proposed the earliest criteria for LT to treat HCC known as the Milan criteria. The 4-year overall survival rate was 85% and the disease-free survival rate after LT was 92% for patients with HCC who were selected in accordance with the Milan criteria (one lesion less than 5 cm, or two to three lesions each less than 3 cm, no macro-vascular invasion and no regional nodal or distant metastasis)[9] In 2001, a research group from the University of California San Francisco reported 5-year survival of over 70% by slightly expanding the tumor criteria (1 lesion < 6.5 cm or up to 3 lesions < 4.5 cm; the UCSF criteria). This good outcome of LT in HCC has now been reproduced consistently in hundreds of patients by different transplant centers.

Both intra-and extrahepatic Cholangiocarcinoma could represent indications for LT when resective surgery is not an option because of underlying liver disease or anatomically unresectable lesions. A well-defined protocol of chemo-irradiation and staging laparotomy before LT has been developed by the Mayo Clinic[10], which has resulted in long term disease-free survival (more than 50% in 5-year) in these patients.

Certain rare malignancies including hepatoblastoma and hemangioendothelioma are other indications for LT with 5-year survival upto 80%.

Clinical trials evaluating liver transplantation for selected patients with neuroendocrine hepatic metastases have shown long-term graft and patient survival comparable with patients transplanted for HCC[11]. Extrahepatic malignancies as well as hepatic metastases from non-neuroendocrine tumors so far remain absolute contraindications for liver transplantation.

Perioperative assessment & evaluation :

Intractable ascites, esophageal variceal hemorrhage, spontaneous bacterial peritonitis, hepatorenal syndrome & hepatic encephalopathy are the major complications associated with end-stage liver disease. The 1-year mortality associated with recurrent Upper G-I bleed & ascites is around 15-45% whereas it increases to around 75% with one episode of hepatic encephalopathy & hepatorenal syndrome.

Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) are the two scoring systems used for determining the disease severity and the prognosis in patients with chronic liver disease and to prioritize them for liver transplantation. The CTP score utilizes five variables: ascites, encephalopathy, serum bilirubin, serum albumin and the prothrombin time for scoring, each scores from 1-3 with total score range of 5-15 and divides the scores into 3 classes of A-C for prognosis. CTP class A, B and C patients have a one year survival of 95, 80 and 45% respectively without transplantation.[13]

Model for End-stage Liver system (MELD) was introduced in 2002 and includes serum bilirubin, creatinine level, and International Normalized Ratio (INR). These parameters are simple, reproducible and objective & MELD has now been universally adopted for prioritization of adult patients (age more than 12 years) on waiting list for liver transplantation. MELD has been validated extensively as a predictor of 3-month mortality from chronic liver disease[12].

Current guidelines recommend patients with CTP score 8 or above and MELD score 15 or above should be listed for Liver transplantation.

Similar to MELD, Pediatric end-stage liver disease (PELD) was developed for pediatric patients aged 12 years or less. This model utilizes five parameters including bilirubin, INR, albumin, growth failure, and age and has been shown to be accurate in the prediction of 3-month mortality for pediatric patients waiting on the liver transplant list.

The King's College Criteria (KCH)[14] are widely used to assess the severity of ALF and to identify patients who are likely to benefit from liver transplantation. In patients with acetaminophen-induced fulminant hepatitis, a pH less than 7.3 at 24 hours or more after overdose is an indication for liver transplantation. Otherwise, liver transplantation should be considered in the presence of all three of these factors: PT greater than 100 seconds, grade III/IV HE, and serum creatinine greater than 300 μmol/L. In nonacetaminophen-related FHF, the decision is based on the presence of

three of the following : (1) non-A, non-B hepatitis; (2) drug-induced hepatitis; (3) halothane exposure; (4) serum bilirubin greater than 300 ìmol/L; (5) PT greater than 50 seconds (INR >3.5); (6) age younger than 10 years or older than 40; or (7) time from jaundice to encephalopathy longer than 7 days. A PT greater than 100 seconds (INR > 6,5) in isolation is considered an indication for liver transplantation.

Deceased donor versus Living donor liver transplantation :

Donation after brain death (DBD) is widely accepted and well established. Donation after cardiac death (DCD) is well established in the US but still controversial elsewhere. Deceased donor liver transplant is safe, technically easier and has demonstrated good outcomes all over the world. There is no age limit to the donor age and livers can be transported from one place to another as long as the cold ischemia time is kept low (preferably less than 12 hours).

In contrast, Living donor liver transplantation mostly happens in Asian countries where the organ donation rates are still low due to social and religious factors. The advantage with LDLT is the availability of a healthy donor, minimal cold ischemia time and the chance of recipient optimization in view of elective surgery. However, the LDLT surgery is technically more challenging with small sized and segmental arteries, veins and bile ducts.

An ideal living liver donor[23] should be aged 18-55 years, have the same or the compatible blood group as the recipient, body mass index lower than 30, macrovesicular hepatosteatosis < 20%[22], Liver attenuation index on CT scan > +5[24] and with calculated remnant liver volume higher than 30% of the total liver volume.

Estimation of graft volume (GV) is critical in LDLT to optimize donor safety and recipient outcome. *Small-for size syndrome*[16] is a clinical condition resulting from the use of a liver with *insufficient volume for the recipient* and accompanied by prolonged cholestasis, coagulopathy and persistent ascites post-transplant. In order to avoid this, the necessary minimum liver volume is calculated in reference to the liver graft's ratio to recipient's body weight or its ratio to standard liver volume measured according to the recipient's body surface area. There is a general consensus that the ratio of graft weight to recipient body weight (Graft to recipient weight ratio; GRWR) in case of living donor liver transplantation must be more than 0.8%[17]. Remnant liver volume has to be above 30% for the safety of the donor[18]. The remaining liver in the donor regenerates within 3 months to 90% of its original volume. The donor surgery is safe, with a risk of 30% morbidity and a mortality risk of up to 0.5%[15].

Immunosuppression :

Much of the progress in the field of Liver transplantation can be attributed to the development of newer immunosuppression medications & treatment regimens are continuously evolving. Daily immunosuppressive therapy is mandatory to prevent organ rejection. The primary workhorse consists of corticosteroid and a calcineurin inhibitor (tacrolimus or cyclosporine). Mycophenolate mofetil (MMF), (a reversible inhibitor of IMP Dehydrogenase enzyme in purine synthesis), is frequently used to minimize the nephrotoxic effects of cyclosporine and tacrolimus[20]. mTor inhibitors such as sirolimus and everolimus lower cancer risk in selected patients and are recommended for patients with malignancy[21].

In the early postoperative period, immunosuppressive drug levels are maintained at a higher level to avoid graft rejection. These levels are tapered with time; Corticosteroids are usually stopped within 3 months in adults and most children can be weaned off the corticosteroid component within 1 year. Long-term immunosuppressive therapy often consist of monotherapy with either tacrolimus or cyclosporine which has to be continued for life-long.

Acute and Chronic graft Rejection :

Hyperacute rejection, mediated by preformed antibodies in the recipient and directed against the graft endotheliumis rarely seen today. It typically occurs in the setting of ABO incompatibility and retransplantationis the only treatment option.

Acute liver rejection usually occurs within the first six weeks after transplantation; it is seen in around 50% of the patients. It may present with signs of fever, malaise, or right upper quadrant abdominal pain. Elevated liver enzyme levels are often detected before physical signs or symptoms occur. The most reliable diagnostic method is liver biopsy which reveals portal inflammation with predominantly mononuclear cells, bile duct inflammation and centrilobular necrosis. The treatment for acute rejection is usually bolus corticosteroids :1000 mg methylprednisolone (Solu-Medrol), followed by a 5-day taper. Patients who do not respond to bolus steroidsmay require additional strategies, including the use of monoclonal antiT-cell antibody therapy (OKT3); this is however rarely required. In contrast to other solid-organ transplants, such as kidney and heart, the occurrence of an acute rejection episode does not seem to reduce the overall liver graft survival, if treatment is initiated promptly[28].

Chronic rejection occurs in approximately 2% of the patients (more commonly in autoimmune related Chronic liver disease).The histological diagnostic criteria, as defined by Banff[29], are cytoplasmic eosinophilia, lymphocytic portal inflammation, obliterative arteriopathy and bile duct loss. Chronic rejection leads to graft loss and requires retransplantation. Combined acute and chronic graft rejection is responsible for about 7% of cases of retransplantation[30].

Complications :

Liver transplant is a very complex surgery associated with a high rate of complications. Postoperative recipient morbidity can be attributed to a wide combination of factors including pre - transplant patient morbidities, graft quality, surgical expertise and the postoperative management.

Table 2 : **Complications after Liver Transplant**

Vascular complications	Hepatic artery thrombosis, Hepatic artery stenosis
	Portal vein Thrombosis, Portal vein stenosis
	Deep vein thrombosis, Pulmonary embolism
Biliary complications	Bile leak Biliary stricture Cholangitic abscess
Renal	Acute renal failure
Pulmonary	Pulmonary Edema, Pleural effusion, Consolidation
Related to liver graft	Acute cellular rejection Primary non-function (PNF) Early Graft dysfunction (EGD) Chronic rejection
Infections	Cytomegalovirus, Pneumocystis Carinii, Fungal, Bacterial
Related to immunosuppression	Diabetes Obesity/Post-transplantation metabolic syndrome Hypertension Nephrotoxicity Neurologic complications

Liver transplant recipients are significantly immunocompromised and infection is the most common cause of death after LT at all time points, directly causing 28% of all deaths in liver transplant patients[25]. Cardiovascular disease becomes a leading cause of death in patients who survive more than 3 years after LT, accounting for more than half of the reported mortality in some series [26].

Post - transplant care

Lifelong care is crucial for long-term graft and patient survival after liver transplantation. During the first 3 months, blood tests are done regularly for surveillance of liver function and to meet the target blood levels of immunosuppressive drugs. Prophylactic treatment for common opportunistic infections like CMV and PCP may have to be given based on donor / recipient risk profile. Regular liver Doppler is performed to assess liver perfusion[19].

The main focus of long term follow-up is to screen for complications and side effects of immunosuppressive therapy, recognition and treatment of acute or chronic graft rejection, recognition and treatment of biliary complications, malignant disease, and recurrence of the primary liver disease. Certain diseases such as Hepatitis B, C and autoimmune etiologies (PBC, PSC) would require long term surveillance so that adequate antiviral therapy and other medications can be started at the first episode of disease recurrence.

Outcomes :

Liver Transplant provides long-term survival and a very good quality of life for the majority of recipients. Survival after OLT has greatly improved as a result of continuing refinements in surgical and anesthetic techniques, perioperative care and immunosuppression regimens. According to UNOS / SRTR 2016 data[27] overall 1, 3 and 5 -year survival rates following liver transplantation are 89%, 81% and 75% with cadaveric liver transplantation and 91%, 87% and 81% with living donor liver transplantation, respectively.

Conclusion :

Liver transplantation has rapidly advanced from an experimental therapy to a mainstream treatment option for a wide range of acute and chronic liver diseases. It is now the only treatment option and potential cure for thousands of patients. With increasing knowledge about disease pathology, liver regeneration, immunosuppression and refinements in surgical technique, outcomes would continue to improve. However timely detection, evaluation and early referral to a transplant center remains the key to good results.

Conflict of interest : None

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