Model for End-stage Liver Disease and Organ Allocation in Liver Transplantation: Where Are We and Where Should We Go?

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The Child-Turcotte-Pugh (CTP) score has been used for decades to measure the severity of chronic liver disease. Recent studies have shown that the model for end-stage liver disease (MELD) more accurately predicts the short- and mid-term survival for patients with cirrhosis compared to the CTP system. MELD, which has 3 parameters (serum bilirubin, creatinine, and prothrombin time) that need logarithmic transformation, has the advantage of a wide-range continuous scale and is more objective and less variable. The liver allocation system has changed from a status-based algorithm using the CTP score, to one using a continuous MELD severity score as a reference system to prioritize adult patients on the waiting list since 2002 in the USA. However, there are potential limitations of MELD. An intrinsic defect is that some important parameters, such as hepatic encephalopathy and ascites, which are common adverse complications in cirrhosis, are not included in MELD. It has been suggested to incorporate a low serum sodium level into the prognostic model to enhance the predictive ability. Moreover, the change of MELD over time may provide updated information for patients on the transplant waiting list. In summary, although there was encouraging evidence supporting the prognostic advantage of MELD, the optimal role of MELD in the setting of outcome assessment for cirrhotic patients needs more study. Appropriate modifications and fine tuning of MELD are necessary for determining the ranking status of patients on the waiting list, to avoid a futile transplantation and improve overall patient survival. [*J Chin Med Assoc* 2006;69(5):193–198]

Key Words: liver cirrhosis, liver transplantation, MELD

Introduction

The formation of liver cirrhosis is usually an irreversible process from a variety of long-standing insults, such as virus, drugs, alcohol, and others. Progression into end-stage cirrhosis is associated with a limited survival, and it has been a challenging issue for physicians to develop a reliable model for predicting the outcome. Liver transplantation is the only definite treatment modality for patients with end-stage liver cirrhosis. A major function of the predictive model is to accurately assess the probability of mortality within a given time interval, so that a timely liver transplantation can be performed. The Child score, which was first proposed in the 1960s and then modified and continuously known as the Child-Turcotte-Pugh (CTP) score (Table 1), has been developed to solve these issues.

The selection of predictors and construction of the CTP system were empirical, and the system contains parameters that were felt very important to affect the outcome. Abundant studies show that it can provide accurate prognostic information associated with various cirrhosis-related complications and clinical situations.[1–6] Although never formally validated as a

Table 1. The Child-Turcotte-Pugh (CTP) scoring system*

	1 point	2 points	3 points
Bilirubin, mg/dL	< 2	2–3	> 3
Albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Prothrombin time prolongation, sec	< 4	4–6	> 6
Ascites	None	Easily controlled	Poorly controlled
Encephalopthy	None	Grades 1–2	Grades 3–4

*CTP class: A, 5–6 points; B, 7–9 points; C, 10–15 points.

prognostic tool, the CTP score is useful to assess the relative risk of mortality in patients with cirrhosis and has been popular for the past 3 decades. However, a major defect of the CTP system is a relatively narrow score range from 5 to 15. While the waiting list of liver transplantation is rapidly growing and patients on the waiting list far outnumber the cadaveric liver donors, the priority of patients with the same CTP score awaiting transplantation becomes difficult to judge. A simple first-come, first-served principle was proposed and used in the transplantation society; however, investigators subsequently found that patients with a longer waiting time may actually have a less severe degree of cirrhosis. It was later demonstrated that waiting time is not a factor that affects survival and was abandoned as a criterion in organ allocation.[7] Another potential inherent flaw of the CTP system is that it contains subjective variables, including the severity of encephalopathy and ascites, which may be greatly influenced by personal judgment from center to center during status interpretation. These drawbacks compromise the fairness of organ allocation in liver transplantation. The concept of a model for end-stage liver disease (MELD), initiated by the Mayo Clinic group in 2000,[8] emerged and was aimed to amend these defects.

MELD for Liver Transplantation

The MELD score was originally developed to predict the survival after transjugular intrahepatic portosystemic shunt (TIPS).[8] The investigators found 4 variables that were independently associated with survival in the Cox multivariate model. These predictors are serum bilirubin and creatinine level, INR (international normalized ratio) of prothrombin time, and the etiology of cirrhosis (alcoholic and cholestatic *vs* others). After modification by the United Network of Organ Sharing (UNOS), the currently used MELD equation to calculate the severity score is as follows:

$9.6 \times \log_e$ (creatinine mg/dL) $+ 3.8 \times \log_e$ (bilirubin mg/dL) $+ 11.2 \times \log_e$ (INR) $+ 6.4$. Minimal values are set to 1.0 for calculation purposes. The maximal serum creatinine level considered within the MELD score equation is 4.0 mg/dL. This equation was tested and adequately confirmed in a study to predict the mortality in cirrhotic patients.[9] Because donor livers are allocated to the recipients according to the severity of underlying disease, the UNOS has suggested using the MELD system to prioritize adult patients on the waiting list of transplantation. Since 2002, the liver allocation system has changed from a status-based algorithm using CTP and other scores, to one using a continuous MELD severity score to prioritize adult patients on the waiting list in the USA.[10,11]

A major step forward of MELD is that renal function is included for prediction. Renal dysfunction is a common event occurring in up to 75% of cirrhotic patients during the course of the disease, and the severity of cirrhosis in patients with or without hepatocellular carcinoma (HCC) was consistently identified as an important factor of renal insufficiency in previous studies.[12–14] In addition, a number of studies have emphasized the influence of renal function in the course of cirrhosis.[1,8,15,16] The occurrence of hepatorenal syndrome in cirrhotic patients usually indicates a dismal prognosis, and liver transplantation is the only definite treatment to prolong survival. These lines of evidence highlight the need to take renal function into consideration in prognostic evaluation.

Validation and Application

The MELD scoring system has been shown to more accurately predict 3-month mortality than the traditional CTP system for UNOS status of 2A (CTP score ≥ 10 plus cirrhosis-related complications such as active variceal hemorrhage, hepatorenal syndrome, refractory ascites/hepatic hydrothorax, or stage 3 or 4

hepatic encephalopathy) and 2B (CTP score ≥ 10, or score ≥ 7 plus complications) patients in a multicenter survey in the USA.[17] Its accuracy for outcome prediction in patients with decompensated cirrhosis has also been confirmed in Europe.[18,19] Most of these comparative studies have adopted an approach by measuring the concordance (c-statistic) equivalent to the area under the receiver operating characteristic (ROC) curve for MELD and CTP score to assess the ability for outcome prediction. Importantly, direct evidence to support the use of MELD is that the mortality rate on the waiting list of liver transplantation is decreasing in the post-MELD era.[20] In addition, patient and graft survival have remained excellent since implementation of the MELD/PELD (pediatric end-stage liver disease) system.[21] In keeping with these studies, MELD has achieved its primary goals by allocating cadaveric livers to the sickest patients without compromising post-transplantation survival.[22]

Although underlying chronic liver diseases may vary in different geographical regions, MELD was suggested as a preferred model for patients with viral hepatitis[23] or alcoholic hepatitis.[24,25] The application of the MELD system has also been shown to be a useful model to predict the outcome in cirrhotic patients undergoing major surgical procedures.[26] The use of the MELD system has been further extended, because the MELD score, in combination with the current staging system for HCC, may further enhance the prognostic capabilities and more accurately predict the survival for HCC patients undergoing arterial chemoembolization.[27]

Although MELD has been used as the primary reference in predicting the mortality for cirrhotic patients, it is controversial which system is best in different clinical conditions. The comparison of the characteristics of CTP, MELD, and Discriminant Function score is shown in Table 2.[28] The Discriminant Function score formula is 4.6 × (patient's prothrombin time (PT) – control PT) + total bilirubin (mg/dL). This scoring system, proposed by Maddrey et al,[29] is used to assess the prognosis of patients with alcoholic hepatitis. Alternatively, a major drawback of the CTP system, compared to MELD, which has the advantage of minimal variability and wide-range continuous scale, is that it has a "ceiling effect" that may limit its application at the population level.[28] However, the CTP system does not need logarithmic transformation and is easy to calculate at bedside evaluation. In addition, it contains indispensable components, such as ascites and encephalopathy, which are considered important prognostic predictors in cirrhotic patients. It is still debatable whether MELD is a better tool than the CTP system in managing patients on a daily practice basis.

For years, liver cirrhosis has been ranked in the top 10 causes of death in Taiwan. With the increasing experience and dedication of physicians involved in liver transplantation, since June 2002, the Department of Health in Taiwan has authorized a nonprofit organization, the Organ Procurement and Transplantation Network (OPTN), to monitor the process of organ transplantation. Patients on the waiting list need to undergo an independent review process and register with the OPTN. Donor organs are then allocated to the recipients, based on their MELD score and source of the donor organ. Although the actual outcome data are waiting to be seen, this strategy allows organ allocation to be judged more objectively and may eliminate decision bias that is solely based on the clinician's own experience or preference.

Table 2. Comparison of Child-Turcotte-Pugh, MELD, and Discriminant Function score*

	Child-Turcotte-Pugh	MELD	Discriminant Function
Indication	Cirrhosis of any etiology	Cirrhosis of any etiology	Alcoholic hepatitis
Number of variables	5	3	2
Selection of variables	Empirical	Statistical	Statistical
"Ceiling effect" for quantitative variables	Yes	No	No
Variables weighted for their influence	Partially	Yes	Yes
Needs logarithmic transformation	No	Yes	No
Needs computation	No	Yes	Yes
Variables influenced by personal assessment	Yes	No	No
Type of score	Discrete	Continuous	Continuous

*Modified from Durand and Valla.[28]
MELD = model for end-stage liver disease.

Limitations of MELD

Although the application of MELD provides a clear advantage in the process of fair organ allocation, some controversial issues arise. Patients with HCC who fulfill the Milan criteria (1 nodule ≤ 5 cm in diameter, or ≤ 3 nodules and ≤ 3 cm in diameter) are indicated for liver transplantation;[30] however, the optimal MELD score for these patients is unclear. The UNOS has arbitrarily assigned a fixed MELD score to prioritize these patients on the waiting list. A higher MELD score may shorten the waiting time and decrease the dropout rate of HCC patients, but could increase the risk of mortality in cirrhotic patients with a relatively lower score on the waiting list.[31] On the other hand, a lower MELD priority score for HCC patients may result in an increased dropout rate of HCC patients and a subsequent increased risk of death. A recent study has suggested a lower MELD score, especially for T1 stage HCC (tumor size < 2 cm), for these patients to be equivalent to the risk of short- and mid-term mortality in the cirrhosis group, provided these HCC patients can be treated with effective loco-regional therapy.[32] The justification of the optimal MELD score in HCC patients may be especially helpful for areas where liver transplantation is a common indication for HCC.

Another intrinsic defect of MELD is that some important parameters, such as hepatic encephalopathy, esophageal variceal bleeding, and spontaneous bacterial peritonitis, which are common adverse complications in cirrhosis, are not included in MELD.[33] The occurrence of these complications indicates a status of ongoing deterioration of residual liver function that precedes the development of eventual hepatic failure. There is evidence to show that patients with these complications may not have a higher baseline MELD, which is necessary to prioritize them on the waiting list, and could potentially be missed during organ allocation in the MELD era.[34] In keeping with this notion, the existence of ascites and hepatic encephalopathy did not correlate with the MELD score,[35] and it would be quite difficult to determine the priority of a patient with cirrhosis-related complications and a low MELD score. There is another study to indicate that MELD has a better performance only in a subset of patients with higher MELD scores.[36] The outcome in patients with lower range MELD scores cannot reliably be predicted solely with their MELD scores, and alternative prognostic markers should be used in conjunction to enhance the predictive accuracy.

Cirrhotic patients tend to have dilutional hyponatremia because of altered vascular hemodynamics.

Serum sodium level has recently been shown as an independent prognostic predictor in patients with advanced cirrhosis.[37–39] A serum sodium level less than 126 mEq/L at listing for transplantation is a strong independent predictor of mortality, and addition of serum sodium to MELD increases the ability to predict short-term mortality in patients with cirrhosis.[37] This finding is largely supported by 2 other studies that evaluated the prognostic value of serum sodium.[38,39] The incorporation of serum sodium into the prognostic model is currently being evaluated by the transplantation community to further assess its predictive value.

Given that MELD is an established prognostic system for end-stage liver disease, there is a concern that a single-point determination of the score may not be able to adequately differentiate the degree of urgency for transplantation. The change of MELD score over time (ΔMELD) was reported to more accurately predict the survival in cirrhotic patients awaiting liver transplantation.[40,41] However, the prognostic value of ΔMELD has not fully been confirmed in another study and deserves further studies for clarification.[42] These studies add to the ongoing debate about the clinical application of MELD, which seems to be still far from a conclusion.

Summary and Perspectives

The MELD scoring system has become the prevailing criterion for donor liver allocation. There is increasing interest in the related field of MELD to investigate its usefulness and application in liver transplantation. Whereas early results support its apparent advantages, the optimal role of MELD in the setting of outcome assessment needs more studies to justify this system, and it is still not the time to abandon the CTP system, which clearly has a solid foundation in differentiating the severity of liver diseases. Since the clinical scenario of patients with early- to late-stage cirrhosis may vary widely, appropriate modifications and fine tuning of MELD are necessary in determining the ranking status of patients on the waiting list, in order to avoid futile transplantations. The mortality of patients on the waiting list and survival data in the pre- and post-MELD era should be analyzed to confirm the prognostic value of MELD. The consensus in organ allocation for cirrhotic patients is urgently needed, especially for areas where MELD has not been adopted as the primary allocation reference. Before these guidelines are agreed upon, medical practice should, nevertheless, be based on currently available outcome data.

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