

Management of the Liver Transplant Patient

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Summary

The outcomes of liver transplantation have improved significantly over the years. The process for placing patients on the transplant waiting list also has improved. Because there are approximately 16,000 people on the liver transplant waiting list and only 5,000 transplants per year, clinicians are searching for effective ways to expand the donor pool. Because of the regenerative potential of the liver, one way to expand the donor pool is through the use of living donors.

Key Points

- Effective immunosuppressants, improvements in surgical technique, effective preservation of organs for transport, and a system for distributing organs have significantly improved the outcomes with liver transplant.
- Current liver transplant outcomes include a median hospital length of stay of five to six days, a one-year survival of 90 to 94 percent, and a five-year survival of 75 to 80 percent.
- The indications for a liver transplant are parenchymal and cholestatic liver disease, inborn errors of metabolism, and tumors.
- Significant deterioration in quality of life, complications of end-stage liver disease, and deteriorating hepatic synthetic function in a patient with liver disease are indicators for needing a transplant.
- The Model for End-Stage Liver Disease Scoring System is used to determine a patient's place on the liver transplant waiting list.
- Because of a chronic shortage of transplantable livers, ways of expanding the donor pool are being developed.
- Living donor liver transplants, which began in the early 1990s, are one way to expand the donor pool.

THE FIRST RESEARCH PROGRAMS FOR LIVER transplantation began in 1958, with the first transplant being performed in 1963. Liver transplants are a topic of interest for managed care because of the cost of the procedures, the post-procedure costs, and the increasing incidence of these transplants. Approximately 5,000 liver transplants are performed per year in the United States, and there are approximately 16,000 people on the waiting list for a new liver. The average waiting time for a patient on the list is more than one year.

The development of effective immunosuppressants, improvements in surgical technique, effective preservation of organs for transport, and a system for distributing organs have significantly improved the outcomes with liver transplant. Current liver transplant outcomes include a median length of stay of five to six days, a one-year survival of 90 to 94

percent, and five-year survival of 75 to 80 percent. The indications for liver transplant are parenchymal and cholestatic liver disease, inborn errors of metabolism, and tumors.

Parenchymal liver disease may be secondary to postnecrotic cirrhosis, alcoholic cirrhosis, acute liver failure, Budd-Chiari syndrome, or cystic fibrosis. Hepatitis C induced cirrhosis and alcoholic cirrhosis are the first and second most common reasons for a liver transplant. Acetaminophen overdose is the most common cause of acute liver failure in the United States. This can be the result of an accidental overdose or suicide attempt. Concurrent ingestion of alcohol can significantly increase the risk of acetaminophen.

Cholestatic liver disease accounts for about 20 percent of all transplants. Cholestatic liver disease results from biliary atresia, primary biliary cirrhosis,

Exhibit 1: Child-Turcotte-Pugh (CTP) Classification

	1	2	3
Encephalopathy Grade	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Albumin (gm/dl)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec prolonged)	<4	4-6	>6
Bilirubin (mg/dl)	<2	2-3	>3
For cholestatic disease	<4	4-10	>10

sclerosing cholangitis, secondary biliary cirrhosis, and familial cholestasis. Congenital biliary atresia is the most common reason for liver transplants in children. Prior to transplant availability, congenital biliary atresia was uniformly fatal.

Inborn errors of metabolism that can result in liver damage include alpha 1 antitrypsin deficiency, Wilson’s disease, and hemochromatosis. Inborn errors of metabolism result in toxic metabolites that damage the liver. Liver disease related to inborn errors of metabolism usually present later in life because it takes time to accumulate significant damage. Diseases that do not directly damage the liver but are the result of a defective liver such as hemophilia, familial hypercholesterolemia, familial amyloid polyneuropathy, and hyperoxaluria can be “cured” with a liver transplant. For example, liver transplants are not done to cure hemophilia but are done in these patients who have developed cirrhosis secondary to blood transfusions with the incidental benefit of eliminating the disease. Liver tumors, which may result in the need for a transplant, may be benign, a primary malignancy, or metastases from cancer somewhere else within the body.

Placing patients on the waiting list for a liver transplant depends on their degree of illness. There are many people who live with liver disease for decades without significant illness. There have to be some complications (ascites or encephalopathy) or clinical deterioration (liver function laboratory tests). Traditionally, patients have to have several abnormalities before being listed for a transplant. Also, just because someone meets the criteria to be on the transplant list may not mean they need the transplant immediately. Significant deterioration in quality of life, complications of end-stage liver disease, and deteriorating hepatic synthetic function are indicators

Exhibit 2: MELD Scoring System

$$\text{MELD Score} = 0.957 \times \text{Loge}(\text{creatinine mg/dl}) + 0.378 \times \text{Loge}(\text{bilirubin mg/dl}) + 1.120 \times \text{Loge}(\text{INR}) + 0.643$$

- Laboratory values <1.0 are set at 1.0 for purposes of MELD calculation
- Score is then rounded to the tenth decimal place and multiplied by 10

for when a transplant will be necessary. The quality of life issues that may be severe enough to prompt a transplant include severe lethargy, intractable pruritis, recurrent cholangitis, intractable ascites, severe metabolic bone disease, and pain. Complications of end-stage liver disease include ascites, variceal hemorrhage, spontaneous bacterial peritonitis, hepatorenal syndrome, and portosystemic encephalopathy. Synthetic dysfunction is marked by decreased albumin and increased prothrombin time.

One scoring system that has been used for cirrhosis is the Child-Turcotte-Pugh (CTP) Classification (Exhibit 1). There are some shortcomings of CTP scores. Two parameters (ascites and encephalopathy) are subjective evaluations. The score does not discriminate between disease severities of the sickest patients (i.e., a patient with bilirubin = 5 is scored the same as someone with bilirubin = 25). Additionally, the score does not include the level of renal function, which has been found to be an independent predictor of survival in patients with end-stage liver disease.

Until 2002, livers were allocated to eligible patients based on CTP scores, need for hospital based intensive care unit care, and duration on the list. Unfortunately, physicians were giving patients higher scores than they deserved on ascites and encephalopathy in order to advance them on the waiting list. Because of the weakness of the CTP scoring system, the Department of Health and Human Services (DHHS) issued a rule on liver transplant. The DHHS rule defines the principles of organ allocation and governs the operation of the Organ Procurement and Transplant Network (OPTN).

The guidelines for liver distribution are based on information from two studies showing a lack of correlation between waiting time and death on the waiting list.^{1,2} The DHSS rule challenged the United Network on Organ Sharing (UNOS) Liver and Intestinal Committee to create an allocation policy that would maximize the use of available organs by medical urgency.

Exhibit 3: MELD Scoring System

- For example, a patient with cirrhosis secondary to hepatitis C has a serum creatinine of 1.9 mg/dl, bilirubin 4.2 mg/dl, and INR 1.2

$$\begin{aligned} \text{– MELD Score} &= 0.957 \times \text{Loge}(1.9) \\ &+ 0.378 \times \text{Loge}(4.2) \\ &+ 1.120 \times \text{Loge}(1.2) \\ &+ 0.643 \\ &= 2.039 \end{aligned}$$

- The MELD score is then rounded to the tenth decimal place (2.0) and multiplied by 10
- Therefore, MELD score = 20 (maximum = 40)

This led to a new scoring system called the Model for End-Stage Liver Disease (MELD) scoring system (Exhibit 2). MELD uses three variables – kidney function, bilirubin, and international normalized ratio – to produce an objective mathematical score. The maximum possible score is 40. The MELD score has been correlated with three-month mortality and survival after surgery (Exhibit 3).³

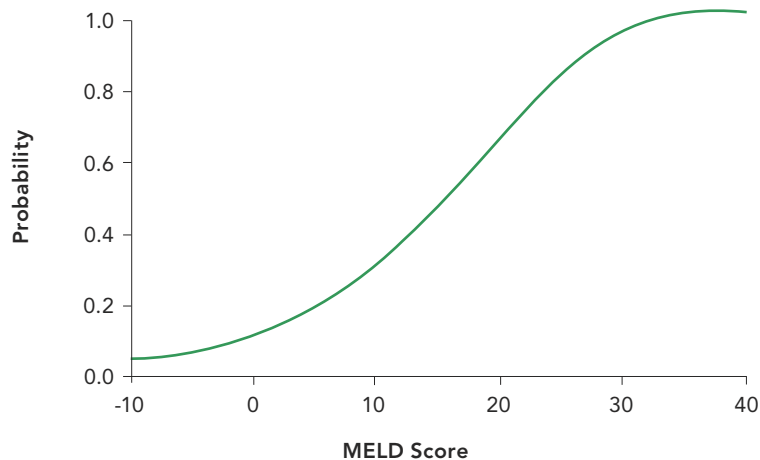
There are some limitations of MELD. Patients with moderate to marked muscle wasting due to chronic liver disease may have falsely low serum creatinine levels. Patients with hepatocellular carcinoma will die from liver cancer before their liver disease is advanced enough by the MELD score to qualify for a transplant. Patients who get frequent bile duct infections, have intractable itching, or disabling encephalopathy may not have high MELD scores.

Once identified as needing a transplant, patients

undergo extensive evaluation. The evaluation includes determination of the cause of liver disease, severity of liver disease, survival possibility, functional ability, concomitant medical problems, psychiatric evaluation, alcohol and medication history, and social evaluation. Various laboratory tests are used to determine the cause of the liver disease, to stage the severity, and to establish the patient's general health. Other tests, including a Doppler ultrasound, liver biopsy, and cholangiogram, are used to determine the condition of the patient's liver. Psychosocial evaluation will evaluate the patients' support systems and potential for compliance with the immunosuppression protocol after transplantation. Concomitant medical problems that can impact the patient's ability to undergo a transplant, including cardiac, pulmonary, and renal disease, have to be identified.

Because many patients still die while waiting for a suitable organ, clinicians are searching for ways to expand the liver donor pool. One way is through expansion of the donation criteria by using marginal donors, older donors (> 70), hepatitis C positive but reasonably well livers, and non-heart beating donation. Non-heart beating donors are controversial. Currently, livers are obtained from patients on life support before life support is removed. Some families are not comfortable that organs are harvested before the heart stops beating. In non-heart beating donors, the donor is taken to the operating room, life support is removed, and the organs harvested as quickly as possible. In this case, the liver is exposed briefly to hypotensive conditions, which may limit the organ's viability. There appears to be a high rate

Exhibit 4



Relationship between the MELD score and estimated 3-month mortality in chronic liver disease patients

of bile duct complications in patients with transplanted livers from non-heart beating donors.

Another way to expand the liver donor pool is to use living donors. The first living donor transplant of a liver was done in the pediatric population in 1990. The first adult living donor transplant in the United States was done in 1999. When an adult-to-adult liver transplant is done, about two-thirds of the donor liver is taken. Because of its regenerative potential, the liver will grow to full size in both the donor and recipient in about two weeks.

There can be no conflict of interest or coercion of the living donor, and risks for the donor must be minimized. Donors must be given every opportunity to change their minds and alternatives should be emphasized to the potential patient and donor. The potential donor has to be extensively evaluated for acceptability. A very careful evaluation of the size of the potential donor liver and the size needed for the recipient must be done. The donor and recipient each need to have different physicians doing their evaluations to prevent potential conflict of interest. Four to five donors will typically be rejected before a living donor is found for an individual. In the case of a living liver donation, the recipient still has

to meet the standard criteria for a transplant. About 500 living donor liver transplants are done in the United States yearly.

Conclusion

Outcomes with liver transplantation have significantly improved over the years. The liver allocation policy in the United States also has been improved with the use of the MELD score. Given the shortage of transplantable organs, living donor liver transplantation is necessary. **JMCM**

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