Selection for Liver Transplantation

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Despite advances in the treatment of chronic liver disease (most notably viral hepatitis), cirrhosis remains the twelfth most frequent cause of death in the United States and results in 33,539 deaths annually.¹ Only a fraction of the individuals with advanced liver disease benefit from liver transplantation (LT), with approximately 7000 recipients per annum. Although innovations such as living and split donor transplantation have modestly enhanced transplant rates, only a substantial increase in the deceased donor pool will increase transplant activity. Currently, 17,000 people await LT, with more than 1500 wait-listed patients dying annually. The Model for End-Stage Liver Disease (MELD) score, an objective method adopted in 2002 for organ allocation in the United States, has resulted in a reduction of deaths on the waiting list. Despite the continuing debate about its application in some circumstances [e.g., hepatocellular carcinoma (HCC)], the MELD score has stood the test of time as an equitable system for the distribution of a scarce resource.

Indications (Table 1)

The commonest indication for LT in adults is decompensated cirrhosis, which in turn reflects the most frequent etiologies of chronic liver disease (Fig. 1); these include chronic hepatitis C virus (HCV), alcohol, cholestatic disease, and fatty liver disease. Another prominent indication for LT is small, nonresectable HCC.

Importantly, even though most adult LT recipients have cirrhosis in the absence of complications, its diagnosis does not imply a need for transplantation. Some simple clinical details, such as the presence of varices, ascites, infection, or renal failure, provide useful prognostic information for the patient with cirrhosis³ (Table 2). A referral for LT should be considered when a patient with cirrhosis experiences an

index complication such as ascites, variceal hemorrhaging, or hepatic encephalopathy that cannot be managed medically or when the MELD score of a patient with declining hepatocellular function approaches 15 (Fig. 2). Importantly, a stable patient with cirrhosis can deteriorate quite precipitously once a major complication such as variceal hemorrhaging supervenes. However, acute decompensation in a previously stable patient with cirrhosis can often respond to prompt medical therapy, such as the control of variceal hemorrhaging via endoscopic banding with other measures, including antibiotic prophylaxis. Implicit in the decision to initiate an LT evaluation is an absence of effective medical therapy (e.g., corticosteroids for autoimmune hepatitis) or a reversible component in hepatic decompensation (e.g., continued alcohol use). Although LT is unequivocally beneficial for recipients with advanced liver disease, the introduction of the MELD score (<http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98>) has helped define which patients should undergo transplantation.⁴ Recipients undergoing LT with a MELD score less than 15 had significantly higher 1-year mortality in comparison with candidates with similar disease severity who remained on the waiting list. A transplant survival benefit was unequivocally observed at MELD scores of 18 and higher, with the magnitude progressively increasing with higher MELD scores⁵ (Fig. 3).

HCC has become a prominent indication for LT, and this reflects not only its rising incidence but also the enhanced priority for organ allocation for HCC within the Milan criteria. Currently, nearly 20% of adult transplants in the United States are performed for HCC. Nearly half of these (9.9% of the overall total) reflect the allocation of 22 MELD points for potential recipients within the Milan criteria (i.e., a single HCC ≤ 5 cm or up to three tumors, none > 3 cm,

Abbreviations: ALF, acute liver failure; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

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TABLE 1 Indications for LT**Chronic noncholestatic liver disorders**

Chronic hepatitis B
Chronic HCV
Autoimmune hepatitis
Alcoholic liver disease

Cholestatic liver disorders

Primary biliary cirrhosis
Primary sclerosing cholangitis
Biliary atresia
Alagille syndrome
Nonsyndromatic paucity of intrahepatic bile ducts
Cystic fibrosis
Progressive familial intrahepatic cholestasis

Metabolic disorders causing cirrhosis

Alpha-1-antitrypsin deficiency
Wilson's disease
Nonalcoholic steatohepatitis and cryptogenic cirrhosis
Hereditary hemochromatosis
Tyrosinemia
Glycogen storage disease type IV
Neonatal hemochromatosis

Metabolic disorders causing severe extrahepatic morbidity

Amyloidosis
Hyperoxaluria
Urea cycle defects
Disorders of branch chain amino acids

Primary malignancies of the liver

HCC
Hepatoblastoma
Fibrolamellar HCC
Hemangioendothelioma

Fulminant hepatic failure (ALF)**Miscellaneous conditions**

Budd-Chiari syndrome
Metastatic neuroendocrine tumors
Polycystic disease
Hepatopulmonary syndrome

Retransplantation

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FIGURE 1 Indications for LT (2011 Organ Procurement and Transplantation Network data).

without vascular invasion, regional node involvement, or distant metastases).⁶ Continued areas of controversy include downsizing larger tumors with chemoembolization to fit

TABLE 2 Stages of Cirrhosis

Stage of Cirrhosis	Criteria	Prognosis: Mortality/Year (%)
1	Compensated, no varices	1
2	Varices	3.4
3	Ascites	20
4	Gastrointestinal bleeding	57
5	Infections and renal failure	67

FIGURE 2 Chart for determining when to refer someone for an LT evaluation. **FIGURE 3** Comparison of mortality risks (expressed as hazard ratios) by MELD scores for LT recipients versus candidates on the LT waiting list. Reprinted with permission from *American Journal of Transplantation*.⁵ Copyright 2005, Blackwell Munksgaard.

these criteria because, in comparison with tumor size alone, tumor biology more accurately reflects the risk of HCC recurrence.⁷ A report from the University of California San Francisco suggested that recipients with a solitary HCC up to 6.5 cm or with up to three lesions, the largest of which was ≤ 4.5 cm with the sum of the diameters no larger than 8 cm, had outcomes similar to those of patients meeting the

TABLE 3 Contraindications to LT

Absolute contraindications
Brain death
Anatomical abnormality precluding LT
Acquired immune deficiency syndrome
Advanced cardiac or pulmonary disease
Ongoing alcohol/illicit drug use
Extensive thrombosis involving superior mesenteric vein and portal vein
Extrahepatic malignancy
ALF with intracranial pressure > 50 mm Hg or cerebral perfusion pressure < 40 mm Hg
Persistent noncompliance
Lack of psychosocial support
Uncontrolled sepsis
Relative contraindications
Advanced age
Severe malnutrition/debility
Morbid obesity
Human immunodeficiency virus
Multiorgan failure
Psychological instability
Cholangiocarcinoma

Milan criteria.⁸ However, expansion beyond the Milan criteria for extra MELD points has not been generally accepted, and this reflects continued uncertainty about the role of LT with a more extensive tumor burden.

Hepatopulmonary syndrome is another complication of cirrhosis that is potentially eligible for extra MELD points because LT can favorably alter its course. Potential recipients must have an arterial oxygen tension less than 60 mm Hg on room air without underlying lung disease to receive these points. However, patients with HPS who have an arterial oxygen tension less than 50 mm Hg alone or in conjunction with a preoperative shunt fraction greater than 20% were 7.5 times as likely to experience perioperative mortality.⁹ Portopulmonary hypertension is another

important extrahepatic complication of cirrhosis. Potential recipients suffering from portopulmonary hypertension with a mean pulmonary artery pressure greater than 35 mm Hg despite vasodilator therapy are usually not candidates for transplantation because of the magnitude of the perioperative and postoperative risk of cardiopulmonary complications. Acute liver failure (ALF) is defined as severe liver injury with encephalopathy and coagulopathy [international normalized ratio (INR) > 1.5] in a patient without preexisting cirrhosis and with an illness of less than 26 weeks' duration. ALF has a variable prognosis depending on the etiology and the likelihood of spontaneous recovery. The acknowledgment of the rapidly progressive course of ALF and its high mortality rate has led to its prioritization for LT if specific criteria are met.

Evaluation Process

Key components of the evaluation for LT include an assessment by a transplant hepatologist and surgeon to confirm that the patient's liver disease is of such severity that LT is reasonable and feasible and that other therapeutic options have been exhausted. A comprehensive medical assessment is undertaken to exclude important comorbidities such as coronary artery disease (Table 3). Once these consultations and investigations are complete, the patient's candidacy is discussed at a formal patient selection meeting. If the patient is accepted and financial clearance is obtained, the patient can be listed to wait for a donor organ for transplantation.

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