

Recent Advances in Liver Transplantation for the Practicing Gastroenterologist

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Abstract: Liver transplantation is the definitive therapy for end-stage liver disease of various etiologies as well as acute liver failure and early-stage hepatocellular carcinoma. The Model for End-Stage Liver Disease (MELD) score is essential for organ allocation in the United States. Addition of the serum sodium level to the MELD score is a recent development that helps prognosticate cirrhotic patients with hyponatremia, a commonly seen manifestation of end-stage liver disease. The currently used Milan criteria for hepatocellular carcinoma have been expanded with some success at certain transplant centers, and tumor downstaging prior to transplant is being used more frequently. The tremendous shortage of donor organs continues to be the major limitation of this life-saving therapy. This has led to the use of extended-criteria donors, donation after cardiac death, split liver grafts, and live donor liver transplants. Renal dysfunction following liver transplant requires close monitoring and dose adjustments of immunosuppressive medications. Although most liver transplants in the United States are for chronic hepatitis C infection and its sequelae, hepatitis C virus recurrence is a common problem that is challenging to treat in the post-transplant population.

Liver transplantation has evolved since Dr. Thomas Starzl performed the first orthotopic liver transplant (OLT) over four decades ago. OLT is the gold standard for treatment of patients with acute liver failure, end-stage liver disease from a variety of causes, and certain early-stage liver tumors. Recent developments in the Model for End-Stage Liver Disease (MELD) era have now shown the potential utility of adding a patient's serum sodium level to their MELD score, for the so-called MELD-sodium model, in an effort to prognosticate cirrhotic patients with hyponatremia. The criteria for liver transplantation in hepatocellular carcinoma (HCC) have also changed over the past several years, with the downstaging of tumors proving to be effective in selected patients who do not meet the traditional Milan criteria for liver transplant. The shortage

Keywords

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of donor organs continues to be the rate-limiting factor for liver transplantation throughout the world. Although the majority of transplants are performed using cadaveric donors, shortage of such organs has led to the use of innovative approaches to liver transplantation, including split liver grafts, marginal- or extended-criteria donors, live donor liver transplantation (LDLT), and the use of organs donated after cardiac death (DCD). The purpose of this review is to update the practicing gastroenterologist on recent advances in this field as well as discuss the current controversies in liver transplantation. We also touch upon two issues commonly seen after liver transplant: recurrent hepatitis C virus (HCV) infection and its management following liver transplant; and renal failure following liver transplant, including the effects of immunosuppressants on renal function and dose adjustments for these medications in patients with impaired renal function.

Allocation of Organs: Model for End-Stage Liver Disease and Model for End-Stage Liver Disease–Sodium

Prior to 2002, organ allocation for liver transplantation was based upon the Child-Turcotte-Pugh score. This subjective scoring system led to much bias and inappropriate use of organs,¹ as waiting list mortality did not correlate with waiting time.² This ultimately led to a mathematical model called the MELD scoring system that utilized three laboratory variables—bilirubin, creatinine, and international normalized ratio—in a log rhythmic formula to predict 3-month mortality from end-stage liver disease.³ Although the MELD score was originally devised for assessing mortality in patients undergoing transjugular intrahepatic portosystemic shunt procedures, further investigation revealed that this score was also able to accurately predict mortality in patients awaiting liver transplantation.^{3,5} The original MELD score also included etiology of the liver disease as one of its variables in addition to the aforementioned ones. The etiology, however, was subsequently removed based upon evidence that it did not add substantial predictive power to the MELD model and, moreover, had the potential for disease-specific bias in liver allocation.^{3,6}

The United Network for Organ Sharing (UNOS) implemented use of the MELD score in February 2002 in the liver allocation policy for patients on the transplant waiting list. Livers are allocated to patients with the highest MELD scores, irrespective of how long they have been on the transplant waiting list.⁷ The MELD scoring system has been validated in several studies in independent cohorts of patients with different etiologies of liver disease.^{8,9} In HCC, however, the MELD score is inadequate for assessing the need for liver transplantation. Currently, organs are allocated to patients with HCC based upon the Milan

criteria proposed by Mazzaferro and associates.¹⁰ These criteria have been expanded in recent years by Yao and colleagues¹¹ and will be discussed later on in this review.

A major limitation of the MELD score is its inability to accurately predict mortality in specific subgroups of patients with cirrhosis, particularly patients with ascites and low serum sodium concentrations.¹² Hypovolemic hyponatremia develops in some patients with late stages of cirrhosis and is due to increased levels of antidiuretic hormone secondary to circulatory dysfunction seen in patients with advanced cirrhosis. Several investigators have shown that incorporation of serum sodium into the MELD score improves accuracy of the score alone for predicting short-term mortality.^{13,14} A recent article by Kim and coworkers¹⁵ compared the utility of adding serum sodium concentration into the MELD score versus the MELD score alone. Study participants included all candidates in the United States on the UNOS transplant waiting list between 2005 and 2006 who had cirrhosis but not liver cancer. The investigators concluded that both the MELD score and the serum sodium concentration were predictive of death at 90 days among patients on the waiting list. They also found that there was a significant interaction between the MELD score and the serum sodium concentration, indicating that the effect of sodium was greater in patients with a low MELD score. Using the MELD-Na formula, the increase in points ranged from 0 points in patients with a serum sodium concentration of 140 mmol/L or more to 13 points in patients with a serum sodium concentration of 125 mmol/L or less. The highest gains were seen in patients with a low MELD score and a low sodium concentration (125 mmol/L), with some of these patients gaining as many as 13 more points than with the MELD score alone. However, the added points progressively decreased as the MELD score increased; thus, patients with a MELD score of 40 did not gain any points, even if the serum sodium concentration was 125 mmol/L or less.

Although incorporation of serum sodium into the MELD score has been shown to represent a further improvement in the assessment of prognosis in cirrhosis, the applicability of the MELD-Na score in organ allocation has some limitations. These include the potential for interlaboratory variability in the measurement of serum sodium concentration and the fluctuations in serum sodium after diuretic therapy. Despite these limitations, the study by Kim and associates is a landmark study quantifying the risk of death among patients with cirrhosis. Further studies are needed to validate these findings not only for the mortality of patients on the transplant waiting list but also for outcomes following liver transplantation. Whether the MELD-Na model will eventually be implemented by UNOS in organ allocation remains to be seen.

Liver Transplantation for Hepatocellular Carcinoma

HCC is the fourth most common malignancy worldwide and accounts for approximately 1 million deaths per year.¹⁶ Although HCV infection and alcoholic liver disease are the major etiologies of HCC in the West, hepatitis B virus (HBV) infection is the leading cause in Asia. The incidence is currently 2.4 per 100,000 individuals and is expected to increase over the next 20 years.¹⁷ Although HCC typically develops in cirrhotic livers, it can develop even in the absence of cirrhosis in patients with HBV infection. The prognosis of symptomatic HCC is poor, with a 5-year survival rate of 3%.¹⁸ A multidisciplinary approach is used in the treatment of HCC and includes hepatologists, surgeons, interventional radiologists, and oncologists. The diagnosis of HCC is usually made during routine screening of the cirrhotic patient, though in some cases, it is made after the patient develops a symptomatic lesion.

Screening involves imaging modalities such as ultrasound, computed tomography, or magnetic resonance imaging in conjunction with tumor markers such as alpha-fetoprotein (AFP). Although AFP is neither sensitive nor specific, a value greater than 200 ng/dL is highly suspicious for HCC.^{17,19,20} Early contrast uptake in the arterial phase of contrast-enhanced imaging studies and washout during the delayed venous phase are typical for HCC.

Primary treatment modalities for HCC include locoregional ablative therapies, surgical resection, or OLT in selected patients.²¹ In patients with cirrhosis and HCC, liver transplant remains the best option for long-term survival based upon stringent pretransplant criteria. The Milan criteria proposed by Mazzaferro and colleagues¹⁰ have been adopted by UNOS for the listing of HCC patients for liver transplantation. Based upon the Milan criteria, a patient is a candidate for liver transplantation if they have a single tumor less than 5 cm in size or 3 tumors with the largest not bigger than 3 cm in size. Patients with HCC who meet the aforementioned criteria are given 22 priority points by UNOS, resulting in a decreased waiting time on the transplant list. However, with the incidence of HCC increasing, there have been several developments in the management of HCC suggesting that an expansion of the Milan criteria is needed.²²⁻²⁴ Yao and coworkers¹¹ proposed the University of California at San Francisco (UCSF) criteria, which consider patients for liver transplant if they have a single tumor less than 6.5 cm in size or 3 tumors with the largest less than 4.5 cm in size, with a total tumor burden of less than 8 cm. The long waiting times for organs and the potential for dropouts

on the transplant wait list have resulted in the use of locoregional therapies such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) prior to liver transplantation in an effort to stabilize and also downstage tumors that do not meet either the Milan or UCSF criteria.^{25,26}

Theoretically, the response of the tumor to downstage with either RFA or TACE will allow for the selection of tumors with favorable biology that will also do well following OLT. A recent prospective study analyzed long-term outcome data on HCC in a cohort of 61 patients with HCC.²⁷ Patients included in the study had to have one of the following: a single tumor larger than 5 cm in size but not larger than 8 cm; 2 lesions with at least 1 lesion larger than 3 cm in size but not exceeding 5 cm, with a total tumor diameter up to 8 cm; or 4–5 tumor lesions, none larger than 3 cm, with a total tumor diameter of 8 cm. These patients were observed for a minimum of 3 months after downstaging and prior to OLT. Tumor downstaging was successful in 70.5% of patients, and of these, 57.4% underwent OLT. Treatment failure was observed in 29.5% of patients due to tumor progression. One factor predicting treatment failure was an AFP level larger than 1,000 ng/mL. No patient experienced tumor recurrence after a median follow-up of 25 months, suggesting that successful downstaging of HCC can be achieved in the majority of carefully selected patients and is associated with excellent post-transplantation outcome.

However, more studies are needed that refine downstaging strategies to further improve outcomes. Tumor recurrence after transplant is a possibility, particularly in patients with microvascular invasion seen on explant. Although there is no widely accepted pathologic assessment to predict recurrent HCC after transplant, a study by Parfitt and coworkers²⁸ showed that patients who did not meet the Milan criteria but did meet UCSF criteria had worse survival and an increased rate of recurrent HCC with long-term follow-up.

Liver Transplantation Using Marginal- or Extended-Criteria Donors, Organs Donated After Cardiac Death, Split Liver Grafts, and Live Donor Liver Transplantation

The growing shortage of cadaveric donors and the rising number of patients on the transplant waiting list continue to be significant challenges in liver transplantation despite advances in surgical technique, stringent patient selection, immunosuppression, and perioperative management. These challenges have led many liver transplant centers to use extended- criteria or marginal donors, as well as to perform split liver and live donor liver transplants.

Extended-Criteria and Marginal Donors

There is no consensus as to what makes a graft marginal in one center and acceptable in another center. The use of marginal grafts typically depends upon the judgment of the transplant surgeon and the needs of the recipient.^{29,31} Cirrhosis from HCV infection is the leading cause of liver transplantation in the United States. HCV viremia persists in approximately 95% of patients post-transplant, and approximately 90% of patients transplanted for HCV will experience hepatitis recurrence 5–7 years following transplant. Among these, approximately 30% will develop cirrhosis.³² Grafts from donors with HCV infection are now routinely transplanted in recipients who have known HCV infection. Several studies have shown that for patients being transplanted for chronic HCV, there is no difference in survival rate among patients who have an HCV-positive donor versus those who have an HCV-negative donor. A biopsy of the donor liver prior to transplant is essential to ensure that there is no significant damage from hepatitis.^{32,33}

Transplantation of grafts from HBV donors (donors who are positive for HBV core antibody) has been successful in HBV-naïve patients. However, prophylactic antiviral therapy (usually oral antiviral medications such as lamivudine with hepatitis B immunoglobulin) are required to reduce rates of de novo infection and result in favorable patient and graft survival.^{34–36}

The increase in the average age of the general population, combined with the shortage of available organs, has led to the use of donors above the age of 60. Several studies have shown that there is no difference in patient and graft survival between patients older than 70 years of age versus those less than 70 years of age. However, these grafts must be used cautiously, as prolonged ischemia or steatosis may lead to graft failure.^{30,37} This is particularly true for patients transplanted for end-stage liver disease secondary to HCV infection, in whom the use of grafts from patients over age 50 has been shown to be associated with more aggressive recurrence of HCV and early allograft failure.³⁸ Thus, consideration of donor age is important for decisions regarding patient selection, antiviral therapy, and organ allocation.³⁹

Nonheart-Beating Donors, or Donation After Cardiac Death

The past decade has seen a renewed interest in nonheart-beating donors, or DCD, as a strategy to increase the pool of available organs for transplant.³¹ In contrast to traditional cadaveric organs that are harvested after documented brain death, DCD organs are retrieved from donors who undergo a controlled circulatory arrest following planned withdrawal of life support in the operation theater. Organs from controlled DCD

donors have less damage and a better chance of recovery as opposed to organs from unplanned cardiac death, failed cardiopulmonary resuscitation, or from patients dead on arrival to the hospital. Grafts from DCD donors have well-defined ischemic times: 30–45 minutes for warm ischemia and up to 8 hours for cold ischemia.^{40,41} Allograft survival is lower in DCD grafts compared to donation after brain death. Although prior studies emphasized 1-year survival differences, Seleck and associates,⁴¹ in a study evaluating long-term results of DCD, found 52% allograft survival versus 71% in donation after brain death, a significant difference. DCD grafts tend to have higher rates of biliary complications as opposed to traditional cadaveric grafts.^{42,43}

In addition, the type of preservative solution used in procurement has been shown to affect graft survival. A recent study by Stewart and colleagues⁴⁴ compared histidine-tryptophan-ketoglutarate (HTK) versus University of Wisconsin solution (UW), which are commonly used in the preservation of donor grafts. After adjusting for donor, recipient, and graft factors that affect graft survival, HTK preservation was associated with an increased risk of graft loss (hazard ratio [HR] 1.14; $P=.002$), particularly with DCD allografts (HR 1.44; $P=.025$) and those with cold ischemia time over 8 hours (HR 1.16; $P=.009$). In addition, HTK preservation was associated with a 1.2-fold higher odds of early (<30 days) graft loss compared to UW preservation (odds ratio [OR] 1.20; $P=.012$), with a more pronounced effect on allografts with cold ischemia time over 8 hours (OR 1.31; $P=.007$), DCD allografts (OR 1.63; $P=.09$), and donors over 70 years of age (OR 1.67; $P=.081$).

Thus, DCD organs can be a significant source of grafts for liver transplantation, provided that the aforementioned criteria are met in order to achieve good patient and graft survival. Additional risk factors such as advanced donor age must also be taken into consideration before using a DCD organ.

Split Liver Transplantation and Partial Graft Transplants

Split liver transplantation and partial graft transplants were also developed as strategies to increase the donor pool for OLT. The source of partial liver grafts can either be from live donors (which will be discussed in the next section) or cadaveric donors, and each is associated with a unique set of technical and physiologic challenges that can affect outcomes.⁴⁵ Several studies have shown the increased risk of vascular and biliary complications with split liver grafts.⁴⁶ In addition, problems such as small-for-size syndrome have been described in split liver grafts. The overall success of a split liver graft relies heavily on underlying illnesses in both the donor and recipient.

Advanced donor age, prolonged cold ischemia time, and low-volume liver transplant centers have been shown to be independent predictors of survival.

In a recent study by Humar and coworkers,⁴⁵ partial liver grafts from a live donor experienced better outcomes than deceased donor split liver grafts, though multivariate analysis showed that this was not necessarily due to the donor source itself. It is likely that the ability to perform transplant earlier in the disease process using partial liver grafts from a live donor led to superior results. Because of technical difficulties and logistic obstacles, there are only a small number of high-volume liver transplant centers performing split liver transplants in the United States. Split liver transplantation for adult recipients is possible in approximately 15% of cadaveric donors. Outcomes and complication rates can be improved by stringent selection criteria for both donors and recipients and perhaps by in-situ splitting in cadaveric donors.

Live Donor Liver Transplantation

LDLT has been controversial since its inception. It began in response to deceased donor organ shortage and waiting list mortality. LDLT was initially performed in pediatric liver transplants in 1989 and nearly one decade later in adult liver transplants.⁴⁷ Among the previously described sources of liver grafts, LDLT is unique because it subjects an otherwise healthy individual to a major surgical procedure without obvious direct therapeutic benefit. LDLT increased exponentially from the late 1990s until 2001, when the numbers dropped significantly, in part due to the loss of a healthy donor at a high-volume liver transplant center in the United States.⁴⁷ The National Institutes of Health funded the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), which established a survival benefit from LDLT, yet LDLT comprises less than 5% of OLT in the United States.⁴⁸ LDLT has the advantage of significantly reduced waiting times, medical optimization of the recipient prior to the anticipated surgery, and use of graft from a healthy donor with minimal ischemic time.

The disadvantages of LDLT include a high rate of surgical complications in both the donor and recipient and the possibility of a smaller-than-adequate graft. The 1- and 3-year patient survival rates of LDLT are comparable to those of deceased donor liver transplants, as are graft survival rates based on numerous studies to date. It is important to ensure that the potential donor is medically and psychologically fit, understands the risks involved, and is making an autonomous and uncoerced decision. The donor should have no liver disease or other significant comorbidities (eg, coronary artery disease or cerebrovascular disease) and must typically be in the age range of 18–55 years. A complete medical history

and physical examination as well as extensive laboratory, radiologic, and cardiac testing must be performed by a physician who is not involved in the transplant recipient's care to prevent conflict of interest. The potential donor should also undergo a formal psychosocial, surgical, and pre-anesthesia evaluation prior to the surgery.⁴⁹ The evaluation of liver size is critical in LDLT, particularly in right lobe donation, which results in higher rates of complications than left lateral lobe donation.

Controversies exist surrounding the use of LDLT in patients with HCC, particularly in patients outside the Milan or UCSF criteria. An article by Fisher and associates has shown that there is a higher risk of HCC recurrence following LDLT as opposed to transplantation from an organ from a cadaveric donor.⁵⁰ Recent studies have shown that LDLT is not a contraindication for patients with HCV, though these patients should not routinely be transplanted early in their disease process.

Thus, although LDLT has decreased in the past several years, it continues to be a valuable source for donor organs.⁵¹ However, in order for LDLT to remain a viable option for liver transplant, the potential benefits must outweigh the risks for both donor and recipient, and donor safety must be of paramount concern.

Renal Failure After Liver Transplant

Renal failure following liver transplant leads to significant morbidity and mortality and complicates medical management of the transplant recipient, particularly with regard to immunosuppressive therapy.⁵² The incidence of renal failure following OLT ranges from 12% to as high as 70%⁵³ and can lead to worse outcomes, including increased cardiovascular events, hepatic allograft dysfunction, and mortality, particularly when renal replacement therapy is needed.^{53,54} Although renal dysfunction is common among patients on the transplant waiting list, it may not be the best predictor of renal function after transplant, particularly in patients with the hepatorenal syndrome.⁵⁵ Risk factors for the development of renal failure following liver transplant include advanced age of the recipient, pre-existing renal disease, hypertension, dyslipidemia, diabetes, hepatitis C, and the use of calcineurin inhibitors (CNIs) after transplant.^{55,56} Early recognition and treatment of renal dysfunction following liver transplant will lead to improved long-term outcomes. General measures to slow deterioration in renal function include good control of diabetes, hypertension, and dyslipidemia as well as avoidance of nephrotoxic drugs.⁵⁷ The doses of CNIs (cyclosporin and tacrolimus) must be reduced. Cyclosporin is associated with a higher rate of renal dysfunction than tacrolimus.⁵⁸ Accepted trough levels for CNIs in patients with renal dysfunction are less

than 50 ng/mL for cyclosporine and less than 4 ng/mL for tacrolimus.⁵⁹ Sirolimus monotherapy may be tried as an alternative CNI-free regimen with close monitoring of hyperlipidemia.⁶⁰ Mycophenolate may be tried with lower doses of CNIs and has been shown in some studies⁵⁹ to result in improvement in renal function along with improved blood pressure and lipid status.

Recurrent Hepatitis C Following Liver Transplantation

HCV infection remains the most common indication for liver transplantation in the United States. Recurrent HCV after liver transplantation is universal and is of great concern, as it is associated with poor graft and patient survival.^{61,62} Advanced donor age is the most important factor associated with accelerated fibrosis progression and poor graft and patient survival in recurrent HCV after liver transplant.^{38,39,63} Other factors contributing to recurrent HCV after OLT include pretransplant HCV viral load, HCV genotype 1, co-infection with HIV or hepatitis B, post-transplant diabetes mellitus, acute cellular rejection, and the use of pulse corticosteroids.⁶⁴ It has also been hypothesized that there is a higher incidence of recurrent HCV in LDLT as opposed to deceased donor liver transplants.⁶⁵

Pretransplant eradication of the virus is the best strategy to prevent recurrent HCV following OLT, though this is not always feasible in many patients due to poor tolerance of the medications (interferon and ribavirin) in patients with decompensated liver disease.⁶⁶ Most patients with high pretransplant MELD scores also have low tolerance to preemptive antiviral therapy started within weeks of transplantation. Response to therapy in terms of sustained virologic response (SVR) can be as high as 39%, with a median of approximately 16%.^{67,68} In some patients who are virologic nonresponders, histologic improvement has been demonstrated.⁶⁹

Initiation of antiretroviral therapy following OLT in patients with evidence of recurrent disease is the most widely accepted therapeutic option. Pegylated interferon and ribavirin for 48 weeks can result in SVR in approximately 30% of treated patients.^{70,71} However, post-transplant therapy for HCV has the same drawbacks as pretransplant treatment and is often poorly tolerated, leading to frequent dose adjustments and even discontinuation. Treatment of HCV post-transplant can be complicated with acute or chronic rejection, which, though rare, are challenging to treat.⁶⁸ Retransplantation for recurrent HCV is controversial, as survival is poor for such patients.⁷² New antiviral therapies are needed to prevent patient and graft loss due to recurrent HCV following liver transplant.

Summary

Liver transplantation has matured from an experimental to a definitive therapy for end-stage cirrhosis, acute liver failure, and hepatocellular carcinoma that meets specific criteria. The implementation of the MELD score has reduced disparities in organ allocation and continues to evolve, as demonstrated by a recent study showing the utility of adding serum sodium concentration to the MELD score to predict 90-day mortality of patients on the transplant waiting list. The traditional Milan criteria have been expanded by the UCSF group, and downstaging of tumors prior to transplant appears to be helpful in some instances. However, further studies are warranted to assess the long-term recurrence rates of HCC after transplantation. Lack of sufficient cadaveric organs has led to expansion of the donor pool using extended-criteria organs, DCD organs, split liver grafts, and organs from live donors. These organs must be used judiciously and preferably by centers that are experienced and have sufficient volumes in order to maximize therapeutic benefit. Renal failure after liver transplantation is often seen with CNIs and requires either dose reduction in these medications or transition to nephron-sparing immunosuppressive therapy. HCV therapy following liver transplantation must be individually tailored to each patient and carefully balanced with the immunosuppressive regimen. Currently available antiviral treatment for recurrent HCV has been used with varying success, and studies with newer agents such as protease inhibitors are yet to be studied prospectively in large multicenter trials.

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