

Decompensated Liver Disease: Liver Transplantation is the Best Option, Not the Last Option

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ABSTRACT

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The incidence of end stage liver disease and liver transplantation is on the rise in Kerala. All practicing doctors should have an insight into the indications, contraindications, evaluation leading to and complications following liver transplantation. Liver transplantation is now an accepted modality of treatment in end stage liver disease and hepatocellular carcinoma. With potent immunosuppression and newer surgical techniques the 5 year survival rate following liver transplantation is above 75%. It is higher than that for surgeries for most gastro-intestinal cancers. The process to reach liver transplantation starts with early referral to the transplant centre, where extensive investigations performed. Once the patient is accepted into the waiting list, then prioritization for the transplant relies on the MELD score as well as matching the blood group and patient size. Immunosuppression after transplant requires a balance between prevention of graft rejection and minimization of the side effects of immunosuppressive drugs. Lifelong after-care is crucial for long-term graft and patient survival after liver transplantation.

Keywords: End stage liver disease, Early referral, MELD score, Better immunosuppression, Cirrhosis Liver, Liver Transplantation, Hepatocellular Carcinoma, Acute liver failure, Metabolic liver diseases

*See End Note for complete author details

INTRODUCTION

Liver transplantation (LT) is now a standard of care therapy for well selected patients with end-stage liver disease (ESLD), acute liver failure (ALF), acute on chronic liver failure (ACLF), and hepatocellular carcinoma (HCC) (Table-1).¹ Liver transplantation (LT) should be considered for any patient in whom anticipated overall survival following LT exceeds life expectancy of the underlying disease or where a significant increase in quality of life can be achieved.²

The first successful LT was done by Thomas Starzl in 1967.³ Over the past 50 years, advent of potent immunosuppressive agents, refinement of surgical techniques and better understanding of peri-operative care have improved the survival rates following LT. At present the one year survival following LT is 90% and the 5 year survival rates following is more than 75%.⁴ In Kerala the first liver transplant was done by Dr Sudhindran in 2004. Since then we have come a long way and nearly 100 liver transplants happen each year in the state. With better expertise, good patient selection and vigilant post operative care, our results match with that of the western world.

Who requires a liver transplantation

The major causes for End stage liver disease in Kerala are alcoholic liver disease, Non-alcoholic steatohepatitis (NASH) and chronic viral hepatitis (B and C) (Table 1). Autoimmune hepatitis, chronic cholestatic liver disease (PBC and PSC) and inherited liver diseases are less common in the state. Despite significant improvements in the medical management of the complications of liver cirrhosis including hepatocellular carcinoma, liver transplantation (LT) remains the only definitive treatment option for patients with end-stage liver disease.⁵

LIVER CIRRHOSIS

Liver cirrhosis is the end result of many chronic diseases affecting the liver. Cirrhosis is defined histologically as altered liver architecture characterized by bridging fibrosis and formation of regenerating nodules.^{6,7} For the clinicians cirrhosis is a syndrome complex characterized by portal hypertension and metabolic abnormalities (synthetic and detoxification) in liver function. Cirrhosis of liver has two stages, the

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Table 1. Indications for liver transplantation	
Acute liver failure	
Toxins and Drugs	
Acute Viral Hepatitis	
Acute presentation of Wilsons disease, autoimmune hepatitis and Budd Chiari Syndrome	
Chronic decompensated liver failure:	
Noncholestatic decompensated liver disorder	
Hepatitis B/C	
Alcoholic liver disease	
Non Alcoholic steatohepatitis	
Budd Chiari Syndrome	
Autoimmune hepatitis	
Polycystic liver disease	
Cholestatic decompensated liver disease	
Primary biliary cirrhosis (PBC)	
Primary sclerosing cholangitis (PSC)	
Secondary biliary cirrhosis	
Biliary atresia	
Alagille Syndrome	
Liver-based metabolic conditions causing systemic disease	
Primary oxaluria	
Familial amyloidosis	
Alpha-1-antitrypsin deficiency	
Wilson's disease	
Hemochromatosis	
Urea cycle enzyme deficiencies	
Glycogen storage disease	
Tyrosemia	
Familial Hypercholestrolemia	
Porphyria	
Malignant disease involving the liver	
Hepatocellular carcinoma (Within established Criteria)	
Hepatoblastoma	
Epitheloidhemangioendothelioma	

compensated cirrhosis and decompensated cirrhosis. During compensated cirrhosis the patient is usually asymptomatic or has only minimal symptoms like pedal oedema or fatigue which are often missed.^{8,9} The diagnosis of compensated cirrhosis is often incidentally

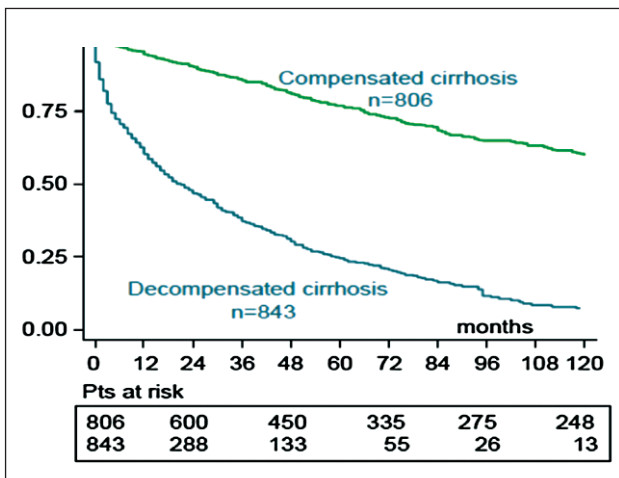


Figure 1. Survival of compensated versus decompensated cirrhosis at diagnosis. (From D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:219;)

Table 2. Child Pugh Turcotte (CTP) Score			
Parameters	Points		
	1	2	3
Serum Bilirubin(mg/dl)	2.0	2-3	>3.0
Serum Albumin(g/dl)	>3.515	2.8-3.5	<2.8
Prothrombin Time (Prolongation (s))	1-4	5-6	>6
Hepatic encephalopathy	None	Minimal	Advanced
Ascites	None	Slight	Moderate
One and two year survival based on CTP Score			
Class	1 yr	2 yr	
A (5-6 points)	100 %	85 %	
B (7-9 points)	80%	60%	
C (10-15 points)	45%	35%	

Data from Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG. The liver and portal hypertension. Philadelphia: Saunders; 1964.p.50-64

tally made when patient is evaluated for some other disease. Compensated cirrhosis should be suspected and evaluated for in any patient who presents with pedal oedema, low albumin, low platelet count, deranged liver enzymes and long standing risk factors for cirrhosis like alcohol, DM, Obesity, viral hepatitis B/C or family history. Decompensated cirrhosis presents with jaundice, ascites, variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis or hepatorenal syndrome. Natural history studies of cirrhosis find that the development of decompensation is associated with a decreased median survival from greater than 12 years to 2 years.^{8,9,10} Once decompensation occurs the prognosis without LT is poor (**Figure 1**). The survival of patients with decompensated cirrhosis at 2 years is only 50%.^{8,10} In the current era the 5 year survival after LT is 75% and any patient with decompensated liver disease should be referred for liver transplantation.⁴

The severity of cirrhosis is assessed using various scoring systems. Most widely used ones are the Child-Pugh- Turcott (CTP) scoring and the Model for end stage liver disease (MELD) score. Child-Turcotte-Pugh (CTP) score is widely used to prognosticate patients with cirrhosis (**Table 2**). Although empirically derived, the CTP has been shown to accurately predict outcomes in patients with cirrhosis and portal hypertension.¹¹ The CTP scoring system incorporates five parameters: serum bilirubin, serum albumin, prothrombin time, ascites, and grade of encephalopathy.^{6,7,11} Based on the sum of the points from these five parameters, the patients are categorized into one of three CTP classes: A, B, or C. Studies involving cirrhotic patients have shown that a patients' CTP score can estimate risk of death at 3-months and 1-year

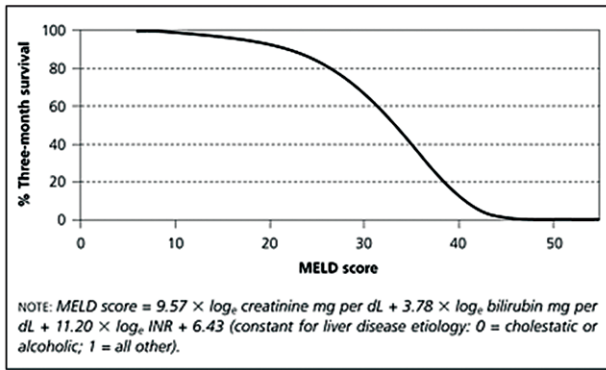


Figure 2. MELD score and survival

and 2-year survival. The two year survival of cirrhotic patients in CTP class A, B, and C are 90%, 70% and 35% respectively.^{6,7,11} Patients with cirrhosis and a CTP score of greater than or equal to 7 should be referred for a liver transplantation evaluation.

MELD is a mathematical model using bilirubin, INR and creatinine. MELD (Figure 2) was initially used to assess three month mortality following Transjugular intrahepatic portosystemic shunting (TIPS).¹² Later it was validated to predict mortality in patients awaiting liver transplantation. MELD is a numerical score ranging from 6 (mildly ill) to 40 (seriously ill). Higher the MELD, greater the mortality and a MELD score more than 15 indicates a one year survival less than 85%.^{12,13,14}

All patients diagnosed to have liver cirrhosis should be prognosticated using CTP or MELD score and patients with higher MELD counseled regarding liver transplantation. American association of liver disease recommends referral for liver transplantation evaluation if CTP score is more than 7 or MELD score is more than 10.¹⁰ CTP and MELD score also helps to assess prognosis in cirrhotics planned for surgeries, TIPS and treatment of Hepatocellular carcinoma.¹⁴

Acute Liver Failure

Acute liver failure is a rare but potentially catastrophic event leading to death unless recognition and effective medical management including intensive care support is instituted early in the disease course. American association for study of liver disease (AASLD) defines acute liver failure as coagulopathy (INR 1.5) and encephalopathy within an illness timeframe of 26 weeks in patients who previously had no liver disease.¹⁵ Acute liver failure due to Acetaminophen over dose is common in the west, where as viral hepatitis, anti-tubercular drugs (ATT) and alternative medicines are the most common cause for acute liver failure in Kerala. ALF due to viral hepatitis usually occur in

Table 3. Prognostic Indicators in ALF

King's College Criteria ¹⁷	
Paracetamol (acetaminophen) overdose	Non-paracetamol aetiology
<ul style="list-style-type: none"> pH <7.3 (irrespective of encephalopathy) Or All of the following: <ul style="list-style-type: none"> Grade III--IV encephalopathy Creatinine >300umol/litre (3.4mg%) Prothrombin time >100 seconds (INR>6.5) Or arterial lactate > 3.5 mmol/L at 4 hours Or arterial lactate >3 mmol/L at 12 hours (after fluid resuscitation) 	<ul style="list-style-type: none"> Prothrombin time >100 seconds (INR>6.5) Or Any 3 of the following: <ul style="list-style-type: none"> Age <10 years or >40 years Prothrombin time >50 seconds (INR>3.5) Bilirubin >300umol/litre (>17.6mg%) Time from jaundice to encephalopathy >7 days Non-A,Non-B hepatitis, drug-induced Acute liver failure

Clinchy's Criteria¹⁸

- Coma and confusion (encephalopathy grade 3 or 4) and
 - Factor V , 20% if age under 30 years or
 - Factor V , 30% if age over 30 years

ALF early dynamic model (ALFED) ¹⁹	Score
Variables over first three days	
• Hepatic encephalopathy persistent or progressed to > Grade 2	2
• INR- Persistent or increased to ≥ 5	1
• Arterial ammonia Persistent or increased to ≥ 123 mmol/L	2
• Serum bilirubin Persistent or increased to ≥ 15 mg/dl	2

ALFED score \geq has high positive predictive value and negative predictive value

MELD Score^{20,21}

Serum bilirubin, serum creatinine and INR
 $10 * ([0.957 * \ln(\text{creatinine})] + [0.378 * \ln(\text{bilirubin})] + [1.12 * \ln(\text{INR})]) + 6.43$

elderly, pregnant women and those with underlying liver disease.¹⁶

In acute liver failure, appropriate organ allocation demands that accurate assessment of prognosis be made in a timely and dynamic way. Various scoring systems are available which predict who will benefit from LT and who will recover without a LT (Table 3).¹⁷⁻²¹ The King's College Hospital criteria (KCH) remains the most widely utilized for those with acetaminophen-induced ALF and non-acetaminophen-induced ALF. In practice, such scoring systems only provide a general guidance and clinical judgement should take precedence. Outcomes of liver transplantation for ALF are comparable to those performed for other indications.²²

Hepatic malignancies

Liver transplantation for malignant disease is a medical and ethical challenge because of questionable long term outcome and donor organ shortage. Childhood hepatoblastoma,²³ epitheloidhemangioen-

dothelioma²⁴ and limited hepatocellular carcinoma (HCC)²⁵ without vascular invasion and extra hepatic spread are standard indications for liver transplantation.²⁶

Hepatocellular carcinoma (HCC) is a major cause of cancer related morbidity and mortality. Surgical treatment of hepatocellular carcinoma confined to liver includes hepatic resection and liver transplantation. Liver transplantation has the advantage that it removes the underlying carcinogenic liver, restores liver function and provides the widest possible resection margins.²⁷ The major limitations for liver transplant are the low availability of donor organs and risk of tumour recurrence with immunosuppression. Major predictors of tumour recurrence post-transplant are the size and number of tumours pre-transplant. Mazzaffero et al²⁸ in 1996 showed that patients with a single lesion less than 5cm or up to 3 lesions each less than 3 cm (Milan criteria) have 4 year recurrence free survival of 83% and overall survival of 75%. Currently most major transplant centers follow the Milan criteria for selection of HCC candidates for LT. Patients diagnosed with HCC exceeding the Milan criteria can still be candidates for liver transplantation, depending on local or national allocation guidelines.

All patients with HCC confined to the liver should be evaluated for transplantation, because there are increasing options for those with tumours that exceed the Milan Criteria. It has been shown that extending the size limits beyond the Milan Criteria may be possible without sacrificing survival outcome. The University of California, San Francisco criteria²⁹ (1 lesion less than 6.5 cm or 2-3 lesions each less than 4.5 cm with total tumour size less than 8 cm) is one expansion model with similar 5-year post-transplant survival rates compared with the Milan criteria (86% vs. 81%). The use of extended HCC criteria for transplant is not the current standard of care and will vary in different centres.

The down staging of HCC with loco-regional therapy [Radiofrequency ablation (RFA), Transarterial chemo-embolization (TACE)] may allow for transplant in patients who are initially outside of the Milan criteria.³⁰ Also if the waiting period is more than 6 months, a down-staging loco-regional treatment modality may be used to prevent disease progression. Patients diagnosed with HCC who are within the Milan Criteria are automatically assigned a MELD priority score depending on national policies in the west.³⁰ Frequently, these patients have low calculated MELD scores and exception points afford them the

chance to receive a donor organ.³⁰

Living-donor liver transplantation (LDLT) will offer a treatment option for selected HCC patients to minimize waiting time or enable liver transplantation in tumours exceeding the Milan criteria.³¹ While the use of LDLT for HCC within Milan criteria is well established, expanding the criteria is still controversial and not based on robust data.³²

Evaluation of potential recipient and listing for liver transplantation

Once a patient is referred for LT, he is evaluated by an interdisciplinary team consisting of Transplant surgeon, hepatologist, intensivist, anaesthetist, social worker and transplant coordinator. The interdisciplinary team have to answer several medical, psychosocial and ethical questions prior to accepting the patient for transplant evaluation.¹⁰ The foremost questions to be answered are (1) does the patient have an irreversible liver disease that warrants a liver transplantation. Have we tried all medical options for him? (2) is the patient fit enough to survive the surgery and immediate post operative period, (3) what is the etiology of liver disease, how severe is it (CTP, MELD score) and are there any complications, (4) does he have any contraindications to LT, (5) will he have a better survival and good quality of life after LT (6) will he be compliant to the medical treatment after transplantation (7) does the patient have the psychosocial and financial support to undergo LT (8) in alcoholics and drug abusers what are their chances of remaining abstinent lifelong. LT is a complex and resource intensive procedure and there should be a lifelong commitment from the recipient and family to be compliant to post LT follow up and management.¹⁰

Once it has been decided to accept the patient for LT, he/she undergoes an extensive evaluation prior to placing them on waiting list (**Table 4**). Many of the comorbidities are found out only on pre transplant evaluation and have to be tackled prior to listing for LT. As the age of the recipient advances there is high risk for cardiovascular diseases which have to be looked for and treated.³³ Many of the cirrhotics are obese and advised weight reduction prior to transplantation.³⁴ Diabetic control should be optimal as it can be difficult to control diabetes post LT.³⁵ Patient's are evaluated for portopulmonary hypertension and hepato-pulmonary syndrome as it might have adverse bearing on the surgery.^{36,37} Hepatorenal syndrome is reversible after LT, but patient's suspected to have advanced chronic kidney disease are evaluated for

Table 4. Pre-transplantation evaluation	
Medical Evaluation	Confirm diagnosis of liver disease Confirm the need for liver transplantation Treat etiology and complications Optimize medical management
Laboratory Tests	Complete blood count, renal function test, liver function test electrolytes, calcium, phosphorus, magnesium, coagulation profile, hepatitis serology, markers of auto-immune, inherited and metabolic liver diseases, CMV,VZ, EBV,RPR,HIV, 24hr urine protein, urine routine, creatinine clearance, blood culture, urine culture, blood grouping and Rh typing, thyroid function tests
Cardiac evaluation	Electrocardiogram, 2D Echocardiography, Stress testing Coronary angiography if stress tests abnormal or high risk for CAD Right heart catheterization if pulmonary pressures abnormal on Echo Cardiology consultation
Radiology	Abdominal ultrasound with Doppler Contrast enhanced liver imaging CT of Chest and PNS Bone mineral density
Surgery evaluation	Any surgical contraindications to transplantation, Any Grafts/reconstruction required
Anaesthesia evaluation	Is the patient fit for surgery
Pulmonology	Chest X-ray, Pulmonary function tests Arterial Blood Gas analysis
Age appropriate cancer screening	PAP smear, mammogram (females) PSA (Males) Colonoscopy
Dental Clearance	OPG
ENT Clearance	Nasal swab, CT PNS
Infectious disease	Vaccinations. Antibiotic policy
Financial counseling	Transplant cost and post-transplantation treatment cost
Nutritional assessment	Counseling regarding diet
Psychosocial assessment	Psychiatric illness, adjustment disorders, substance abuse, social support

combined or sequential liver-kidney transplantation.^{38,39} All patients with HCC are evaluated for size and number of tumors, vascular invasion and extrahepatic spread. Candidates are advised to abstain from alcohol, smoking and substance abuse. Patients with Alcohol related liver disease should be abstinent from alcohol for at least six months prior to placing them on waiting list.⁴⁰ The six month period is arbitrary and allows time for liver to recover from alcohol induced injury and thus prevent an unnecessary transplant. This period also helps us to identify people at increased risk of recidivism and give intense counseling and therapy.^{41,42} Malnutrition is more common than obesity and is multifactorial. It can be due to a combination of reduced appetite, ascites, catabolic chronic disease and aetiology specific nutritional disorders.⁴³ All patients planned for LT should be counseled by a dietician regarding calorie and protein intake as well as assessed for need of enteral or paren-

teral nutrition.⁴⁴ Incidence of osteoporosis in cirrhosis is as high as 55%.⁴⁵ Bone mineral density decreases further early post transplant and increases the risk of fractures. Bone mineral density should be checked for patients evaluated for LT and calcium and Vit D supplemented.⁴⁵

Hepatic dysfunction is a major risk factor for infections and all pre-transplant candidates should be screened for active infections. All active infections should be controlled before listing the patient. Screening for HBV, HCV, HIV, and prior infection with HAV, EBV, CMV, Varicella and latent tuberculosis should be done.⁴⁶ All patients should be vaccinated against hepatitis A, hepatitis B, Influenza (inactivated), Tetanus, Pertusis (Tdap), Pneumococcus (polyvalent), Meningococcus, Varicella Zoster (IgG-Neg) and Human Papilloma Virus (females).⁴⁷ Latent tuberculosis will require treatment as per institutional protocol. Depending on the age of the recipient and institutional protocol screening for extrahepatic malignancies is mandatory.¹⁰ Pre-transplant psychosocial evaluation should look at (1) presence of active psychiatric illness or substance abuse, (2) evidence of compliance with medical advice and (3) adequate social support. However, even the most psychiatrically complex patient have a successful outcome with proper evaluation and preparation, as well as adequate social support.⁴⁸ All candidates for LT should have a financial counseling regarding the expected cost of pre-transplant work up, transplant surgery and post-transplant care.

After extensive evaluation, the final listing of the patient is done by an interdisciplinary team consisting of transplant surgeons, transplant hepatologists, anaesthesiologists, intensivists, infectious disease specialist's, radiologists, transplant coordinators, and psychiatrists. All participate in the decision of listing the patient formally for transplantation.¹⁰ Candidates who have a suitable live donor are listed for live-donor liver transplantation (LDLT). Others are placed on the cadaver organ waiting list for deceased-donor liver transplantation (DDLT).

Once the patient is listed for a cadaveric liver transplantation the organ allocation is based on blood group, graft size and the model for end stage liver disease (MELD) scores of the recipients.¹² The donor and recipient should be of the same blood group. The donor organ should match the size of the recipient. Both too large and too small grafts can cause post transplantation problems. Weight of the donor organ must be at least 0.8% of recipient weight. Patients with

higher MELD have more severe disease more preference on the waiting list.^{12,13,14}

In Kerala state the cadaver organ waiting list is managed by the Kerala network for organ sharing (KNOS <http://www.knos.org.in>). KNOS is the nodal authority for cadaver organ allocation in Kerala. All potential candidates have to be registered with KNOS. KNOS follows a center based allocation system. The cadaveric organ is allocated to each transplant center by turn and the transplant team decides which recipient on their waiting list receives the organ based on blood group, MELD scores and graft size.

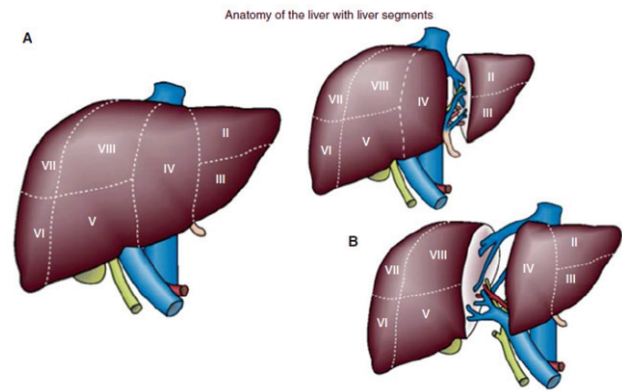
MANAGEMENT WHILE ON WAITING LIST

All patients on the transplant list should be managed with the assistance of a transplant hepatologist. The aims are obviously to avoid unnecessary complications of cirrhosis as far as possible, manage complications when they occur and screen for changes in the medical condition such as worsening hepatic function or HCC that might change the priority for transplantation. We should make sure that the patient is in the best possible condition when a donor organ becomes available. Any condition that can change the position of patient in the waiting list should be watched for. Patients with higher MELD require closer follow up than patients with lower MELD. While on waiting list if the disease progresses to such an extent such that candidate cannot withstand a major surgery or the survival benefit following transplant no longer holds, then it may be better to delist the patient. Patients on waiting list who resume alcohol or substance abuse should be delisted. Temporary inactivation is done for listed candidates who have clinical deterioration leading to mechanical ventilation, hemodialysis or who develop active infection.

LIVER TRANSPLANTATION SURGERY

Orthotopic liver transplantation (OLT) involves removing the recipients liver by dissecting it out from inferior vena cava, hepatic artery, portal vein, bile ducts and replacing it with a whole graft or a partial graft. The donor organ (graft) can be from a deceased donor (brain dead) when it is called deceased-donor liver transplantation (DDLT) or from a living donor (relative) when it is called a living-donor liver transplantation (LDLT).

In Kerala 80% of liver transplantations are Living-donor liver transplantation (LDLT). The advantage of



Anatomy of Liver: A- Left lateral segment of Pediatric LDLT, B- Right lobe graft for adult LDLT

Figure 3. Liver Segments

LDLT is the use of an optimal healthy donor, minimal ischemic time, elective surgery, and timing of transplantation as per recipients needs. A further advantage of LDLT is the possibility of ABO-incompatible transplantation.⁴⁹ However, the donor has a risk of 30% morbidity and a mortality risk of up to 0.8%.^{50,51} The risk to the recipient must equal or exceed risk to the donor to justify a LDLT.⁵²

LDLT is possible because of segmental anatomy of the liver (**Figure 3**). Surgeons are able to create grafts of varying sizes depending on the recipients and donors requirement for liver mass.⁵³ For all LDLT, careful selection and extensive evaluation of the donor are very important. A precise imaging evaluation with three phase CT angiography and volume measurement of the future liver remnant of the donor as well as of the graft size have to be performed. The remnant liver volume should be adequate for the donor and the remaining liver in the donor regenerates within 3 months to 90% of its original volume. The graft size should be 0.8% of recipient body weight or 40% of recipient's standard liver volume (SLV) to avoid risk of small for size syndrome.⁵³ Thus LDLT is surgically more demanding and with some risk to the healthy donor.^{55,56,57}

In DDLT brain death in donor is usually due to a large stroke or massive trauma to the head from blunt injury (as in, impact to the head in a road traffic accident). The trauma has stopped all brain function although other organs including the liver may continue to function normally. There are strict definitions as to what constitutes brain death based on the complete absence of any type of brain function. Because patients that meet criteria for brain death are legally dead, they are appropriate organ and tissue donors. In Kerala state brain death has to be certified by two independ-

ent neurologists approved by the government. Once a person is declared brain dead the family must provide consent for organ and/or tissue donation. In other countries, such as France, consent for organ donation is presumed and allowed, unless the family objects. In Kerala state brain death certification and organ donation is governed by Kerala network for organ donation (KNOS <http://www.knos.org.in>).

The sequence of events in a liver transplantation surgery involves removal and preparation of donor liver, mobilization of recipient liver, isolation and transaction of recipient liver from inferior vena cava, portal vein, hepatic artery and common bile duct, removal of recipient liver and implantation of donor liver in the recipient. Depending upon the donor and recipient anatomy the inferior vena cava, the portal vein, the hepatic artery, and the bile duct are connected or reconstructed.⁵⁴ First the venous out flow is re-established by connecting the donor and recipient inferior vena cava, and then the donor organ is reperfused by joining the portal veins and finally the hepatic arteries. Once the organ is well perfused the biliary drainage is achieved by joining the donor bile duct to the recipient's bile duct or the small bowel depending on the anatomy or recipient disease.^{57,58}

POST TRANSPLANTATION CARE

Lifelong aftercare is crucial for long-term graft and patient survival after liver transplantation. During the early postoperative phase, daily blood tests are necessary for surveillance of liver function, coagulation, electrolytes, infections and target blood levels of immunosuppressive drugs. Prophylactic antibiotic therapy is given perioperatively. Prophylactic treatment for CMV, fungus and Pneumocystiscarinii (PCP) infections should be given according to the donor/recipient risk profile. Daily Doppler sonography is performed to assess hepatic artery, portal vein and hepatic vein blood flow in the initial few days.⁵⁹

Immunosuppression after transplant requires a balance between prevention of graft rejection and minimization of the side effects of immunosuppressive drugs. Commonly used immunosuppressants include, calcineurin inhibitors like cyclosporine and tacrolimus, mTor inhibitors like everolimus and sirolimus, mycophenolatemofetil (MMF), Azathioprine, basiliximab (chimeric monoclonal T-cell IL-2-receptor Antibody) and steroids.^{60,61} Calcineurin inhibitors are the back bone of immunosuppressive therapy. Initial few months patient's are on triple regime consist-

Table 5. Post liver transplantation Complications

Early Complications

Hemorrhage
Primary nonfunction
Early graft dysfunction
Acute cellular rejection
Hepatic artery Thrombosis
Portal vein Thrombosis
Hepatic vein thrombosis
Biliary stricture
Biliary leak
Infections (Bacterial, Viral, Fungal)

Late Complications

Recurrence of disease (HCV, HBV, NASH, Autoimmune diseases)
Chronic rejection
Biliary strictures
Metabolic syndrome (HT, Dyslipidemia, Diabetes, coronary artery disease)
Malignancies (Skin, Post transplantation lymphoproliferative diseases)
Immunosuppression side effects

ing of a calcineurin inhibitor, MMF/mTor inhibitor and steroid (Methyl Pred/Prednisolone). Steroids are tapered and stopped by 3 months unless patients have a rejection episode or etiology for liver disease is autoimmune (AIH/PBC/PSC).^{60,61} MMF/mTor inhibitor is stopped by one year and patient is continued on calcineurin inhibitor lifelong unless contraindicated.⁶² mTor inhibitors are preferred over MMF in patients with HCC because of their anti-neoplastic property.⁶³ Basiliximab induction is used in patients at risk of renal dysfunction as it helps to delay the introduction of calcineurin inhibitors.⁶⁴ Because immunosuppressive drugs can interact with many other medications and dietary components, target levels must be checked lifelong on a regular basis, and interactions must be considered when new medications must be introduced.

Immediate Post transplantation complications

The complications that can occur immediately after a LT include (**Table 5**) (1) Primary non-function or poor function of the newly transplanted liver which occurs in approximately 1-5% of new transplants. Indicators of good graft function are hemodynamic stability, awakening from anaesthesia, lactate clearing, INR improving, no hypoglycemia and normothermia. If the function of the liver does not improve sufficiently or quickly enough, the patient may urgently require a re-transplant,^{65,66,67} (2) Hepatic artery thrombosis occurs in 2-5% of all deceased donor transplants. The risk is doubled in patients who receive a living donor transplant,⁶⁸ (3) Ischemic reperfusion injury usually manifests as rise in transaminases post operatively which settles over time. INR is usually stable

Table 6. Common side effects of Immunosuppression	
Drug	Adverse effect
Tacrolimus	Nephrotoxicity, neurotoxicity, diabetes, hyperkalemia, metabolic acidosis, hypertension, hyperlipidemia
Cyclosporine	Nephrotoxicity, neurotoxicity, diabetes, hyperlipidemia, gingival hyperplasia, hypertrichosis, hypertension, hyperkalemia, metabolic acidosis
MMF	Myelosuppression, gastrointestinal side effects, viral infections (CMV, HSV), spontaneous abortions in pregnant women
Sirolimus	Hyperlipidemia, myelosuppression, proteinuria, poor wound healing, pneumonitis, skin rash
Corticosteroids	Diabetes, hypertension, obesity, osteoporosis, avascular necrosis, growth retardation, Cushingoid features, psychosis, poor wound healing, adrenal suppression, cataracts

and correctable with plasma,^{65,66} (4) Portal vein thrombosis is infrequent and can be managed surgically or radiologically,⁶⁵ (5) Biliary complications: can be biliary leak or biliary stricture. Biliary complications are tackled by ERCP and placing a stent across the leak or stricture till it heals,^{69,70} (6) Bleeding is a risk of any surgical procedure but a particular risk after liver transplantation because of the extensive nature of the surgery and pre existing coagulopathy. In general, approximately 10% of transplant recipients will require a second operation for bleeding, essentially most of these can be managed conservatively,⁶⁵ (7) Infection - Infections can occur during the healing of the wound created by any operation. The base line immunosuppressive state and immunosuppression medications increase the liver transplant recipient's risk for developing an infection after transplantation,⁶⁵ (8) Rejection: Acute cellular rejection occurs in 25-50% of all liver transplant recipients within the first year after transplantation.⁷¹ Rejection typically causes no symptoms and the first sign is usually abnormally elevated liver laboratory test results. When rejection is suspected, a liver biopsy is performed. The first line of treatment is high dose corticosteroids. A small proportion of acute rejection episodes, approximately 10-20%, does not respond to corticosteroid treatment and are termed "steroid refractory," requiring additional treatment.⁷¹

Long term care and complications

The long term aftercare focuses on screening for complications and side effects of immunosuppressive therapy (Table 6), opportunistic infections, acute or chronic rejection, screen for malignancy and recurrence of disease in the graft. Patients on long term immunosuppressants run the risk of metabolic syndrome

and should have good control of their blood sugars, lipids and body weight.⁷²

Some of the processes that led to the failure of the patient's native liver can damage the new liver and eventually lead to graft failure. The most common ones are hepatitis B and C.⁷³ In patients who develop HCV recurrence post-transplant, treatment with direct acting anti-virals (DAA's) achieve a sustained virologic response rate to the tune of 96% across all genotypes.^{74,75} The peri-transplant use of Hepatitis B immunoglobulin and oral antivirals has reduced the rate of HBV recurrence from 80% to less than 10%, but it comes with a very high cost.⁷⁶ The use of newer oral antivirals has been shown to permit a hepatitis B immunoglobulin free regimen for post-transplant prophylaxis.⁷⁷ With the use of HBIG and oral nucleos(t)ide therapy, the 5-year graft survival for those transplanted for HBV is 85% and retransplantation for recurrent HBV cirrhosis is rare.⁷⁸

Several other diseases may also recur after transplantation, but typically the disease is mild and only slowly progressive. Autoimmune hepatitis, Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) recur approximately 10-20% of the time and, only very rarely, result in recurrent cirrhosis and end stage liver disease.⁷⁹ Fatty liver disease can occur in those transplanted for NASH but also in patients who were transplanted for other indications and develop risk factors for fatty liver disease.⁸⁰

LT recipients are on long term immunosuppressants and are at increased risk of infections and cancers.⁷² The risk of opportunistic infections like CMV, PCP and Tuberculosis is maximum during 1 to 6 months post liver transplantation. Long term immunosuppressant's increases the risk for cancers like post transplant lymphoproliferative disorder (PTLD) and skin cancers. All transplant recipients must undergo screening for cancers as per age and sex.⁷² Chronic rejection occurs in 5% or less of all transplant recipients. Today, with our large selection of immunosuppressive drugs, chronic rejection is more often reversible.⁷²

As the results after LT continued to improve over the last few decades, increasing attention has been directed toward management of preexisting or de novo chronic medical conditions and some unique long-term complications of LT. LT recipients are known to have an increased risk of metabolic syndrome including obesity, diabetes, hypertension, hyperlipidemia, and cardiovascular disease. Management of these chronic medical conditions and their risk factor modifica-

tion are critical to ensure continued excellent graft function and overall survival of the recipient decades after transplant.⁸¹

CONCLUSION

Liver transplant is now an accepted treatment for not just end stage liver disease and HCC, but also for certain metabolic conditions and symptomatic liver disease. Significant progress has been made over the last 2 decades with regard to allograft and patient survival, and OLT has had a favorable impact on chronic liver disease mortality. The process to reach liver transplantation starts with early referral to the transplant centre, where extensive investigations are performed. Evaluation includes a detailed medical evaluation to make sure that transplantation is technically feasible, medically appropriate, and in the best interest of both the patient and family.

Once the patient is accepted into the waiting list, then prioritization for the transplant relies on the MELD score as well as matching the blood group and patient size. It is also important to recognize that not all patients with end stage liver disease or its complications are suitable for liver transplantation. Finally medical management of the patient on waiting list is crucial to optimize the patient's condition prior to transplantation.

END NOTE

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Key Messages

1. Liver Transplantation is the standard of care for selected patients with end stage liver disease and hepatocellular carcinoma.

2. Early counseling and referral to a transplant center is the key to success of liver transplantation.
3. Pre-transplant evaluation includes a detailed multidisciplinary evaluation to make sure that transplantation is technically feasible, medically appropriate, and in the best interest of both the patient and family.
4. Lifelong aftercare is crucial for long-term graft and patient survival after liver transplantation.

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