7 Indication and Contraindications for Liver Transplantation

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Patients undergoing liver transplantation should benefit from the extension of life expectancy beyond the natual course of survival or should have an improved quality of life.

Liver transplantation is the treatment of choice for patients with decompensated liver disease, cirrhosis with liver cancer, liver-based metabolic conditions causing systemic disease.

Since the time, liver transplantation was first attempted, continuous refinements in surgical techniques and an in-depth understanding of the immunological role in the rejection and discovery of newer effective immunosuppressants have changed the perception of liver transplantation to a comparatively safer and standard procedure for patients with end-stage liver failure.

Acceptance of liver transplantation as a treatment of choice has broadened the indications for liver transplantation and an increase in referrals [1].

Graft liver can be obtained from either a living donor (LD) or deceased donor (DD). Rationing of the scarce resource is vital as also the requirement of a replacement in the affected patient.

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7.1 Indications

Indications can be classified into end-stage liver disease, fulminant liver failure, benign and malignant liver tumour [2] (Table 7.1).

7.1.1 Acute Liver Failure

Acute liver failure (ALF) is a potentially reversible, often sudden, persistent and progressive liver dysfunction characterized by the occurrence of encephalopathy within 4 weeks of symptoms in the absence of pre-existing liver disease [3]. ALF is relatively rare, but carries a short-term (3 week) mortality above 40%. However, if the patient survives, typically the liver recovers fully, both structurally and functionally (except in autoimmune hepatitis and Wilson's cases) [4].

Assessment is required to segregate patients who can survive with supportive measures alone or require liver transplantation (LT). Several models have been proposed to prognosticate patients with ALF. These include King's College Hospital (KCH) criteria, Clichy criteria, serum Group-specific component protein levels, liver volume on CT scanning, blood lactate levels, hyperphosphataemia, Acute Physiology and Chronic Health Evaluation II score, etcetera. Dynamic models like ALF early dynamic model (ALFED) [5] can also be used to stratify patients needing LT and to pre-

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Table 7.1 Indications for liver transplantation

Acute liver failure Hepatitis A/B Drug induced (eg. Paracetamol, Anti- Tuberculosis therapy, etc) Wilson's disease Budd–Chiari syndrome	
Chronic liver failure	
Noncholestatic cirrhosis Hepatitis B/C Autoimmune hepatitis Alcohol-induced cirrhosis	**Cholestatic cirrhosis** Primary biliary cirrhosis (PBC) Primary sclerosing cholangitis (PSC) Secondary biliary cirrhosis
Metabolic Wilson's disease Hemochromatosis α-1 Antitrypsin deficiency Amyloidosis Cystic fibrosis	**Vascular** Budd–Chiari syndrome
Other indications Primary oxalosis Glycogen storage diseases Hyperlipidaemia Polycystic liver disease	**Malignant disease** Hepatocellular carcinoma (HCC) Fibrolamellar carcinoma (FLC) Hepatoblastoma Epithelioid haemangioendothelioma Cholangiocellular adenocarcinoma Neuroendocrine liver metastases
Liver transplantation in paediatric patients Biliary atresia Byler's disease Alagille's syndrome Neonatal hepatitis/neonatal viral hepatitis Autoimmune hepatitis Hepatoblastoma	**Chronic liver failure** Tyrosinemia **Benign liver tumours** Adenomatosis

Table 7.2 King's College Hospital (KCH) criteria [6]

Paracetamol-induced ALF	Non-Paracetamol-induced ALF
Arterial blood pH < 7.30 (irrespective of the grade of encephalopathy) OR All of the following • Prothrombin time >100 s (INR >6.5) • Serum creatinine >3.4 mg/dl • Grade III or IV hepatic encephalopathy	Prothrombin time >100 s (INR > 6.5) (irrespective of the grade of encephalopathy) OR Any 3 of the following (irrespective of the grade of encephalopathy) • Age <10 or >40 years • Aetiology: non-A/non-B hepatitis, drug-induced • Duration of jaundice to encephalopathy >7 days • Prothrombin time >50 (INR > 3.5) • Serum bilirubin >18 mg/dl

dict mortality. Among the above, the King's College hospital criteria are the most validated and widely practiced guidelines across the world (Table 7.2).

The King's college criteria have a high positive predictive value (around 80% in paracetamol-induced ALF, 70–90% in non-paracetamol cases). Their negative predictive value is, however, lower (70–90% in paracetamol-induced ALF, 25–50%, only, in non-paracetamol induced cases) [4]. Nevertheless, the criteria will select around 20% of patients for OLT, who might have survived without LT. More importantly, perhaps, not meeting the criteria does not guarantee sur-

vival without a transplant, particularly in non-paracetamol cases [4].

Aetiologically, variations occur featuring a high incidence with paracetamol (acetaminophen) induced ALF in the West as compared to hepatitis viruses, specifically hepatitis E and B in Southeast Asia including India [5, 7]. Establishing an aetiologic diagnosis accurately is vital in the management of ALF as the diagnosis impacts scoring as well as therapeutic strategy and prognostication. Any patient meeting the above criteria should be offered LT as a treatment option.

Table 7.3 The Child-Pugh score

	Score		
Parameter	1	2	3
Ascites	None	Controlled	Refractory
Encephalopathy (grade)	None	1–2 (minimal)	3–4 (coma)
Bilirubin (micromol/L)	<34	35–50	>51
Albumin (g/L)	>35	28–35	<28
INR	<1.7	1.8–2.3	>2.3

7.1.2 Chronic Liver Disease

How to assess and determine the candidature for liver transplantation in patients with chronic liver disease.

Tools:

MELD (Model for End-stage Liver Disease)
CTP (Child Turcotte Pugh) score
UKELD (United Kingdom model for End stage Liver disease)
Disease-specific indices for primary biliary cirrhosis and sclerosing cholangitis
UNOS System

Referral for transplantation to be done for patients with cirrhosis when they develop evidence of hepatic dysfunction (CTP $\geq$ 7 and MELD $\geq$ 10) or when they experience their first major complication (ascites, variceal bleed or hepatic encephalopathy). Expedited referral for LT if a patient is diagnosed with type I hepatorenal syndrome [8] (Tables 7.3 and 7.4).

Table 7.4 Old UNOS system—classification of candidates [9]

Status	Characteristics
Status 1	Fulminant liver failure with life expectancy <7 days: 1. Fulminant hepatic failure as traditionally defined 2. Primary graft nonfunction <7 days of transplantation 3. Hepatic artery thrombosis <7 days of transplantation 4. Acute decompensated Wilson's disease
Status 2a	Hospitalized in ICU for chronic liver failure with life expectancy <7 days, with a Child-Pugh score of ≥10 and one of the following: 1. Unresponsive active variceal haemorrhage 2. Hepatorenal syndrome 3. Refractory ascites/hepatic hydrothorax 4. Stage 3 or 4 hepatic encephalopathy
Status 2B	Requiring continuous medical care, with a Child-Pugh score of ≥10, or a Child-Pugh score ≥7 and one of the following: 1. Unresponsive active variceal haemorrhage 2. Hepatorenal syndrome 3. Spontaneous bacterial peritonitis 4. Refractory ascites/hepatic hydrothorax, or presence of hepatocellular carcinoma
Status 3	Requiring continuous medical care, with a child-Pugh score of ≥7, but not meeting criteria for Status 2B
Status 7	Temporary inactive

MELD score equation = 9.57 × loge(creatinine) + 3.78 × Loge(total bilirubin) + 11.2 × Loge(INR) + 6.43 [10].

The Child-Pugh score should be reassessed periodically since the patient's clinical condition may improve or deteriorate with time (Table 7.5).

UKELD = [5.395 × INR] + [1.485 × Creatinine(micromol/L)] + [3.13 × Bilirubin(micromol/L)] − [81.565 × Sodium (mmol/L)] + 435

Table 7.5 Percentage of survival in cirrhotic liver disease

Child-Pugh grade	Child-Pugh score	1-Year survival (%)	5-Year survival (%)	10-Year survival (%)
A	5–6	84	44	27
B	7–9	62	20	10
C	10–15	42	21	0

7.1.2.1 Viral Hepatitis

Chronic liver disease secondary to infection with hepatitis C virus (HCV) and hepatitis B virus (HBV) is the most common indication for liver transplantation in the West. Listing in HBV infections for Liver Transplantation is done for patients with hepatocellular carcinoma (HCC) and well compensated Liver function and decompensated liver function with or without HCC [11]. Survival rates once decompensation (ascites, bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome) occurs falls to 50% at 5 years [12]. Chronic alcohol abuse accelerates the process. HCC develops at a rate of 3.4% per year in patients with HCV infection [13].

HBV infection acquired during birth or early life is a risk factor for developing cirrhosis and HCC.

7.1.2.2 Alcoholic Liver Disease

There is a reluctance for LT in alcoholic liver disease since patients themselves are responsible for their illness and are likely to resume alcohol after LT.

Severe alcoholic hepatitis which is nonresponsive to medication (Lille score ≥0.45) has a survival rate of 30% at 6 months. Hence LT is indicated after careful assessment of patient's addiction profile, though studies show recidivism up to 35% [14].

Alcoholic liver cirrhosis is one of the leading causes for end-stage liver disease and the most common indication for liver transplantation around the world. Broad consensus but though not a rule is for abstinence from alcohol for a duration of 6 months preceding LT, though there is a relapse in alcohol abuse even after 2 years of abstinence with geographical differences existing [15].

LT benefits most when a patient with alcoholic cirrhosis with Child's C status undergoes LT with a 5-year survival of 58% compared to 35% in patients without LT [16]. It is much more liberal when an alcoholic recipient is receiving a graft from a related living donor and not from the pool of deceased donors.

7.1.2.3 Cholestatic Liver Disease

These are a heterogeneous disorder group which can progress to biliary cirrhosis and LT is the only definitive therapy for patients in whom condition has progressed to end-stage liver disease.

Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis is a rare disease with an estimated 10-year survival approximating 65%. There is geographical variation in the number of LTs being done for PSC with highest done in Scandinavian and Nordic regions. The American Association for Study of Liver Disease recommends against using disease-specific models for predicting outcomes in individual patients [17]. Two unique indications for LT in PSC apart from indications of chronic liver disease are cholangiocarcinoma (CCA) and recurrent bacterial cholan-

gitis. About 25–50% of PSC patients waitlisted for LT may not have radiographic and/or histologic evidence of cirrhosis or complications of portal hypertension [18]. Patients with PSC may also develop longstanding cholestasis including weight loss, metabolic bone disease and refractory pruritis which resultantly lead to significant morbidity, which uniquely affects this group of patients [18].

Inclusion Criteria for Liver Transplantation in PSC

- Intraluminal brush or biopsy showing evidence of positive tumour cells or cells strongly suspicious for CCA, or
- Radiographically malignant appearing stricture, and one of the following criteria:
  - Ca 19–9 > 100 U/mL in the absence of acute bacterial cholangitis
  - Polysomy on fluorescence in situ hybridization (FISH)
  - Well-defined mass on cross-sectional imaging

Exclusion criteria for Liver Transplantation in PSC

- Evidence of extrahepatic disease or regional lymph node involvement
- Previous malignancy (excluding skin or cervical cancer) within the 5 years before a diagnosis of CCA
- Previous abdominal radiotherapy
- Uncontrolled infection before treatment
- A prior attempt at the surgical resection of the tumour leading to violation of the tumour plane
- Any medical condition precluding transplantation
- Any transperitoneal biopsy, including percutaneous and/or endoscopic ultrasound-guided FNA

Primary Biliary Cirrhosis (PBC)

PBC is a disorder of unknown aetiology and believed to have a genetic susceptibility, with a female predominance. PBC is characterized by fatigue and pruritis, which are common initial symptoms. Pathologically ductopenia is a characteristic feature of PBC. PBC is considered one of the best indicators for LT. EASL guideline suggests referral of patients to LT when serum bilirubin reaches 6 mg/dl, a Mayo risk score ≥7.8 and/or MELD score of 12 or higher is calculated. Exceptions to these are when a patient concomitantly has associated HCC, which develops in patients with cirrhosis (PBC 4–12% at 10 years) [19].

7.1.2.4 Malignancy

Hepatocellular Cancer (HCC)

Evolution of multidisciplinary approaches has resulted in a new era of Transplant Oncology, with the amalgamation of surgical oncology and transplant surgery. Substantial risk exists in patients with cirrhosis for development of hepatocellular malignancy which reaches up to 3% incidence per year and carries a dismal prognosis. Mazzaferro et al. in 1996 laid down Milan criteria in their original study and found that patients meeting the criteria (*patients with a single tumour ≤5 cm in diameter, or no more than three tumours ≤3 cm,*) had 4-year overall and recurrence-free survival of 85 and 92 per cent respectively. The Milan criteria are presently well-accepted and recommended guidelines for LT in HCC [20].

A considerable subset of patients who were excluded from strict Milan criteria would have had a better prognosis with LT; hence several extended criteria have been reported with acceptable outcomes. In acceptable outcomes such as Pittsburg criteria, University of California at San Francisco (UCSF) criteria and Up to 7 criteria (Table 7.6).

Downstaging of advanced HCC to reduce and comply within Milan or UCSF criteria with Transarterial Chemoembolization, Transarterial Radioembolization, and Radiofrequency ablation can achieve similar outcomes as those primarily fulfilling Milan/UCSF criteria.

Due to social and cultural practices existing in the East, there is a shortage of deceased donation and hence approximately 70% of LDLT recipients are from Asian countries, indirectly bearing advantages by reducing pre-transplantation waiting time for patients with HCC, alleviating ischaemic reperfusion injury and providing an optimal donor graft for those with end-stage liver disease [21].

Cholangiocarcinoma

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangio carcinoma is currently not an accepted standard indication, but as part of clinical trials with neoadjuvant chemotherapy and LT.

Table 7.6 Extended criteria for transplant in patients with HCC [21]

UCSF	Tumour ≤6.5 cm, or ≤3 nodules with the largest ≤4.5 cm and a total tumour ≤8 cm
Up-to-7	The sum of the tumour number and the size of the largest tumour no larger than 7 cm
Tokyo	Tumours no larger than 5 cm and no more than 5 nodules
Kyoto	Tumour ≤10 nodules, all ≤5 cm, and a serum DCP level ≤400 mAU/mL
Shanghai	Tumour ≤9 cm, or ≤3 lesions with the largest ≤5 cm, tumour ≤9 cm without macrovascular and lymph node invasion and extrahepatic metastasis
ASAN	Tumour ≤5 cm in diameter, ≤6 in nodule number, and free of gross vascular invasion

Table 7.7 New Wilson Index for predicting mortality [26]

Score	Bilirubin (μmol/L)	INR	AST (IU/L)	White cell count (10^9/L)	Albumin (g/L)
0	0–100	0–1.29	0–100	0–6.7	>45
1	101–150	1.3–1.6	101–150	6.8–8.3	34–44
2	151–200	1.7–1.9	151–300	8.4–10.3	25–33
3	201–300	2.0–2.4	301–400	10.4–15.3	21–24
4	>301	>2.5	>401	>15.4	<20

Hilar Cholangiocarcinoma (H-CCA)

Surgical resection is the standard care with the primary goal of R0 resection, in the absence of metastatic or locally advanced disease or PSC. Negative margins are obtained only in 60–80% of patients with long-term survival ranging from 20% to 40% at 5 years. Investigators from Mayo Clinic reported a 5-year survival of 82% after transplantation in selected patients including unresectable, solitary tumours, less than 3 cm in radial diameter, without evidence of lymph node metastases, and resectable disease in the setting of PSC [22].

Metastatic Neuroendocrine Tumours

Though there are multeity of choices for managing patients with metastatic neuroendocrine tumours including somatostatin or radioactive metaiodobenzyl-guanidine therapy, surgical excision, radiofrequency ablation among others, LT is primarily indicated in scenarios where (1) nonaccessible tumour for curative surgery or major tumour reduction, (2) tumours not responding to medical or interventional treatment and (3) tumours causing life-threatening hormonal symptoms [23].

7.1.2.5 LT in Metabolic Liver Disease

Wilson's disease (WD) is due to mutations which encode copper-transporting ATPase, resulting in accumulation of copper in affected tissues. Presentation varies widely with key features being liver disease and cirrhosis, neuropsychiatric disturbances and Kayser–Fleischer rings. The affected liver may present as acute or in chronic forms. Acute liver failure predominantly affects young females. Many patients may present with signs of chronic liver disease with decompensation. Neurological and psychiatric symptoms usually follow. Wilson's disease is universally fatal if untreated. Since biochemical defect lies in the liver itself, orthotopic liver transplantation corrects the underlying problem. Patients with revised WD prognostic index (RWPI)/revised King's College score for WD of >11 should be referred for LT in an acute setting. In chronic cases, LT is indicated as per MELD scores [24, 25] (Table 7.7).

7.1.2.6 Vascular Causes

Budd–Chiari syndrome (BCS) consists of a group of disorders characterized by hepatic venous outflow obstruction at the level of hepatic venules, large hepatic veins, inferior vena cava or right atrium. Characteristic features include abdominal pain, hepatomegaly and ascites. LT is indicated in likely situations of fulminant BCS, BCS with cirrhosis and failure of a portosystemic shunt. The five-year survival rate among patients with LT for BCS is as high as 95%. Complications after LT in BCS involve arterial and venous thrombosis and bleeding due to anticoagulation. However, multiple aetiologic factors may be present and therefore the recommendation is for long-term anticoagulation after LT [27].

7.2 Liver Transplantation in Paediatric Patients

Most common indications for LT in the paediatric age group include (1) Extrahepatic biliary atresia, (2) Intrahepatic cholestasis: sclerosing cholangitis; Alagille's syndrome; progressive familial intrahepatic cholestasis, (3) Metabolic diseases: Wilson's disease; α1 antitrypsin deficiency; Crigler–Najjar syndrome, (4) Acute liver failure, (5) Others; primary liver tumour and cystic fibrosis.

Biliary Atresia Single most common cause of liver failure in infancy and childhood. Kasai procedure is successful in one-half of all patients if jaundice is fully relieved. Primary LT is routinely not indicated unless the patient has signs of severe liver damage like coagulopathy, hypoalbuminemia and ascites.

Progressive Familial Intrahepatic Cholestasis (PFIC) This is a chronic cholestasis syndrome which begins in infancy and usually progresses to cirrhosis within the first decade of life.

Liver Tumours in Children Hepatoblastoma is the most common liver tumour in children and when non-resectable, transplantation is the treatment of choice [28, 29].

7.3 Contraindication

Contraindication, can be divided into relative and absolute [30] (Table 7.8).

Obesity Obesity Patients with BMI ≥ 40 (severe obesity) tend to have adverse outcomes post LT; hence it is a relative contraindication [31].

Age In the absence of significant comorbidities, the older recipient (>70 years) is not a contraindication for LT.

Portopulmonary hypertension (POPH) Mild and moderate POPH if controlled with medication are not contraindication for LT but severe POPH with pulmonary systolic arterial pressure ≥60 mm of Hg is considered a contraindication for LT in most centres.

Extrahepatic Malignancy Having an extrahepatic malignancy is a contraindication for liver transplantation. Having a tumour-free period of 2–5 years is accepted in general as a requirement before LT. Benten et al. [32] in their series of 37 patients with a history of various solid tumours and myeloproliferative disease and who underwent OLT, the overall recurrence rate was 2.8%. Such series have

Table 7.8 Contraindications for Liver Transplant

Absolute contraindications	Relative contraindications
• Brain death • Extrahepatic malignancy • Active uncontrolled infection • Active alcoholism and substance abuse • AIDS • Severe cardiopulmonary disease • Uncontrolled sepsis • Inability to comply with medical regimen • Lack of psychosocial support • Anatomic abnormalities precluding liver transplantation • Compensated cirrhosis without complications (Child-Turcotte-Pugh score, 5–6)	Advanced age Cholangiocarcinoma HIV infection Portal vein thrombosis Psychologic instability

been published more often now questioning the past wisdom of absolute contraindication in patients with extrahepatic malignancy. In the coming times, extrahepatic malignancy may not be an absolute contraindication when an appropriate selection of such patients is done and subjected to OLT.

Active Uncontrolled Infection Any sort of ongoing active infection in the body is an absolute contraindication for LT. LT may proceed after adequate control of infection.

HIV Infection HIV infection per se is not a contraindication for LT, in the era of highly active antiretroviral treatment (HAART). Though it requires well-coordinated team management by the transplant and HIV teams [8].

Anatomical Causes LT requires a viable mesenteric venous circulation; portal vein thrombosis is no more a contraindication. Portal vein thrombosis may be addressed with either thrombectomy or jump grafts.

Active Alcohol and Substance Abuse Ongoing alcohol or substance abuse is an absolute contraindication for LT. Existing shortage of organs and potentially harmful effects of alcohol relapse posttransplant necessitate providing LT only for deserving candidates. One of the risk factors for relapse is the shorter duration of pretransplant abstinence, hence the recommendation of 6 months minimum abstinence before LT.

Inability to Comply with Medical Regimen and Lack of Psychosocial Support Post LT complying with regular follow-up and investigations are mandatory for long-term survival of the graft and patient. Patients need psychosocial support for this lifelong compliance within the recommended lifestyle changes and adherence to the same [33].

7.4 Contraindications for Live Liver Donors as per OPTN (Organ Procurement and Transplantation Policy) [34]

Age less than 18 years with a lack of mental capacity for informed decision-making

HIV infection, unless the requirements for a variance are met

Active malignancy

High suspicion of donor coercion

High suspicion of illegal financial exchange between the donor and recipient

Evidence of acute symptomatic infection

Active mental illness requiring treatment before donation, including any evidence of suicidality

HCV RNA positivity

HBsAg positivity

Donors with ZZ, Z-null, null-null, and S-null alpha-1-antitrypsin phenotypes

Expected donor remnant volume less than 30 per cent of native liver volume

Prior living liver donation

In India, only a related donor will be considered for donation.

7.5 Summary

Organ availability is scarce and rationing the resource to suitable and eligible candidates is of prime importance. Patients should meet the recommended minimum criteria for LT and not have any of the absolute contraindications. The recommendations and guidelines are dynamic and with gradually increasing indications and declining contraindications. The King's College Hospital criteria are used globally for assessing the need for LT in acute Fulminant Liver failure. MELD and CTP score are used for non-malignant aetiology of cirrhosis for LT. The Milan criteria are presently used for eligibility in HCC patients.

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