Evaluation of Liver Transplant Recipients

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The outcome of liver transplantation (LT) is dependent on many factors including graft quality, surgical techniques, postoperative care, immunosuppressive regimens and most importantly, careful pre-transplant recipient evaluation and selection. Currently, the expected 1-year and 5-year survival rates after LT are 85–95% and 75–85%, respectively. The improvement in outcomes and better awareness has resulted in an increasing demand for LT around the world including India. Transplant physicians have responded to this increased demand by developing several strategies including the use of older donors, grafts from hepatitis C positive donors or those with previous hepatitis B infection (positive hepatitis B virus [HBV] core immunoglobulin G [IgG] antibody), graft from nonheart beating donors, domino transplantation (liver from patients with familial amyloid polyneuropathy transplanted into older recipients), split-liver grafts, and live donor liver transplant (LDLT). Currently, the only treatment that prolongs survival in those with end-stage acute or chronic liver failure is transplantation of either partial or full liver donor graft. Because of the enormous disparity in supply and demand for donor organs, costs, and potential morbidity and mortality of live donors in LDLT, it has become incumbent on the transplant community to ration the available organs in a way that provides the best outcomes and in the process, serves the best interest of the population as a whole. When evaluating a potential candidate for LT, it is imperative to determine whether the recipient is going to benefit from the procedure immediately and in the long-term. In this review, we will discuss the process of selection and optimal evaluation of potential LT recipients. (J CLIN EXP HEPATOL 2011;1:199–203)

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grafts from hepatitis C virus (HCV) positive donors or those with previous hepatitis B infection (positive hepatitis B virus [HBV] core immunoglobulin G [IgG] antibody), graft from nonheart beating donors, domino transplantation (liver from patients with familial amyloid polyneuropathy transplanted into older recipients), split-liver grafts, and live donor liver transplant (LDLT). Although there has been promising research in the field of xenotransplantation, artificial liver support systems, hepatocyte transplantation, and stem cell research, the progress in this field has been very slow. Currently, the only treatment that prolongs survival in those with end-stage acute or chronic liver failure is transplantation of either partial or full liver donor graft. Because of the enormous disparity in supply and demand for donor organs, costs, and potential morbidity and mortality of live donors in LDLT, it has become incumbent on the transplant community to ration the available organs in a way that provides the best outcomes and in the process serves the best interest of the population as a whole. When evaluating a potential candidate for LT, it is imperative to determine whether the recipient is going to benefit from the procedure immediately and in the long-term. The most common causes of mortality in liver transplant recipients are infections, disease recurrence, malignancy, cardiovascular event, and renal failure.^{2–6} To improve immediate and long outcomes after LT, these potential complications need to be minimized. In this review, we will discuss the process of selection and optimal evaluation of potential LT recipients.

Keywords: Hepatocellular carcinoma, live donor liver transplant, liver transplantation

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Abbreviations: AFP: alfa-feto protein; ANA: anti-nuclear antibody; CMV: cytomegalovirus; CT: computed tomography; CTP: Child-Turcotte-Pugh; CXR: chest X-ray; DEXA: dual-emission X-ray absorptiometry; EBV: Epstein-Barr virus; EGD: esophagogastroduodenoscopy; ERCP: endoscopic retrograde cholangiopancreatography; FAP: familial amyloid polyneuropathy; HAV: hepatitis A virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; HTN: hypertension; INR: international normalized ratio; LDLT: live donor liver transplant; LT: liver transplantation; MELD: model for end-stage liver disease; MRI: magnetic resonance imaging; PSA: prostate-specific antigen; PSC: primary sclerosing cholangitis; RPR: rapid plasma reagin
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RECIPIENT SELECTION PROCESS

When evaluating potential recipients for LT, the following four questions need to be addressed by the transplant team:

1. Will the patient benefit from LT with an acceptable quality of life? If so, how soon does that patient require a LT? Is the disease sufficiently advanced to meet the minimal listing criteria for LT? If the recipient is considering an LDLT, the risk/benefit to both donor and recipient should be carefully assessed.
2. Are there any co-morbid conditions that would prohibit an acceptable outcome of LT?
3. In recipients with the past or current history of alcohol or drug use, what are the chances of recidivism?
4. Is there a social or financial system that allow for adequate follow-up care after transplantation?

Many of these questions could be answered easily, but it is important to remember that there are no rigid criteria or guidelines for the transplant team to address all these important questions. Published studies, team experience, and a multidisciplinary team are important resources that help the transplant centers make the right decision. Transparent discussions in a multidisciplinary team that comprise hepatologists, surgeons, social workers, psychologists, and transplant coordinators are essential before making difficult decisions. Moreover, the rationale for these decisions should be clearly documented and conveyed to the referring physician or to a patient in a timely fashion. The following sections would examine the patient evaluation process in more detail by addressing the above four important questions.

Will the patient benefit from liver transplantation with an acceptable quality of life? If so, how soon does that patient require an liver transplantation? Is the disease sufficiently advanced to meet the minimal listing criteria for liver transplantation?

The broad indications for LT are given in Table 1, and most of these indications, except for hepatocellular carcinoma (HCC), are complications of portal hypertension. Common etiologies for LT are viral hepatitis (HCV and HBV), alcoholic cirrhosis, autoimmune liver diseases (primary biliary cirrhosis, autoimmune hepatitis), biliary atresia, and hepatocellular carcinoma. Rare indications include Budd–Chiari syndrome, Wilson’s disease, α_1 -anti-trypsin deficiency, polycystic liver, glycogen storage disease, familial amyloid polyneuropathy (FAP), and hereditary oxalosis. The presence of these diseases alone does not warrant immediate evaluation or transplantation. Based on history, clinical, biochemical, or radiological evaluation, there should be sufficient evidence to indicate that the life expectancy of the patient is <1–2 years without transplantation. The exceptions to this rule are the presence of a small, unresectable HCC or extremely poor quality of life due to extreme pruritus or refractory encephalopathy.

Table 1 Common indications for liver transplantation.

Common indications

- Decompensated cirrhosis from any etiology and MELD >15
- Refractory ascites or hepatic hydrothorax
- Spontaneous bacterial peritonitis
- Refractory hepatic encephalopathy
- Hepatopulmonary syndrome
- Type 1 hepatorenal syndrome (HRS type 1)

Fulminant hepatic failure

Hepatocellular carcinoma (unresectable and fulfill Milan criteria)

Other potential indications

- Small cholangiocarcinoma in patients with PSC
- Hereditary oxalosis
- Porphyrias
- Familial amyloidosis
- End-stage polycystic disease of liver

MELD: model for end-stage liver disease; PSC: primary sclerosing cholangitis; HRS: hepatorenal syndrome.

Table 2 Childs–Turcotte–Pugh score.

Points	1	2	3
Encephalopathy	None	Grades 1–2	Grades 3–4
Ascites	None	Slight (or diuretic controlled)	At least moderate (despite diuretics)
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3

Child A=5–6 points; Child B=7–9 points; Child C=10–15 points

INR: international normalized ratio.

Table 3 Model for end-stage liver disease.

Formula

$MELD = 3.8 * \log_e(\text{bilirubin [mg/dL]}) + 11.2 * \log_e(\text{INR}) + 9.6 * \log_e(\text{creatinine [mg/dL]}) + 6.4$

Dialysis patients get a creatinine of 4 mg/dL

MELD scores could be calculated from many websites including that UNOS <http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98>

Guideline for recalculation of points while on the transplant list

Points	Intervals for re-calculation
>25	7 days
19–24	30 days
11–18	3 months

MELD: model for end-stage liver disease; UNOS: United Network for Organ Sharing.

In general, patients with spontaneous bacterial peritonitis, refractory ascites, recurrent bleeding despite shunt surgery or TIPS, and Child C cirrhosis with complications (which is unlikely to improve with treatment or abstinence from alcohol or medications) are good indications for immediate LT. Both Child–Turcotte–Pugh (CTP) scores (Table 2) and model for end-stage liver disease (MELD)

Table 4 Diagnostic testing.**Laboratory tests**

- Blood counts, INR, complete metabolic profile, AFP, HbA_{1c}, vitamin D
- ANA, ASMA, alpha-1AT phenotype, iron studies
- PSA
- Serology for HBV, HCV, HAV, HIV, CMV, EBV, HSV, RPR
- Urine microalbumin, protein

Imaging and endoscopy

- CXR, noncontrast CT of the chest (in those with HCC or cholangiocarcinoma)
- Abdomen MRI or CT with contrast
- Mammogram for women
- EGD and colonoscopy
- ERCP to assess the dominant strictures in PSC
- DEXA scan (in women and elderly men)

Cardiac evaluation

- Echocardiogram (bubble/contrast)
- Dobutamine echo or thallium (in patients >45 years)
- Cardiac catheterization in high-risk recipients (in the presence of microalbuminuria, type 2 diabetes mellitus, peripheral vascular disease, angina, high calcium score)
- Carotid duplex (>50 years and in high-risk subjects)
- Right heart catheterization in suspected portopulmonary HTN

Pulmonary evaluation

- Complete lung function tests (interpret with caution in those with severe ascites and general weakness)
- Arterial oxygen in hepatopulmonary syndrome

INR: International normalized ratio; AFP: alpha-feto protein; ANA: anti-nuclear antibody; PSA: prostate-specific antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HAV: hepatitis A virus; HIV: human immunodeficiency virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; RPR: rapid plasma reagin; CXR: chest X-ray; CT: computed tomography; HCC: hepatocellular carcinoma; MRI: magnetic resonance imaging; EGD: esophagogastroduodenoscopy; ERCP: endoscopic retrograde cholangiopancreatography; PSC: primary sclerosing cholangitis; DEXA: dual-emission X-ray absorptiometry; HTN: hypertension.

(Table 3) scores have been shown to predict the immediate mortality in both cholestatic and noncholestatic liver diseases, but MELD scores, because of its objectivity and probability of better predictability are increasingly used to prioritize organ allocation for patients on the transplant list in many countries. Patients are usually evaluated for LT when MELD score reaches around 14 and transplanted when it is >20. These rules also apply to LDLT, but there could be some flexibility depending on the special circumstances. Nevertheless, it is important to remember that patients with low MELD scores are unlikely to benefit from LT unless they have cirrhosis complicated by HCC.

The decision to list a patient for LT does not indicate that the patient is in need of immediate transplantation, and similarly the patients should be listed only if they are likely to require an LT in the next 1–2 years. Once listed, these patients should be followed at regular intervals to assess the progression of the disease and timing for transplantation. Patients who are waiting and have a stable course should not be offered deceased or live donor transplantation just because of graft availability. This is especially true for

conditions such as HCV with very high recurrence rates and low 5-year survival rates.

Are there any co-morbid conditions that would prohibit an acceptable outcome of liver transplantation?

The patient's ability to withstand a transplant operation and emerge with an acceptable quality of life is of paramount significance in the selection process. If the mortality associated with transplantation outweighs that of the liver disease, then clearly transplant is not in the best interest of the patient. Additionally, given the limited number of organs, it is in the best interest of the transplant community to allocate the organs to those who will benefit to the greatest extent.

The process of liver transplant evaluation starts with a detailed history and physical examination, focused not only on the liver-related issues and findings, but on all major organ systems. Great care should be taken to elicit any history of cardiopulmonary risk factors, other systemic diseases, extrahepatic malignancy, or other chronic ailments. Although recipient age is often taken into consideration, there is no absolute cut-off and should view the patient's age in the context of their medical co-morbidities as well as their overall life expectancy. Of particular importance is a history of coronary artery disease or other vascular diseases, and this is especially true in the presence of diabetes, hyperlipidemia, and severe obesity. Patients with previous history of cancer (only exception is skin cancer other than melanoma) could be evaluated if they are free of cancer for 5-years. Assuming that there are no obvious contraindications found on initial screening, the next stage of the evaluation consists of diagnostic testing and visits with the comprehensive transplant team.

Diagnostic testing includes comprehensive blood tests (Table 4), contrast-enhanced CT or MRI of liver (to exclude HCC and to assess vascular anatomy), pulmonary function tests, electrocardiogram, 2D-echocardiogram, and a chest X-ray (CXR) in all candidates. In patients over the age of 45 years, a dobutamine stress echocardiogram is also performed. Coronary arteriogram is done in high-risk subjects or those with a history of angina. Right heart catheterization is performed if there is a suspicion of pulmonary hypertension. Noncontrast CT scan of the chest is performed in patients with HCC to rule out lung metastases. In elderly subjects or those with risk factors, carotid duplex is also performed. If patients were found to have correctable abnormalities (e.g., significant coronary artery disease or carotid stenosis), those should be corrected before LT.

Potential recipients must meet with all members of the transplantation team. It includes hepatologist, transplant surgeon, social workers, psychologist, and the transplant coordinator. If there are any concerns during the diagnostic work-up, appropriate consultation is requested from a cardiologist, pulmonologist, or anesthesiologist. It may

also be appropriate to involve a nephrologist, if the recipient has renal failure, to rule out intrinsic renal disease and to get advice on the potential combined liver–kidney transplantation.

The immediate and late outcome of LT is dependent on many factors including age, race, body mass index (BMI), the presence of diabetes or coronary artery disease, pre-transplant serum creatinine, cause, and severity (MELD score, intensive care unit [ICU] status, or on ventilation) of liver disease at the time of transplantation.^{7–13} All these variables are available to the transplant physician before LT. Other factors such as cold ischemia time, ABO mismatch, donor age, graft quality, gender, and race are other predictive variables that are known only at the time of transplantation in deceased donor LT.¹⁴ In LDLT, most of the donor factors are available to the transplant team. In addition, surgical expertise, ICU care, and immunosuppression regimen may also play a role in the outcome.

There have been many attempts to develop survival models, but those models lacked sufficient discriminating power needed for routine clinical care. Artificial neural network has been suggested as a possible alternative to the traditional multivariate models, but to date, despite showing some promises, these models have not been used to reliably predict the outcome after LT. Previous work from my group has shown that post-transplant outcome could be predicted in a reliable manner based on the pre-transplant recipient characteristics alone.¹² A reliable prediction model is an important tool that could be used by physicians to advise their patients of potential mortality, prioritize organ utilization, and compare outcomes between different transplant centers. In our model, the seven pre-transplant variables that had a significant influence on the post-transplant outcome were age, race, BMI, United Network for Organ Sharing (UNOS) status (ICU vs non-ICU), diagnosis, serum bilirubin, and creatinine. The most important variables that determined a 30-day mortality were serum creatinine, severity of liver disease (serum bilirubin), etiology of liver disease, and UNOS status of the patient. While UNOS status became less important at 1 year, the influence of diagnosis, as a negative predictive factor, increased at 1 year. The cause of liver disease (HCV and HCC are negative predictors) and serum creatinine had a major effect on the immediate as well as on the late outcome. Unexpectedly, age had less effect on the immediate outcome and had more negative impact with long-term survival. Socio-economic status was not an important predictor in our studies, but this could be extremely relevant in India. Other factors such as donor age, race, sex, blood loss, cytomegalovirus (CMV) status, immunosuppressive regimen, and cold ischemia time are also important factors that determine the outcome of LT, but these factors will be available only at the time of transplantation in deceased donor LT (DDLT) and hence has limited or no value to predict the outcome before transplantation. In LDLT, however, some of this

information is available to the team. Many previous studies, using both donor and recipient factors, had attempted to predict the survival using multivariate regression models with mixed results. On a cautionary note, the predicted mortality is only an approximation and may not apply to an ‘individual’ patient. The decision not to transplant a patient should be based on sound clinical judgment and the expected outcome is used only for guidance.

In recipients with past or current history of alcohol or drug use, what are the chances of recidivism?

A significant proportion of potential recipients may have a history of obvious or occult alcohol or drug use. These recipients are at significant risk of resuming this behavior if it is not appropriately addressed prior to LT. In most transplant centers, recipients have a complete pre-approved alcohol or drug rehabilitation program with documented abstinence for at least 6 months prior to consideration for transplant. Although there have been successful outcomes in patients with alcoholic hepatitis, in general, patients with ongoing drug or alcohol use should not be offered LT. Social worker and the transplant psychologist play an important role in assessing the risk or recidivism in previous drug or alcohol addicts.

Is there a social or financial system that allow for adequate follow-up care after liver transplantation?

Often the most difficult and challenging issue that faces the transplant committee is whether the appropriate social or financial support system exists for a potential candidate. Many potential patients, especially those with alcoholism and drug use, have had troubled pasts and lack a nurturing environment to care for them after transplant. Failure to follow-up with laboratory examinations and appointments as well as missed medications can have extremely deleterious effects on post-transplant patients leading to rejection and late diagnosis of associated complications. It is therefore important for all patients to undergo an evaluation by a social worker and a psychologist dedicated to the transplant program in order to make the most educated decision possible. Social worker or another experienced member of the team should also evaluate and address the financial implications of liver transplant to the recipient (also the donor in LDLT).

Evaluation of Patients with Acute Liver Failure

Patients with acute liver failure present a variety of unique issues with regard to LT. Due to the acuity of their illness, the luxury of detailed medical and psychosocial testing is not always feasible. In general, these tend to be younger patients often with acute viral hepatitis or drug overdose and have only few co-morbidities. In addition to the blood tests, these patients should have electrocardiogram, 2D-echocardiogram, triple-phase CT (or MRI) scan of the liver,

and a CXR. Patients with Budd–Chiari syndrome should be tested for clotting abnormalities. Although patients with suspected alcoholic hepatitis are not offered LT in most centers, a history of alcohol intake or other drug use would not necessarily lead to exclusion in this scenario. These difficult issues should be decided upon on a case-by-case basis.

Deceased Donor Versus Living Donor Liver Transplantation

A potential recipient must be evaluated in the same fashion irrespective of whether they are going to have DDLT or LDLT.¹⁵ The availability of a live donor should not reduce the stringent criteria that are necessary for being listed for DDLT. This will also allow for re-transplantation with a deceased donor should the LDLT fail. If a patient is considered suitable for LT, then they could be considered for both DDLT and LDLT. In countries such as India, most patients depend on suitable live donors. Therefore, some of the criteria developed in North America and Europe may not be completely applicable to Asia. Few general rules, however, apply when making a decision with regard to LDLT.

In critically ill patients (ICU patients and those on ventilator), DDLT may afford them the best opportunity for a successful outcome. Similarly, recipients with very advanced cirrhosis (very high MELD scores) may require larger donor volume, which may not be achieved by LDLT. Furthermore, since donor safety is of paramount importance, LDLT should not be recommended to recipients whose predicted postoperative survival is poor based on their pre-transplant health status. The LDLT in acute liver failure is a serious ethical and moral dilemma for the transplant team and the immediate family members. If a patient were likely to receive a DDLT in a timely manner, this should be the chosen option since it does not involve any donor risks. However, if a patient is unlikely to receive a DDLT in a timely fashion, LDLT should be considered taking into consideration the risks to the donor and the potential benefits to the recipient. Patients who are unlikely to benefit from DDLT should not be offered LDLT under any circumstances. This includes large HCC (outside San Francisco or Milan criteria), low MELD scores or those with prohibitive co-morbid illnesses.

Management While Waiting for Liver Transplantation

Patients who are considered suitable for either DDLT or LDLT should be evaluated at periodic intervals until LT. If MELD scores were used to prioritize organ allocation for DDLT, the scores should be recalculated at fixed intervals depending on the severity of liver disease. If there has been a change in co-morbid illness (e.g., a serious cardiovascular event) or a change in the primary diagnosis (development

of HCC or increase in the size of HCC), the suitability for LT should be re-evaluated by the transplant team. If a patient was deemed unsuitable due to a new medical or social (including drug or alcohol use) condition, then they may be taken off the list or temporarily deactivated until the issue is resolved. Hospitalized patients, whether in the ICU or in the regular wards, should be reassessed on a daily basis, especially to exclude active bacterial and fungal infections.

In summary, the evaluation and selection of patients for LT is complex and requires a team of dedicated professionals. Medical, psychological and social factors must all be taken into consideration in order to achieve the best outcomes, and a team approach is critical for the success.

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