

Liver transplantation: Evolving patient selection criteria

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AS Yu, A Ahmed, EB Keeffe. Liver transplantation: Evolving patient selection criteria. Can J Gastroenterol 2001;15(11): 729-738. The widespread recognition of the success of liver transplantation as a treatment for most types of acute and chronic liver failure has led to increased referrals for transplantation in the setting of a relatively fixed supply of cadaver donor organs. These events have led to a marked lengthening of the waiting time for liver transplantation, resulting in increased deaths of those on the waiting list and sicker patients undergoing transplantation. Nearly 5000 liver transplantations were performed in the United States in 2000, while the waiting list grew to over 17,000 patients. The mounting disparity between the number of liver transplant candidates and the limited supply of donor organs has led to reassessment of the selection and listing criteria for liver transplantation, as well as revision of organ allocation and distribution policies for cadaver livers. The development of minimal listing criteria for patients with chronic liver disease based on a specific definition for decompensation of cirrhosis has facilitated the more uniform listing of patients at individual centres across the United States. The United Network for Organ Sharing, under pressure from transplant professionals,

patient advocacy groups and the federal government, has continuously revised allocation and distribution policies based on the ethical principles of justice for the individual patient versus optimal utility of the limited organ supply available annually. Beginning in 2002, it is likely that the Model for End-stage Liver Disease (MELD) score will be implemented to determine disease severity and direct donor organs to the sickest patients rather than to those with the longest waiting times.

Key Words: *Liver transplantation; United Network for Organ Sharing*

Greffe du foie : Évolution des critères de sélection des patients

RÉSUMÉ : On reconnaît de plus en plus la greffe du foie comme traitement efficace dans la plupart des types d'insuffisance hépatique aiguë et chronique, ce qui a créé une disproportion entre la demande d'organes et

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Received for publication November 10, 1999. Accepted January 18, 2000

le nombre stagnant d'organes transplantables provenant de donneurs décédés. Cette situation contribue à l'allongement des listes d'attente et à une hausse du nombre de décès parmi les patients en attente d'une greffe; en outre, les patients sont plus hypothéqués lorsque vient le temps de les opérer. Près de 5 000 greffes du foie ont été effectuées aux États-Unis en l'an 2000, alors que la liste d'attente s'allonge et compte désormais plus de 17 000 patients. L'écart croissant entre le nombre de candidats à la greffe du foie et le nombre limité d'organes provenant de donneurs est à l'origine d'une réévaluation des critères de sélection pour la greffe hépatique et des politiques de répartition et de distribution des foies provenant de personnes décédées. L'établissement de critères minimaux pour les insuffisants hépatiques inscrits sur les listes sur la base d'une

définition spécifique de la cirrhose décompensée a permis d'uniformiser l'inscription des patients dans les centres aux États-Unis. Sous la pression des professionnels œuvrant dans le domaine des transplantations, des groupes de défense des intérêts des patients et du gouvernement fédéral, le *United Network for Organ Sharing* a régulièrement mis à jour les politiques de répartition et de distribution en fonction de principes déontologiques de justice à l'égard des patients et d'optimisation de l'utilisation du nombre restreint de foies disponibles chaque année. À compter de 2002, il est probable qu'un modèle de maladie hépatique terminale sera mis en application pour déterminer la gravité de la maladie et pour réserver les organes prélevés aux patients les plus malades plutôt qu'à ceux qui sont sur la liste depuis le plus longtemps.

Liver transplantation is the definitive treatment for most acute and chronic liver diseases for which no alternative therapy is available (1-4). Liver transplantation has expanded dramatically over the nearly three decades following the National Institutes of Health (NIH) Consensus Development Conference in 1983, which concluded that liver transplantation was no longer experimental (1). Refinement in surgical techniques, safer and more effective immunosuppressive regimens, better patient selection and improved overall medical management increased the one-year survival rate from 30% in the early 1980s (5) to 74% among the first 1000 transplantations performed at the University of Pittsburgh, Pittsburgh, Pennsylvania, in the mid-to late 1980s (6) and to 85% to 90% in the late 1990s (2).

The performance of approximately 4500 liver transplantations in 125 liver transplant centres in the United States in 1998 attests to the growth of liver transplantation (2). From 1988 to 2000, the number of liver transplantations increased 2.9-fold (from 1713 to 4950), but the number of patients on the United Network for Organ Sharing (UNOS) liver list increased 27.8-fold (from 616 to 17,132) and the mortality of listed patients increased 7.6-fold (from 214 to 1636) (7). The current supply of cadaveric organs is obviously insufficient to meet the demand. Organ donation has been stagnant or increased by only a few per cent in recent years. These facts underscore the importance of appropriate selection of candidates for liver transplantation.

The major goals of liver transplantation are to prolong survival and to improve the quality of life. Data from the UNOS on 24,900 adult patients undergoing liver transplantation from October 1, 1987 to September 29, 1998 showed that the one-year, four-year and 10-year patient survival rates were 85%, 76% and 61%, respectively (2). The best survival occurred among patients who underwent liver transplantation for chronic cholestatic liver diseases, including primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). On the other hand, patients who underwent liver transplantation for hepatic malignancy had the worst outcome (Table 1). Multiple quality of life studies have consistently demonstrated significant improvement in the cognitive, physical and psychological functioning of the liver recipients after transplantation (8-11).

The prolonged waiting time for a donor organ has hindered the effort to achieve ideal timing of liver transplanta-

TABLE 1
Survival of 24,900 patients from the United Network for Organ Sharing database after adult liver transplantation, by diagnosis (1987 to 1998)

Diagnosis	Survival (%) after liver transplantation		
	One year	Four years	Seven years
Primary sclerosing cholangitis	91	84	78
Primary biliary cirrhosis	89	84	79
Autoimmune hepatitis	86	81	78
Chronic hepatitis C	86	75	67
Alcoholic liver disease	85	76	63
Cryptogenic cirrhosis	84	76	67
Chronic hepatitis B	83	71	63
Malignancy	72	43	34

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tion during the course of advanced chronic liver disease. The minimal listing criteria were developed in 1997 at a consensus conference and adopted by UNOS, with the intention of preventing inappropriate access to organ supply by early listing for individual patients (12,13). Individual transplant centres have established guidelines for selecting liver transplant candidates that generally fulfill accepted national criteria (3,4,12-15). A selection committee composed of key personnel (including transplant surgeons, hepatologists, nurse coordinators, psychiatrists and social workers) determines the suitability of potential candidates and, in the late 1990s, their priority for transplantation based on disease severity as defined by UNOS (Table 2).

As the organ shortage progressively worsens, it is increasingly more difficult to decide whether organs should be allocated to potential recipients with a less favourable outcome. Furthermore, it has become more controversial to offer a cadaver liver to a patient with a failing allograft versus others on the waiting list for their first transplant, in light of the reduced survival and increased resource utilization generally associated with retransplantation (16,17). The constriction in health care budgets is yet another motivation for refinement in the selection and timing of transplantation to achieve the most cost effective outcome, realizing that sicker patients incur greater costs with trans-

TABLE 2
United Network for Organ Sharing Liver Status* for patients aged 18 years or older according to disease severity

Status 1	Fulminant liver failure with life expectancy less than seven days – Fulminant hepatic failure as traditionally defined – Primary graft nonfunction less than seven days after transplantation – Hepatic artery thrombosis less than seven days after transplantation – Acute decompensated Wilson's disease
Status 2A	Hospitalized in intensive care unit for chronic liver failure with life expectancy less than seven days, with a Child-Pugh score of 10 or higher and one of the following: – Unresponsive active variceal hemorrhage – Hepatorenal syndrome – Refractory ascites or hepatic hydrothorax – Stage 3 or 4 hepatic encephalopathy
Status 2B	Requiring continuous medical care, with a Child-Pugh score of 10 or higher, or a Child-Pugh score 7 or higher and one of the following: – Unresponsive active variceal hemorrhage – Hepatorenal syndrome – Spontaneous bacterial peritonitis – Refractory ascites or hepatic hydrothorax Or the presence of hepatocellular carcinoma
Status 3	Requiring continuous medical care, with a Child-Pugh score of 7 or higher, but not meeting criteria for status 2B
Status 7	Temporarily inactive

*Initially implemented in July 1997, later modified in January 1998 and August 1998 (<http://www.unos.org>)

plantation (18-20). In this short review, factors important in the selection of adult patients for liver transplantation, evolving national listing policies in the United States and the determination of the optimal timing of surgery are reviewed.

GENERAL SELECTION CRITERIA FOR LIVER TRANSPLANTATION

Advanced chronic liver disease, acute liver failure, unresectable hepatic malignancy and inherited metabolic liver disease are the four major adult categories for which liver transplantation has been performed. The majority of adult liver transplantations are performed for various chronic liver diseases, of which chronic hepatitis C and alcoholic cirrhosis are the most common (Table 3) (2). Acute liver failure accounts for only 6.2% of indications for liver transplantation. Unresectable hepatic malignancy is a controversial and relatively uncommon indication for transplantation in current practice, although this indication may increase over the next several years secondary to the prevalence of chronic hepatitis C and cirrhosis. Inherited meta-

TABLE 3
Liver disease in adult transplant recipients in the United States (United Network of Organ Sharing database 1987 to 1998; n=24,900)

Primary liver disease	n (%)
Chronic hepatitis C	5155 (20.7)
Alcoholic liver disease	4258 (17.1)
Alcoholic liver disease and hepatitis C	1106 (4.4)
Chronic hepatitis B	1368 (5.5)
Cryptogenic cirrhosis	2719 (10.9)
Primary biliary cirrhosis	2317 (9.3)
Primary sclerosing cholangitis	2178 (8.7)
Autoimmune hepatitis	1194 (4.8)
Acute liver failure	1555 (6.2)
Hepatic malignancy	951 (3.8)
Metabolic diseases	923 (3.7)
Other	1050 (4.2)
Unknown	126 (0.5)

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TABLE 4
Contraindications to liver transplantation

Compensated cirrhosis
Active alcohol or substance abuse in previous six months
Systemic sepsis
Advanced cardiopulmonary disease
Extrahepatic malignancy
Cholangiocarcinoma
Human immunodeficiency virus seropositivity
Anatomic abnormality precluding liver transplantation

bolic liver disease, in which the inborn error of metabolism resides in the hepatocytes, is curable by liver transplantation (21). Most patients with inborn errors of metabolism, eg, hereditary hemochromatosis, Wilson's disease, alpha₁-antitrypsin deficiency, tyrosinemia and glycogen storage diseases, have obvious hepatic parenchymal damage (21). They undergo transplantation for either liver failure or early hepatocellular carcinoma arising from a cirrhotic liver. On the other hand, recipients may undergo liver transplantation to correct the metabolic defect residing in the hepatocytes, despite no clinical or histological evidence of liver injury, eg, type 1 hyperoxaluria, urea cycle enzyme deficiency, familial homozygous hypercholesterolemia, and hemophilia A and B (22-25).

Other general patient selection criteria include the absence of alternative forms of therapy that may reverse liver failure and defer the need for liver transplantation, and the absence of contraindications to liver transplantation (Table 4). The ability to comply with longitudinal follow-up care, which is a major focus of the pretransplantation psychosocial assessment, is another important

consideration. Finally, it is essential for patients to provide for the substantial costs of liver transplantation, medications and long term medical care. Adequate insurance coverage for transplantation is typically verified by a financial counsellor at the transplant centre.

UNOS LISTING POLICIES

The disparity between organ demand and availability led, in the late 1990s, to considerable debate among transplant professionals, potential recipients and the federal government regarding UNOS allocation and distribution policies (26-28). Distribution determines over which geographical area organs are allocated, and allocation determines which patients receive an available liver within a geographical area. Historically, the UNOS allocation scheme was based on the principle that the sickest patients who waited the longest underwent transplantation first. Furthermore, the UNOS distribution scheme dictated that patients at transplant programs served by a local organ procurement organization (OPO) had the first priority for livers obtained by that OPO.

UNOS has adopted the principles of justice and utility in standardizing organ allocation. Justice recognizes the medical urgency of the individual patient and gives priority to the sickest person who has the greatest risk of dying before receiving a transplant. On the other hand, utility focuses on optimizing the resources of society and gives priority to the patient with the greatest likelihood of a successful outcome. With a geographically restricted distribution scheme, prioritization of recipient candidates favours medical utility at the expense of medical urgency. A less ill patient in one OPO may receive a transplant earlier than a sicker patient who unfortunately is listed in another OPO with a longer waiting list. Broadening the distribution of donor organs, if this change in policy is ever adopted, may allow justice to prevail over utility.

In the late 1990s, the categories of UNOS status were modified to define more precisely disease severity, exclude chronic liver disease patients from status 1 and increase priority for patients with hepatocellular carcinoma (Table 2). Finally, the transplant community is attempting to address the reality of managed care, which has transferred financial risk from insurers to providers (18). High risk patients are a significant financial liability to transplant centres in the managed care marketplace (19,20). Thus, appropriate patient selection to achieve a cost effective outcome may be an equally important issue along with allocation and distribution policies.

POTENTIAL SOLUTIONS TO THE ORGAN SHORTAGE

Current approaches to the organ shortage include maximized efforts for organ procurement, expanded use of 'marginal donors', cadaveric split liver transplantation and adult living donor liver transplantation (LDLT). Xenotransplantation may be a potential option in the future, but several hurdles need to be overcome, including hyperacute and

acute vascular rejection, and the potential transmission of infectious agents from graft to recipient.

Major efforts have been made since 1995 to increase organ donation, with the first substantial increase of 5.6% in cadaveric organs noted in 1998 (7). The United States has a very respectable organ donation rate of approximately 20 per million population compared with that of other countries with major transplant programs, eg, 25 per million population in Spain and less than 10 per million population in Italy.

Expansion of the donor pool in recent years has included the use of organs with substantial fatty change, grafts from older individuals, and grafts from those infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). The organ shortage appears to justify the use of organs from older donors or with higher fat content, despite the associated risk of primary graft nonfunction (29-31). Organs from older donors are associated with poorer graft survival that is, nevertheless, compensated by transplantation technology and superior medical management (32). Moreover, an allograft judged as good quality by the surgeon at the time of procurement is associated with excellent patient and graft survival rates after transplantation (33).

Allografts from donors positive for hepatitis B core antibody have been transplanted into recipients with a clinical condition that would require an unacceptably prolonged waiting period under the current allocation system. The incidence of de novo HBV infection is as high as 72% in susceptible recipients (34,35). Prophylaxis has been successful with combination hepatitis B immune globulin and lamivudine or, more recently, lamivudine alone (35,36). In addition, patients with chronic hepatitis C who receive HCV-positive allografts have a similar five-year graft survival to those who receive HCV-negative organs (37).

Split liver transplantation allows two liver transplants from a single cadaveric liver, usually using a right trisegment (segments 4 to 8) transplanted into an adult recipient and a left lateral segment (segments 2 and 3) implanted into a child (38). The two methods for split liver transplantation are the ex vivo technique and the in vivo technique. The ex vivo technique involves splitting the liver on the bench after its removal from the cadaver. Its early experience was fraught with biliary complications and reoperations (39), but patient and graft survival rates were substantially improved in the recent King's College Hospital series (40). In vivo technique involves dissection of the liver in the cadaver before procurement, and may be superior to ex vivo technique. In a series of in vivo split grafts involving 102 adult and pediatric recipients at the University of California at Los Angeles, California, patient and graft survival rates were comparable with those achieved with whole organ transplantation (38).

LDLT reduces waiting time and allows elective liver replacement before progression of liver failure that might compromise the surgical outcome. Furthermore, transplantation can be carried out for patients with hepatocellular carcinoma or PSC, with the associated risk of cholangiocar-

cinoma at an earlier stage. Other advantages include better quality organs that were procured from healthy donors and subjected to less cold ischemia time. Unfortunately, donors must accept morbidity and mortality risks of 10% and 0.5%, respectively. The recipient undergoing LDLT experiences the same surgical complications as those of cadaveric liver transplantation, but with a higher likelihood of biliary problems. The graft to recipient body weight should be at least 0.8% to ensure an adequate hepatic volume for the patient. The transplanted liver segment takes only a few weeks to regenerate into full volume.

LDLT was first employed in children in 1988 and subsequently in adults in 1994 (41,42). Adult to pediatric LDLT, using the left lateral segment of the liver, is associated with low morbidity in the donor and excellent survival in the recipient (43). Surgical outcomes have been improving in recent years with elective adult to adult LDLT using the right lobe of the liver (segments 5 to 8), right trisegment (segments 4 to 8) for larger recipients to ensure adequate hepatic volume or left lobe (segments 2 to 4) for small-sized recipients (44-46). The surgery has achieved excellent survival rates even when applied to emergent cases (47). Unfortunately, LDLT only offers a partial solution to the organ shortage for adult liver transplantation, because only a small percentage of donors are qualified candidates after full evaluation. Among 100 potential living donor recipients at the University of Colorado, 51 were rejected based on recipient characteristics, and only 15 of the remaining 49 were able to identify a suitable donor and undergo LDLT (48).

MINIMAL LISTING CRITERIA FOR LIVER TRANSPLANTATION

Minimal listing criteria for liver transplantation were developed in 1997 at a consensus conference sponsored by the NIH (13). The minimal listing criteria were established based on large scale natural history studies of patients with compensated cirrhosis due to chronic hepatitis C or other miscellaneous causes (49-51). Patient survival is significantly reduced after decompensation of cirrhosis, ie, ascites, portal hypertensive bleeding or hepatic encephalopathy. In a natural history study of patients with chronic hepatitis C, the probabilities of decompensation at five and 10 years after the diagnosis of compensated cirrhosis were 18% and 29%, respectively. In addition, the five-year survival rates were 91% for cirrhotic patients without decompensation and 50% for those with decompensation (49). Ascites carries a poor prognosis that is at least partly attributable to spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome. For patients with cirrhotic ascites who survive an episode of SBP, the one-year survival rate is reduced from 66% to 38% (52). Type 1 hepatorenal syndrome implicates an even more ominous mean survival of 1.7 weeks (53). Finally, patients who bled from varices carry a poor prognosis regardless of endoscopic therapy, transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt placement (54,55). In summary, a patient with compen-

sated cirrhosis, ie, Child-Pugh class A with a score of 5 or 6, will remain stable for a considerable period of time. Survival is markedly diminished once decompensation occurs. Hence, the onset of liver decompensation rather than the presence of cirrhosis per se should trigger referral and, if qualified, listing for transplantation. Based on the natural history of cirrhosis and the expected outcomes of liver transplantation, the minimal listing criteria adopted at the NIH were as follows (13).

- Immediate need for liver transplantation
- Estimated one-year survival rate 90% or less
- Child-Pugh score 7 or higher (Child-Pugh class B or C)
- Portal hypertensive bleeding or a single episode of SBP, irrespective of Child-Pugh score

BIOCHEMICAL AND CLINICAL INDICATIONS FOR LIVER TRANSPLANTATION

Advanced chronic liver disease and acute hepatic failure are associated with diminished quality of life and abnormal biochemical indexes that reflect impaired synthetic and excretory functions of the liver. Identifying threshold laboratory parameters and specific hepatic decompensations allows prompt referral and evaluation for liver transplantation (3,14,15).

Chronic liver failure: Progressive end-stage cirrhosis accounts for over 80% of all patients undergoing liver transplantation (Table 3) (2). The criteria for listing these patients may be divided into biochemical and clinical indications. The biochemical indexes of patients with chronic cholestatic diseases differ somewhat from those of patients with chronic hepatocellular diseases such as hepatitis C or alcoholic liver disease. Serum albumin level less than 28 g/L or prothrombin time greater than 3 s over that of control subjects in patients with chronic hepatocellular diseases should warrant consideration for liver transplantation. On the other hand, serum bilirubin level higher than 171 $\mu\text{mol/L}$ serves as a biochemical indication for transplantation in patients with chronic cholestatic liver diseases. These laboratory abnormalities, even occasionally in the absence of clinical decompensation, indicate severely impaired liver function and allow patients to achieve a Child-Pugh score of 7 and to satisfy the minimal listing criteria.

Recurrent or severe hepatic encephalopathy, refractory ascites, SBP, recurrent or refractory portal hypertensive bleeding, incapacitating fatigue and weakness, progressive malnutrition, hepatorenal syndrome and detection of a small hepatocellular carcinoma are all clinical reasons for performing transplantation in patients with either hepatocellular or cholestatic liver diseases. Clinical indications for liver transplantation that are unique to cholestatic liver diseases include intractable pruritus, progressive bone disease with fractures and, in the setting of PSC, recurrent bacterial cholangitis (Table 5).

Acute liver failure: Liver transplantation for acute hepatic failure has been associated with substantial improvement in

TABLE 5
Biochemical and clinical indications for liver transplantation in chronic liver disease

Cholestatic liver disease
Bilirubin level greater than 171 $\mu\text{mol/L}$
Intractable pruritus
Progressive cholestatic bone disease
Recurrent bacterial cholangitis
Hepatocellular liver disease
Serum albumin level less than 30 g/L
Prothrombin time higher than 3 s above control
Both cholestatic and hepatocellular liver diseases
Recurrent or severe hepatic encephalopathy
Refractory ascites
Spontaneous bacterial peritonitis
Recurrent portal hypertensive bleeding
Severe chronic fatigue and weakness
Progressive malnutrition
Development of hepatorenal syndrome
Detection of small hepatocellular carcinoma

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survival over the past 10 years (2,56,57). Contributing factors to the improved outcome include a national organ procurement network and a multidisciplinary intensive care approach, with anticipation and treatment of such complications as infection, bleeding and cerebral edema. Early referral of patients suffering from acute hepatic failure to a transplant centre is essential to secure aggressive supportive care and to expedite transplant evaluation and listing. Certain biochemical and clinical features, as established by the King's College Hospital in London and the Paris group at Villejuif, allow selection of patients who are likely to die from acute liver failure and, therefore, would benefit from liver transplantation (Table 6) (58,59). Based on a clinical series of over 500 patients, the British group defined separate criteria for patients with fulminant hepatic failure due to acetaminophen overdose and for those caused by viral or drug-induced hepatitis (58). These criteria have high specificity and positive predictive value but low negative predictive value for a poor outcome (60). Lack of criteria fulfillment cannot be reliably interpreted to predict spontaneous survival, and liver transplantation should still be considered, especially in cases unrelated to acetaminophen (61). On the other hand, the French group established the selection criteria based on hepatic encephalopathy and factor V level of less than 20% in patients who are younger than 30 years of age or less than 30% in older patients (59).

Aggressive supportive care is necessary in patients with fulminant hepatic failure to prevent and treat medical problems that may complicate or even contraindicate liver transplantation, including bleeding, infection, cerebral

TABLE 6
Criteria for liver transplantation in fulminant hepatic failure

Criteria of King's College, London, United Kingdom*

Acetaminophen patients

- pH less than 7.3 or
- Prothrombin time greater than 6.5 (INR) and
- Serum creatinine greater than 300.56 $\mu\text{mol/L}$

Nonacetaminophen patients

Prothrombin time greater than 6.5 (INR), or

Any three of the following variables:

- Younger than 10 years or older than 40 years of age
- Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reaction
- Duration of jaundice before encephalopathy longer than seven days
- Prothrombin time greater than 3.5 (INR)
- Serum bilirubin greater than 300.96 $\mu\text{mol/L}$

Criteria of Hopital Paul-Brousse, Villejuif, France[†]

Hepatic encephalopathy and

Factor V level less than 20% in patient younger than 30 years of age

Factor V level less than 30% in patient 30 years of age or older

*Data from reference 58; [†]Data from reference 59. INR International normalized ratio

edema, respiratory failure and renal failure (3,56). The prognostic criteria established by the British and French groups allow determination of the need for liver transplantation before the onset of advanced hepatic encephalopathy with its risk of cerebral edema. Extradural monitoring of intracranial and cerebral perfusion pressures allows better neurological assessment once stage 3 or 4 encephalopathy develops (62,63).

TIMING OF LIVER TRANSPLANTATION

Timely referral and performance of liver transplantation early after the onset of liver decompensation is associated with improved survival and reduced costs. The one-year survival at the University of Pittsburgh was 86% for recipients who were not hospitalized before transplantation but only 70% for those who were in the intensive care unit at the time of surgery (6). However, liver transplantation has a 10% to 15% one-year mortality and should not be performed until onset of major cirrhotic complications or biochemical evidence of severe liver dysfunction. Referral and listing for liver transplantation should take place when patient survival is unlikely to extend beyond one to two years, but before the development of ominous clinical features such as SBP.

The best prognostic survival models to identify the ideal timing and predict the outcome of liver transplantation in chronic liver disease have been applied to PBC (64-68). The Mayo model for PBC includes five independent variables prognostic of survival, including age, serum bilirubin, serum albumin, prothrombin time, and the presence or

absence of peripheral edema (65,66). The Mayo model has shown that liver transplantation favourably interrupts the natural history of PBC and improves patient survival compared with supportive therapy (66,67). The optimal timing for liver transplantation occurs when the Mayo risk score is 7.8, above which the risk of death after transplantation rises progressively (69). The Mayo model for PBC is shown to be superior to the Child-Pugh score and can accurately predict the level of resource utilization after transplantation, including intraoperative blood requirement, and the duration of time that the recipient is on the ventilator, in the intensive care unit and in the hospital (70).

PSC has a less predictable natural history and may be punctuated by jaundice from dominant biliary strictures or episodes of recurrent bacterial cholangitis (71-76). Furthermore, cholangiocarcinoma may develop and preclude liver transplantation, except for the occasional cases when the tumour is localized without extensive microscopic involvement (77,78). Age, serum bilirubin, histological stage, and the presence or absence of splenomegaly are the independent predictive variables in the recently revised Mayo model for PSC (67,71,72). However analysis of the National Institutes of Diabetes, and the Digestive and Kidney Diseases Liver Transplantation Database demonstrated the prognostic superiority of the Child-Pugh score to the Mayo model in terms of patient survival and resource utilization for PSC patients who underwent liver transplantation (79).

MODEL FOR END-STAGE LIVER DISEASE

The prognostic parameters of the traditional Child-Pugh classification may be susceptible to variability among different observers or laboratories. Hepatic encephalopathy and ascites are subjective and manipulable findings that may be modified by medical therapy. In addition, the assessments of these clinical features are difficult to standardize and may be subject to further refinement depending on the rigour of the examination, eg, psychometric tests may detect previously unnoticed subclinical encephalopathy, and radiological imaging may discover minimal ascites. Even for objective parameters such as serum albumin level and prothrombin time, normal ranges are not standardized among laboratories. Nevertheless prothrombin time can be expressed as the standardized international normalized ratio (INR) in the calculation of Child-Pugh score.

The Child-Pugh score has several additional shortcomings in prioritizing organ allocation. The finite categories of disease severity for advanced cirrhosis, ie, statuses 2A, 2B and 3 (Table 2), limit the ability to discriminate among transplant candidates and necessitate the frequent use of waiting time as a tiebreaker. An inevitable consequence is the practice of many transplant physicians to pad the list with patients suffering from less severe liver disease, with the intention of achieving longer waiting times and a higher priority for donor organ. Second, each of the five parameters in the Child-Pugh classification is assigned the same weight with the maximum score of 3, even though the

variables may differ from each other in terms of clinical significance. Third, the Child-Pugh scoring fails to recognize the continuum of disease severity beyond the laboratory 'ceiling', eg, patients would be assigned a score of 3 for serum bilirubin whether the laboratory value is 68.4 $\mu\text{mol/L}$ or 684 $\mu\text{mol/L}$. Last, the Child-Pugh classification does not incorporate renal function, which is proven to be an independent predictor of survival in patients with advanced liver disease (80,81).

Recently, the Department of Health and Human Services has been working on improving organ allocation policies with an emphasis on medical urgency (82). The Institute of Medicine, which was contracted to review liver allocation and distribution policies, recommended that the waiting time be de-emphasized and replaced with a scientifically validated triage system based on liver disease severity (83). The UNOS Board of Directors approved for organ allocation the use of the Model for End-Stage Liver Disease (MELD), which employed objective, standardized, reproducible and easily verifiable laboratory values. The MELD scoring system was originally named the Mayo TIPS model to estimate patient survival after TIPS placement, based on four prognostic variables including serum bilirubin level, serum creatinine level, INR and liver disease etiology (84). Subsequently, MELD was demonstrated to be a reliable measure of mortality risk in patients with end-stage liver disease and an accurate disease severity index to determine organ allocation priorities (85).

The MELD model was tested on four separate populations:

- patients hospitalized for hepatic decompensation (n=282);
- ambulatory patients with noncholestatic cirrhosis (n=491);
- patients with PBC (n=326); and
- a historical cohort of patients diagnosed with cirrhosis between 1984 and 1988 (n=1179).

It was validated by the concordance (c) statistic that ranges from 0 to 1, with 0.5 corresponding to what is expected by chance alone and 1.0 to perfect discrimination. In general a c statistic greater than 0.7 indicates a useful test, whereas a value greater than 0.8 implies excellent diagnostic accuracy. The c statistics for predicting three-month mortality in the four groups were 0.87, 0.80, 0.87 and 0.78, respectively. They decreased only slightly in predicting one-year mortality, with c statistics ranging between 0.73 and 0.85. The accuracy of the model was only minimally affected after incorporation of the individual's portal hypertensive complications or the etiology of the underlying liver disease; thus, the current MELD score includes three parameters: serum bilirubin, INR and serum creatinine.

For listed patients with chronic liver disease, UNOS is currently considering implementation of the MELD scoring system. Fulminant hepatic failure remains a separate entity and continues to hold the highest priority for available organs. Patients with hepatocellular carcinoma will be assigned a MELD score equivalent to a 40% three-month

mortality risk before transplantation, with bonus points added every three months until they receive a transplant, die or become no longer suitable for transplantation (86). In the MELD system, the maximum serum creatinine level will be capped at 353.6 $\mu\text{mol/L}$, which will also be the value assigned automatically to patients on renal replacement therapy (87). Laboratory values less than 1.0 will be set to 1.0 to prevent calculation of a negative score. The Regional Review Boards of UNOS will handle any special cases not addressed by the MELD system, such as hepatopulmonary syndrome or familial amyloidosis (86). An individual patient's MELD score will be updated regularly. Also underway is the development and validation of a Pediatric End-Stage Liver Disease (PELD) scoring system.

CANDIDATE ASSESSMENT FOR LIVER TRANSPLANTATION

The prospective candidate for liver transplantation undergoes a pretransplant evaluation that can usually be completed on an outpatient basis over two to three days; sick patients undergo an inpatient evaluation. The transplant coordinator and transplant hepatologist facilitate a comprehensive evaluation to determine whether medical or psychosocial contraindications are present. Routine evaluation includes blood typing, complete blood count, liver and kidney chemistry, viral serologies (HBV, HCV, human immunodeficiency virus, cytomegalovirus), chest x-ray and abdominal imaging to confirm patency of hepatic vasculature and to exclude a coincidental hepatocellular carcinoma. Transplant candidates over 50 years of age or with coronary risk factors should pursue cardiology consultation and additional studies that may include stress echocardiogram or thallium and, in unsettled cases, cardiac catheterization (88). Doppler study of carotids and peripheral vessels is mandated only by clinical suspicion. Electrocardiogram and skin testing for tuberculosis are routinely performed. History of lung disease or chronic tobacco use necessitates pulmonary function tests. Renal function is assessed by cre-

atinine clearance. Consultations with a social worker and financial counselor are routine, whereas psychiatric evaluation is reserved for patients with a history of substance abuse or mental illness. Depending on age and other risk factors, cancer screening with occult fecal blood testing, lower gastrointestinal endoscopy and, in women, mammogram and pap smear may be necessary.

Once pretransplant evaluation is completed, the patient is presented to the selection committee and assigned subsequently to one of the four categories:

- suitable and ready, with listing for a donor organ;
- suitable but medically too well, with placement on inactive status and continued follow-up with the referring physician;
- potentially reversible contraindication that prompts further conservative management and temporary deferral from listing; or
- absolute contraindication, with denial of transplantation.

Once approved for transplantation, the patient is listed for a donor organ with UNOS.

The average waiting time for a listed patient continues to increase and may be as long as three to four years depending on the local OPO where the patient is listed. Furthermore, it varies with blood type and the UNOS status of the transplant candidate. For example, patients with O blood type on average wait the longest; status 3 patients who are at home wait longer than those listed as higher status. Status 1 and status 2A are status-dependent, irrespective of waiting time and take priority over patients listed as status 2B or 3. Local referral and transplant centres together support patients during this crucial waiting period. A decreasing majority of, and unfortunately not all, listed patients eventually undergo liver transplantation, achieving 85% to 90% one-year survival and 65% to 80% long term survival.

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