MELD and PELD: Application of Survival Models to Liver Allocation

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In 1998, the Department of Health and Human Services (DHHS) issued the final rule,[1] in which the principles of organ allocation were defined, to govern the operation of the Organ Procurement and Transplant Network (OPTN). This rule included the following guidelines for organ allocation: (1) organs should be allocated to transplant candidates in the order of medical urgency; (2) the role of waiting times should be minimized, and (3) attempts should be made to avoid futile transplants and to promote efficient use of our scarce donor organs. The consensus opinion to minimize waiting time was based on 2 recent reports that analyzed the impact of waiting time on survival of liver patients on the United Network for Organ Sharing (UNOS) waiting list: one from the Institute of Medicine[2] and a second report from Freeman et al.[3] Both studies concluded that waiting time did not correlate with death on the waiting list and therefore should be de-emphasized in developing a new allocation algorithm. The challenge put forth by this conclusion was to create an allocation policy that made the most effective use of organs especially by making them available, whenever feasible, to the most medically urgent patients who are appropriate candidates for transplantation.

This challenge was accepted by the UNOS Liver and Intestinal Committee, whose task it was to (1) make an assessment of the current allocation policy including the Child-Turcotte-Pugh (CTP) score, (2) evaluate a number of previously published survival models that were developed to estimate survival of patients with end-stage liver disease, and (3) develop a new disease severity index to be utilized to allocate liver donor organs in the future.

After careful deliberation and extensive input from transplant hepatologists and surgeons, a number of guidelines were established for creating an index of disease severity to estimate survival in patients with chronic liver disease. By consensus, it was determined that such a disease severity index should rely on a few, readily available, objective variables that would be generally applicable to a heterogeneous group of patients with end-stage liver disease, to determine the risk of dying. Finally, the severity index should be clinically and statistically validated and be able to predict the probability of death in groups of patients with chronic liver disease who are demographically diverse and of varying etiology and disease severity. There was agreement among the committee that such a new index should not be introduced without careful prospective evaluation of the potential impact that such a model may have on the gravely ill patients awaiting liver transplant.

The Child-Turcotte-Pugh Classification

The CTP classification, which has been used since minimal listing criteria were first defined in 1998,[4] is a widely used index of disease severity for patients with end-stage liver disease and is currently applied to assess severity of liver disease in the UNOS allocation algorithm. Historically, the purpose of CTP classification was to assess the operative risk of patients with end-stage liver disease with variceal bleeding undergoing portosystemic shunt surgery.[5,6] It was based on 5 variables including ascites, encephalopathy, nutritional status, and serum levels of bilirubin and albumin. In 1973, Pugh et al[7] used a modified version of this severity index in describing the outcome of patients undergoing surgical ligation of esophageal varices. Pugh assigned a score ranging from 1 to 3 to each of the variables in the classification. Classes A, B, and C were designated by criteria applied to the sum of the individual scores (Table 1). Nutritional status in the Child-Turcotte classification was replaced with prothrombin time.

While the development of the CTP classification was based on empiric assessment and never prospec-

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Table 1. CTP Classification

A. Original Child-Turcotte classification Variable	Class A	Class B	Class C
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	3.0-3.5	<3.0
Encephalopathy grade	None	Minimal	Advanced "coma"
Ascites	None	Easily controlled	Poorly controlled
Nutritional status	Excellent	Good	Poor "wasting"
B. Pugh's modification of the Child-Turcotte classification Variable	**1**	**2**	**3**
Encephalopathy grade	None	1-2	3-4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec prolonged)	<4	4-6	>6
Bilirubin (mg/dL)	<2	2-3	>3
For cholestatic disease	<4	4-10	>10

NOTE. Child-Pugh score class A = 5-6, B = 7-9, and C = 10-15.

tively validated, many subsequent studies have shown the CTP index to be useful in the assessment of prognosis in patients with end-stage liver disease.[8-11] One such example is the work by Christensen et al,[8] in which the Child-Pugh score was applied in a group of patients with liver cirrhosis of diverse etiology. These studies demonstrated that each of the 5 individual clinical variables as well as the overall Child-Pugh classification had prognostic significance. However, routine tests of renal function have been found to significantly improve the prognostic accuracy of the Child-Pugh score and to be an independent predictor of survival in patients with end-stage liver disease (Fig. 1).[12-15] Thus, an assessment of renal function is now considered a critical component in the development of a future liver disease severity index for patients with end-stage liver disease.

Figure 1. Survival of patients with cirrhosis and ascites as a function of serum creatinine level. (Reprinted with permission from Gines P, Fernandez Esparrach SG. Prognosis of cirrhosis with ascites. In: Arroyo V, Gines P, Rodes J, Schrier RW (eds). Ascites and Renal Dysfunction in Liver Disease. Blackwell Science.[15])

Limitations of the UNOS Liver Allocation Policy

While the current allocation system utilizes the CTP classification for determining medical urgency, a number of limitations of both the UNOS allocation algorithm and the CTP score have become obvious. The most important shortcoming is that the UNOS allocation policy defines only 3 categories of disease severity for patients with end-stage liver disease: Status 3 (CTP score ≥7), status 2B (CTP score ≥10), and status 2A (CTP score ≥10, in the intensive care unit [ICU] and less than 7 days to live).[16] With only 3 categories of disease severity, it is obvious that waiting time has become an important factor as a tiebreaker within each category. This is particularly problematic for patients classified as status 2B, who form the largest group of patients undergoing liver transplantation (56%) and who exhibit a broad range of liver disease severity.[17] In status 2B, patients range from those who are at home and working full time to those who require continuous hospitalization for complications related to their liver disease, but who do not meet the strict criteria for 2A status.

Waiting time was introduced into the current allocation scheme based on the principle that in case of the

same degree of disease severity, donor organs should be allocated to those patients who have waited the longest. However, with only 3 categories of disease severity for patients with chronic liver disease, by default, waiting time has become the major determinant for prioritization of donor organs. This problem has been further magnified by the fact that currently waiting time accrued while on the waiting list in status 3 is applied when the patient advances to 2B status. Therefore, waiting time has become a dominant factor in prioritization of donor organs with almost complete disregard to the severity of liver disease.[16]

Finally, the criteria for 2A status are also problematic, as uniform guidelines for admission to the intensive care unit are lacking. In addition, a consensus is lacking regarding what constitutes criteria for a patient having less than 7 days to live. It is not surprising that the current liver allocation scheme has led to substantial debates, resulting in widespread mistrust among regional liver transplant centers. This has ultimately led to a call for change of the present allocation algorithm to one which would direct organs to patients based on severity of their liver disease rather than to patients with the longest waiting time.

Shortcomings of the CTP Score

While the UNOS allocation scheme has clearly failed to prioritize liver allocation on the basis of medical urgency, the CTP score itself was also found to have limited usefulness as an index of disease severity. These limitations mainly are related to the limited discriminatory ability and variability of the CTP score. The CTP index, as used in organ allocation, not only has a limited number of disease categories, but is also limited by its inability to discriminate disease severity among the sickest patients. For example, patients with serum bilirubin levels of 3 mg/dL and 30 mg/dL are given the same CTP score (Table 1), which suggests the same severity of liver disease, despite the fact that serum bilirubin level has been shown to be an important prognostic parameter in patients with chronic liver disease. Similarly, based on the CTP score, 2 patients with a serum albumin of 2.8 g/dL and 2.1 g/dL, respectively, are placed in the same category of severity, despite the marked differences in hepatic synthetic function.

The CTP score is further limited by its marked variability. The assessment of 2 parameters used in the CTP score, namely ascites and encephalopathy, depend on how they are evaluated. Should ascites be assessed by subjective findings on physical examination, as it was when the original CTP score was developed, or should the more sensitive ultrasonography method for detecting ascites be used? Do vague symptoms such as forgetfulness, fatigue, and insomnia constitute the diagnosis of portosystemic encephalopathy, or should more objective criteria be required? Not only is there a lack of uniform standards for diagnosing and grading the severity of ascites and encephalopathy, but these symptoms can improve or even resolve with simple dietary or medical treatment. Therefore, the time of assessment of these symptoms plays a role in defining the CTP score for organ allocation.

Even the more objective laboratory elements in the CTP system may vary from one institution to another. In particular, the measurement of prothrombin time depends on the sensitivity of the thromboplastin reagent used for the assay,[18] which creates variability between centers in the reporting of prothrombin time. Similarly, while electrophoresis is usually considered to be the gold standard for measurement of albumin levels, clinical laboratories frequently use the less expensive, but also less sensitive, colorimetric method. Based on these shortcomings, the UNOS Liver and Intestinal Committee unanimously agreed that change of the UNOS allocation algorithm was necessary to meet the final rule guidelines for liver allocation issued by the DHHS.

Survival Model Development

Given the limitation of both the current allocation scheme and the CTP score, implementation of the final rule required the development of an index, which accurately assessed severity of liver disease on a continuous and broad scale and was based on sound clinical and statistical validity. Therefore, previously published prognostic models developed for patients with primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease, and Wilson's disease were evaluated.[19-26] However, after careful assessment it was felt that these models were often applicable only to patients with a specific end-stage liver disease, but not to patients having a wide spectrum of liver disease etiologies. Moreover, a number of these models required a liver biopsy for risk stratification, which was felt to be inappropriate for a generally applicable model to predict survival because of sampling variability and inconsistent histologic interpretation.[21-23,27,28] Many of these models excluded patients with decompensated cirrhosis[22,23,29] and many used quantitative measures of hepatic function such as aminopyrine breath test, galactose elimina-

tion capacity, and monoethylglycinexylidide test, studies which are currently not uniformly performed nor provide incremental prognostic information.[9,30-35] Other models utilize variables such as plasma levels of norepinephrine, pseudocholinesterase, and renin, laboratory tests which are usually not readily available at most institutions and frequently are determined using local assays, which may not be comparable.[36,37] Still other models used subjective variables such as cognitive dysfunction, degree of encephalopathy, nutritional status, degree of ascites, and hepatorenal syndrome, all of which are poorly defined and open to wide range of interpretations.[12,22,28,38] Finally, a number of models use politically charged variables such as age, gender, and race, or third-party payer status, which would discriminate against some groups of patients and therefore could not be incorporated in a model to be used nationally to select patients for organ allocation.[19-21]

Model for End-Stage Liver Disease (MELD)

The MELD model (model for end-stage liver disease), which was derived from a heterogenous group of patients from 4 medical centers throughout the United States and was validated on an independent data set from The Netherlands, was originally developed to assess the short-term prognosis of patients with liver cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedure (Fig. 2).[39] This recently described model uses serum creatinine, total serum bilirubin, international normalized ratio (INR) of prothrombin time, as well as etiology of cirrhosis as its parameters (Fig. 3).[39] Since it has previously been shown that survival following portosystemic shunt surgery is predominantly determined by severity of underlying liver disease, it was hypothesized that the MELD model could be used as a prognostic indicator for patients with advanced chronic liver disease and potentially could be applied to prioritize patients waiting for liver transplantation on the UNOS waiting list. In addition, the model had many characteristics for an ideal model: it relies on a few objective parameters using standardized tests, which should be readily available and reproducible. Finally, none of the parameters are subjective or have political overtones that might make utilization of such a model controversial.

$$\text{Meld Risk Score} = 10 \times [0.957 \times \log_e(\text{creatinine mg/dL}) + 0.378 \times \log_e(\text{bilirubin mg/dL}) + 1.120 \times \log_e(\text{INR}) + 0.643 \times \text{Cause of cirrhosis (0 alcohol, cholestatic, 1 other etiologies)}]$$

Figure 2. MELD survival model. The original MELD score included etiology of liver disease; the future MELD model will be used without using liver etiology.

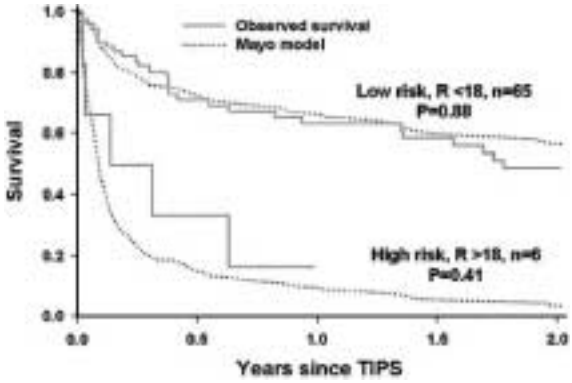

Figure 3. Survival of 71 independent TIPS patients from The Netherlands who were stratified according to their risk score into 2 risk groups, namely a high-risk group with a median survival less than 3 months ($R > 18$) and a low-risk group with a median predicted survival more than 3 months ($R < 18$). Actual and expected survivals using the Mayo model were compared using the one-sample log-rank test. For the low- and high-risk patients, observed and expected survivals were similar ($P = .88$ and $P = .41$, respectively.) (Modified and reprinted with permission.[39])

Validation of the MELD Model

Since the MELD model was developed to determine the short-term prognosis for patients undergoing a TIPS procedure, its prognostic usefulness needed to be assessed in patients with end-stage liver disease not undergoing TIPS. To validate the MELD model, a group of 282 adult patients hospitalized at the Mayo Clinic between January 1994 and January 1999 for complications of liver disease were studied.[40] Individual hospital records were reviewed to verify the diagnosis of cirrhosis and extract other relevant disease related information and laboratory data. Patients with concurrent hepatocellular cancer, alcohol use within 30 days of hospitalization, and advanced cardiopulmonary comorbidity, sepsis, or intrinsic renal disease, and those who were hospitalized for liver transplantation were excluded from the study. Patient survival was assessed as the interval from the day of hospitalization until death or last follow-up. Since the aim was to validate the MELD score as a severity index of liver disease to predict short-term mortality, 3-month mortality was cho-

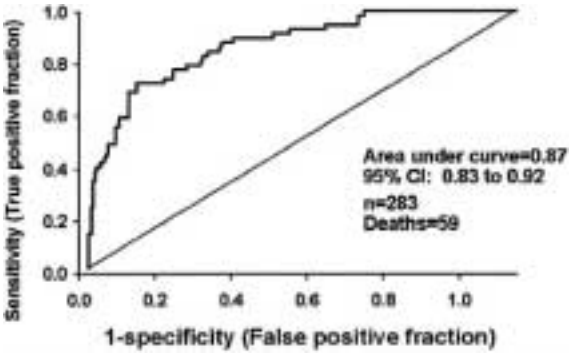

Figure 4. ROC curve for the MELD score in hospitalized cirrhotic patients predicting 3-month mortality.

sen as the primary outcome measure. The validity of the model was determined using the c-statistic (concordance—equivalent to the area under the receiving/operating/characteristic curve).[41] In this context, the c-statistic is the probability of assigning greater risk to a randomly selected patient with 3-month mortality when compared with a randomly selected patient without 3-month mortality. The receiver operating characteristic graph depicts the true-positive proportion plotted against the false-positive proportion for the different cutoff values of the decision criterion. The c-statistic may range from 0 to 1, with 1 corresponding to perfect discrimination while 0.5 would be the result expected from chance alone. A c-statistic of 0 would result if the prediction was wrong 100% of the time. The c-statistic is used commonly in evaluating prognostic models.[42,43] A c-statistic between 0.8 and 0.9 indicates excellent accuracy, while a c-statistic >0.7 is generally considered a useful test result. In this study, the c-statistic for prediction of 3-month mortality by the MELD model was 0.87 (95% confidence interval 0.82 to 0.92) (see Table 2 and Fig. 4). Moreover, when this group of patients was stratified according to the CTP score, the 3-month mortality in patients with CTP class A was 4%, CTP class B was 14%, and CTP class C was 51%. The c-statistic for the CTP score for predicting 3-month mortality was 0.84% (95% confidence level 0.78 to 0.90). The relationship between the MELD score, the CTP score, and the 3-month mortality is shown in Table 3.

In summary, the MELD score appeared to be at least as good as the CTP score in predicting mortality and had the distinct advantage of using variables that were readily available, standardized, reproducible, and objective.

Further Validation of the MELD Score

In addition to the initial group of 282 Mayo Clinic patients (group A), the MELD model was further validated in 3 other groups of patients: patients with compensated cirrhosis from a Palermo (Italy) database (group B), outpatient PBC patients from the Mayo Clinic (group C), and a retrospectively generated cohort of "historical" patients, diagnosed with cirrhosis between 1984 and 1988 at the Mayo Clinic (group D). The ability of the MELD model to predict 3-month mortality in these 4 groups of patients, expressed as the c-statistic, ranged from 0.78 to 0.87 (Table 2). The 3-month death rates in relation to the MELD scores for the patients in these 4 groups are shown in Table 4. These validation studies confirm that the MELD model is a reliable predictor of both short-term and medium-term mortality risk in patients with cirrhotic-stage liver disease of diverse etiologies and is applicable over a wide spectrum of disease severity. The results support the hypothesis that the MELD model can be used as an index of liver disease severity and therefore may be of value to prioritize patients waiting for liver transplantation.

Table 2. Summary of Validation Studies: Concordance in Predicting 3-Month and 1-Year Mortality

	No. of Patients	No. of Deaths Within 3 Mo	3-Month Mortality (concordance)	1-Year Mortality (concordance)
Hospitalized cirrhotics (group A)	282	59	0.87 (0.82-0.92)	0.85 (0.80-0.90)
Outpatient cirrhotics (group B)	491	34	0.80 (0.69-0.90)	0.78 (0.70-0.85)
PBC outpatients (group C)	326	5	0.87 (0.71-1.00)	0.87 (0.80-0.93)
Historical cirrhotics (group D)	1,179	220	0.78 (0.74-0.81)	0.73 (0.69-0.76)

NOTE. Concordance expressed as c statistic.

Table 3. Relationship Between MELD, CTP Score, and 3-Month Mortality in Hospitalized Cirrhotics (Group A)

	3-Month Death Rates				
MELD	≤9	10-19	20-29	30-39	≥40
Mortality	4 (6/148)	27 (28/103)	76 (16/21)	83 (5/6)	100 (4/4)
CTP		A	B		C
Mortality		4 (3/77)	14 (13/93)		51 (35/69)

NOTE. Values expressed as percent (number/total).

Do Complications of Portal Hypertension Add to the MELD Score's Ability to Predict Mortality Risk?

It has been suggested that complications of portal hypertension such as ascites, encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis are predictors of mortality for patients with liver cirrhosis.[44-47] However, in studies comparing surgical or endoscopic treatment for variceal bleeding , survival appears to be solely dependent on the severity of the underlying liver disease.[48-50] It is now recognized that the degree of hepatic dysfunction is of overriding prognostic significance for patient survival.

Therefore, the following question needed to be addressed: Do complications of portal hypertension provide further prognostic information in predicting mortality above and beyond the MELD score? Hereto the initial group of 282 patients (group A) with a history of variceal bleeding, ascites, and encephalopathy was studied. The impact of spontaneous bacterial peritonitis (SBP) was analyzed in our historical patient group (group D) by reconstructing the diagnosis of SBP using the results of the peritoneal fluid analysis. In addition, a data set of 64 patients was evaluated who were diagnosed with ascites and SBP, using conventional criteria (absolute neutrophil count $> 250/\mu L$), which was provided by Dr Miguel Navasa from Barcelona, Spain.

The impact of variceal bleeding was analyzed in the historical patients group (group D) and in an additional group of 404 patients who underwent endoscopic therapy for variceal hemorrhage in the Mayo Clinic between 1988 and 1999. The test results, collected immediately prior to the initial endoscopic intervention, were used to compute the MELD model, and all patients were followed for at least 3 months.

Finally, the impact of ascites and encephalopathy on the MELD score's ability to predict mortality was evaluated in the group of outpatient PBC patients (group C). Overall, minimal change was noted in the MELD score's ability to predict 3-month mortality by adding individual complications of portal hypertension (Table 5). These results strengthen the hypothesis that severity of liver disease, as measured by the MELD score, gives us important prognostic information that is nearly independent of the development of complications of portal hypertension.

The Importance of Liver Disease Etiology in the MELD Model

The MELD model, by using liver disease etiology, gives a lower risk score to patients with alcoholic and cholestatic liver disease compared to other diagnoses. In this context two concerns were raised at the initial public hearing, where the MELD model was proposed for use in organ allocation. The first concern was that using etiology in the MELD score for patients with alcoholic liver disease would discriminate against such patients for the purpose of organ allocation. It is well known that

Table 4. 3-Month Death Rates

MELD Score	≤9	10-19	20-29	30-39	≥40
Hospitalized (group A)	4 (6/148)	27 (28/103)	76 (16/21)	83 (5/6)	100 (4/4)
Outpatient cirrhotics (group B)	2 (5/213)	6 (14/248)	50 (15/30)	—	—
Ambulatory PBC (group C)	1 (3/308)	13 (2/16)	0 (0/2)	—	—
Historical (group D)	8 (55/711)	26 (90/344)	56 (47/84)	66 (23/35)	100 (5/5)

NOTE. Values expressed as percentage of mortality (number/total).

Table 5. Impact of Complications of Portal Hypertension on MELD Score Outcome of 3-Month Mortality

Ascites	Hospitalized (Group A)		Cholestatic (Group C)
No. of patients	116		94
MELD	0.87		0.80
MELD + ascites	0.88		0.83
Variceal bleeding	**Hospitalized (Group A)**	**Historical Cirrhotics (Group D)**	**Bleeding Team (Mayo)**
No. of patients	30	107	404
MELD	0.87	0.78	0.83
MELD + bleed	0.88	0.78	0.83
SBP	**Historical Cirrhotics (Group D)**		**Barcelona Group**
No. of patients	18		64
MELD	0.78		0.85
MELD + SBP	0.78		0.86
Encephalopathy	**Hospitalized (Group A)**		**Cholestatic (Group C)**
No. of patients	52		21
MELD	0.87		0.80
MELD + encephalopathy	0.88		0.81

NOTE. All values expressed as c statistic (concordance) for 3-month mortality.

long-term absence from alcohol use improves overall liver function. The fact that the MELD model was developed in patients who were recently using alcohol therefore seems to inappropriately discriminate against alcoholic patients on the waiting list, most of whom have been abstinent for 6 months or longer and who are less likely to experience further improvements in liver function and prognosis with additional abstinence.[51] The consensus opinion was that the mortality risk of such alcoholic patients listed for liver transplant is unlikely to be different from patients with other chronic liver diseases of similar disease severity. Thus, the recommendation was that etiology should not be used in the MELD score to avoid potential discrimination against patients with alcoholic liver disease.

A second concern was that the MELD model, like the CTP score, discriminates against patients with cholestatic liver disease who in general have the best long-term outcome following liver transplantation.[52,53] Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) patients often suffer from extreme fatigue, pruritus, osteoporosis, fat malabsorption, and malnutrition, which significantly diminish quality of life. In addition, patients with PSC often have associated inflammatory bowel disease and have an increased risk of developing colon cancer as well as an increased risk of developing cholangiocarcinoma; conditions which can impact negatively on prognosis.[54] A further concern is that PSC patients are frequently on ursodeoxycholic acid treatment which may lower serum bilirubin levels.[55] While this biochemical improvement has not been shown to be associated with a survival benefit, it would result in an inappropriately low MELD score and consequently such patients would be given an inappropriately low priority to receive a donor organ. For all these reasons, it was felt that a severity index to be used to allocate liver organs should not discriminate against the patients with cholestatic liver disease.

Based on these concerns, we further analyzed the impact of etiology of liver disease on the MELD model's predictive ability. We found that excluding liver disease etiology in the MELD model had minimal influence on its overall ability to predict mortality as expressed by c-statistic (Table 6). Based on these findings and concerns, a consensus was reached that in the future the MELD model should be used without including cause of liver disease so as not to discriminate against patients solely on the basis of etiology.

Applying the MELD Model to the UNOS Waiting List

To compare the 3-month mortality predicted by the MELD model with the actual pretransplant mortality on the waiting list, the MELD model was applied to a group of 311 pretransplant patients with chronic liver

Table 6. Impact of Excluding Cause of Liver Disease on MELD Score's Predictive Ability

	Hospitalized (n = 282)	Ambulatory Noncholestatic (n = 491)	Ambulatory PBC (n = 326*)	Historical (n = 1,179)
With cause in the model	0.87 (0.82-0.92)	0.80 (0.69-0.90)	0.87 (0.71-1.00)	0.78 (0.74-0.81)
Without cause in the model	0.86 (0.81-0.92)	0.82 (0.73-0.91)	0.87 (0.71-1.00)	0.78 (0.74-0.81)

NOTE. Values expressed as concordance (95% confidence interval).
* Because all patients included in these data had PBC, there is no effect from excluding the cause.

disease who were added to the UNOS waiting list between November 1999 and June 2000.[56] During this period of time, a total of 2,732 patients were listed as status 2A or 2B for liver transplantation on the UNOS list. Of this group, 514 had complete data at listing with many patients reporting a prothrombin time instead of an INR. Transforming a prothrombin time to an INR would be, at best, a guess; therefore, we attempted to keep the data as pure as possible for MELD model scoring. Of this group, 166 patients were transplanted within 3 months, 13 were removed from the list for being "too sick," 17 patients at the end of the study had $<$ 3 months of follow-up, 2 refused transplant, and 5 patients were transferred to another center or downgraded to status 3, leaving a study group of 311 patients. The mean age was 49 years, 65% were male, and 71% were white. The patients had the following diagnoses: chronic hepatitis C (41.5%), alcohol-related liver disease (21.5%), cryptogenic cirrhosis (10.6%), and cholestatic liver disease (5.1%). For the 26 patients listed on UNOS status 2A the median MELD score was 27, while for the 285 patients listed on status 2B it was 14. At 3 months after listing, the group of patients with a MELD score greater than 18 experienced a 29% death rate compared to 6% in those patients, who had a MELD score of less than 18 ($P < .01$). Using the MELD model without etiology of liver disease, the c-statistic (concordance) for 3-month mortality in the 311-patient cohort was 0.82, which indicated an excellent ability of the MELD model to predict pretransplant mortality on the UNOS waiting list. By comparison, the c-statistic for the Child-Turcotte-Pugh score for 3-month mortality was only 0.73.

As this analysis was based on only a small sample of patients on the UNOS waiting list, a consensus developed in the Liver and Intestinal Committee that further studies using larger numbers of patients would be important prior to general application of the MELD model in organ allocation. However, the data did suggest that use of the MELD model could eliminate waiting time as a major factor in determining organ allocation. In addition, the MELD model might have a significant impact by reducing the number of deaths on the waiting list, as donor organs will be allocated to the patients with the highest MELD score but prior to the development of the life-threatening disease (i.e., UNOS status 2A).

Impact of a Continuous Severity Score for Liver Allocation

One of the UNOS regions recently developed a variance to the UNOS liver allocation policy, which redefined status 2A by more rigid criteria and prioritized allocation for 2B patients by using a continuous medical urgency score based on the CTP score in combination with certain complications of liver disease.[57] In this variance, waiting time was only used as a tiebreaker for 2B candidates with equal medical urgency scores. The outcome of 67 patients listed for transplantation during the 6 months prior to the implementation of the continuous system were compared with 75 patients who were followed prospectively for a 6-month period after implementation of the continuous score. The results revealed a significant reduction in the number of liver transplantations, performed in patients listed as status 2A (46.3% v 14.7%, $P = .002$), and an increase in the number of patients listed as 2B status who received a liver transplant (70.7% v 44.8%) (Fig. 5A and 5B). More dramatically, a 37.1% reduction in overall deaths on the waiting list was found during the period in which the continuous medical severity score was used ($P < .005$), while patient and graft survival following liver transplantation were similar in both periods. From this pilot study, it was suggested that by using a system with a continuous medical urgency score, donor livers were more fairly allocated to those with the most medical need. The variance appeared to reduce waiting list mortality without sacrificing efficacy. This study also suggested that de-emphasizing waiting time for liver allo-

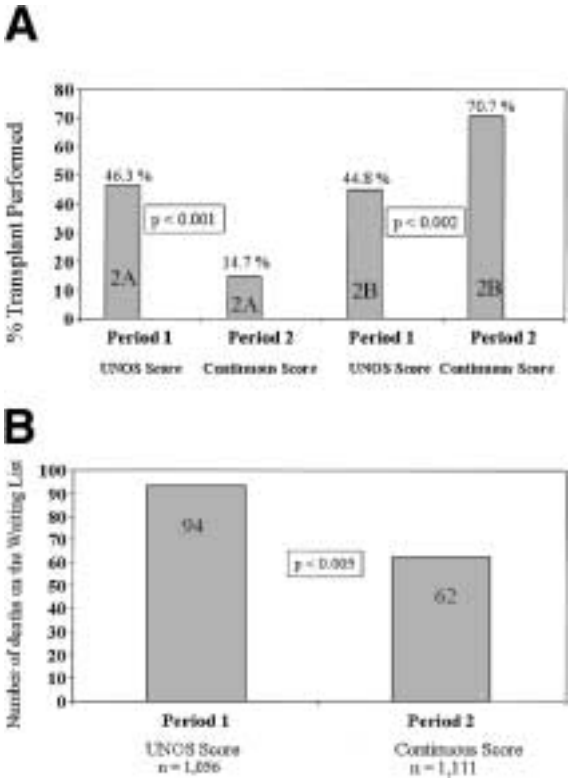

Figure 5. (A) Percentage of patients who underwent transplantation at status 2A and 2B during period 1 (old score used) and period 2 (continuous severity score applied to liver organ allocation). (Data from Freeman et al.[57]) (B) Total number of deaths or removal from UNOS waiting list because patient was too ill to transplant during period 1 (old scheme) and period 2 (continuous severity score applied for liver organ allocation). (Data from Freeman et al.[57])

cation prioritization directed organs to more severely ill patients in the 2B category. As a consequence, patients at status 2B were less frequently advanced to status 2A, which is often associated with decreased survival as well as increased resource utilization following liver transplantation.

Pediatric Liver Disease Severity Score (PELD)

Because the development of the MELD model was based on data from adult patients, its applicability to pediatric patients is unknown. Since there were no known data sets with large numbers of pediatric patients to evaluate the MELD model, we used the Studies of Pediatric Liver Transplantation (SPLIT) database.[58,59] On June 15, 2000, 884 pediatric patients with chronic liver disease without a prior liver transplant were registered into the SPLIT database. Of these 884 patients, 779 were not in the intensive care unit at the time of listing for liver transplantation. For the purpose of development of a severity index, primary outcome was defined as death, transplant, or admission to the intensive care unit prior to receiving a liver transplant. Admission into an intensive care unit was considered an endpoint, since the current UNOS allocation scheme allows these pediatric patients to be listed at UNOS status 1. Seventy-four of the 779 patients had a primary outcome. Death occurred in 41 children without a transplant and 33 pediatric patients were transferred to an intensive care unit because of deterioration in their condition.

When the outcome of pediatric patients on the UNOS waiting list was analyzed, it showed that 14% of children under age 1 year died or were transferred to an intensive care unit pretransplant, compared to 6.3% of children above 1 year of age. Furthermore, children with a height and weight of 2 standard deviations below normal experienced a higher incidence of one of the primary outcomes, 14.2% versus 7.2%. Using multivariate analysis with factors that were found to be significant in univariate analysis, 3 models to predict primary outcome were developed: (1) Pediatric Severity Scale Model (PSS), which included serum albumin level, total serum bilirubin level, INR, and growth failure; (2) Pediatric Severity Scale Model Plus Age (PSSAGE), which included the same factors as in the PSS model plus age; and (3) the Pediatric Death Severity Scale Model (PDSS), which was developed to predict death using age, total serum bilirubin level, and INR as predictors of outcome. The best model for predicting the primary outcome (pretransplant death, or transfer to the ICU) was the PSS model, which did not include age. However, age was found to be highly predictive of pretransplant death in both univariate analysis and in the PDSS model. Because of the perception that age <1 year is a strong predictor of death, an arbitrary decision was made by the Pediatric Liver Group to add age <1 year to the final pediatric model because of its perceived clinical significance.

In contrast to adult patients, serum creatinine did not reach significance as a univariate variable, and thus was not a predictor of the primary outcome in the pediatric patients. Therefore, the MELD model was found to be not applicable to pediatric chronic liver disease patients. A comparison between the three pediatric severity models and the MELD model was assessed by computing the area under the curve for receiver operating characteristics (ROC) predicting the primary outcomes at 3 months. Using the SPLIT database, the 3 pediatric severity scores consistently performed better

Table 7. Comparison of Pediatric Liver Severity Score Using the Area Under the ROC Curve to Determine the c Statistic for 3-Month Mortality/ICU Admission

	Pretransplantation Death or ICU Admission	Pretransplantation Death
PSS	0.82	0.91
PSS AGE	0.82	0.92
PDSS	0.76	0.88
MELD	0.71	0.82

than the MELD score (Table 7), and the area under the curve of the ROC for the PSSAGE model was at least 10% higher than the MELD score. The PSSAGE model (which will be further referred to as the Pediatric End-Stage Liver Disease [PELD] model) was the best overall model and, therefore, has been proposed as the model to be assessed further for prioritization of pediatric patients for liver transplantation (Fig. 6A). However, since the PELD model was developed on a single data set, additional validation is needed to assess its overall predictive ability. Preliminary data from the University of Pittsburgh's pediatric database suggests concordance of >0.80 in predicting 3-month mortality, thus validating the PELD model. Like the MELD model, the PELD model will prioritize patients by estimating probability of 3-month mortality. Further, this estimated probability of mortality at 3 months using the PELD score can be equated to a MELD score, which predicts the same probability of 3-month mortality. Note, for two survival probability estimates based upon Cox-Regression, the numerical score for the one can be converted to the numerical score of the other by adding a constant. This demonstrates that the conversion of a PELD to MELD or MELD to PELD should be a practical matter (Fig. 6B). A conversion factor for possible use in organ allocation should first be described following validation of the PELD in ranking patients and calibration of both the MELD and PELD in terms of actual survival probabilities using patients listed for transplantation.

Limitations of The PELD and MELD Models

The MELD model has been validated using a number of retrospective databases and has performed well with regard to its ability to predict short- and medium-term mortality in patients with chronic liver disease. However, in order to apply the MELD model for the purpose of prioritizing patients for liver allocation, several concerns need to be addressed. First, the effect of age, gender, and body mass on serum creatinine level may introduce a bias independent from severity of liver disease. In many patients with chronic liver disease, who have moderate to marked muscle wasting, serum creatinine levels may be falsely low and not reflective of true renal dysfunction. For example, using the MELD model, in which serum creatinine is an important factor, a nutritionally wasted 40-kg woman will be disadvantaged by having a low serum creatinine level, which is reflective of decreased muscle mass. A recent study, however, has shown that the contribution of lean body mass to serum creatinine is only 2.9%.[60] Indeed, our initial assessment of body mass index did not seem to significantly improve the MELD model's predictive ability, but further assessment is needed.[40] Therefore, the UNOS validation study, which will start in 2001, will incorporate the Crockoff-Gault equation in which estimates of creatinine clearance will be used to determine the potential impact that body mass on the prognostic capabilities of the MELD model.[61]

A second issue is related to how patients with hepatocellular cancer, who often have less severe liver disease, will be incorporated in the new algorithm. Presently, patients with cirrhosis and hepatocellular cancer are given UNOS status 2B, if their cancers meet the

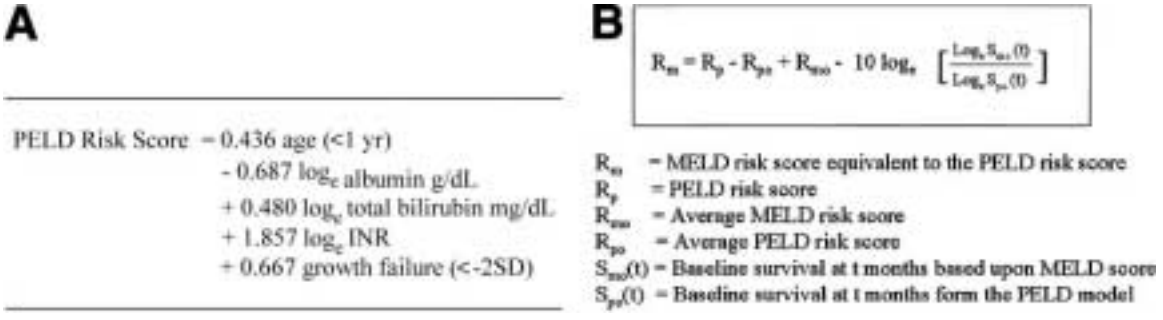

Figure 6. (A) PELD survival model. (B) Formula for conversion of PELD score to MELD score.

following conditions: (1) one lesion less than 5 cm, or (2) three lesions less than 3 cm without evidence of metastatic disease. As survival in this group of patients with hepatocellular cancer is similar to that of patients undergoing liver transplantation for other chronic liver diseases,[62,63] discrimination against these patients with regard to organ allocation is not justified. Currently, a proposal is being considered to enter chronic liver disease patients with qualifying concomitant hepatocellular cancers on the waiting list at a MELD score reflecting a 40% probability of dying in 3 months. The rationale for choosing a 40% probability of dying in 3 months is based on the tumor doubling time, particularly in those patients who have a rapid doubling time. Every 3 months additional points would be added to the MELD score until the patient is transplanted, dies, or becomes medically unsuitable for liver transplantation.Similarly, patients with conditions in which the severity of disease is not reflected by the MELD score, like the hepatopulmonary syndrome and familial amyloidosis, will also need to be prioritized in a manner in which they are able to compete for donor allocation.

A third concern is how waiting time will enter into the allocation scheme. The current proposal from the UNOS Liver and Intestinal Committee is that waiting time would only be a tiebreaker for patients with whole-integer MELD scores. In this system, waiting time will move backward but not forward. If a patient improved from a MELD score of 24 to a score of 22, waiting time will be applied as a tiebreaker with other patients at the lower MELD score. On the contrary, waiting time for a patient with a MELD score of 22 would not be applied if the patient advanced to a MELD score of 24. In general, severity of liver disease would remain the major prioritization factor.

The major limitation of the PELD score is that it has not been prospectively validated on an independent UNOS data set at this time. However, the PELD score like the MELD score is based on only a few variables, which can be objectively assessed and are reproducible. Special conditions such as metabolic liver diseases or hepatoblastoma will need to be dealt with on an individual basis by regional review boards.

Finally, many experts questioned if the PELD and MELD models would be able to predict outcome following liver transplantation. An additional component of an ideal allocation model was thought to be the ability to identify which patients can benefit most from liver transplantation resulting in optimal use of our scarce donor resource.[1]

MELD Model for Predicting Outcomes of Liver Transplantation

The impact of the pretransplant MELD score on posttransplant mortality and resource utilization was analyzed using a multicenter database comprising a select group of adult recipients who underwent liver transplant since January of 1990 at the Mayo Clinic Rochester and Baylor University Dallas.[64] Patients with fulminant liver disease or malignancy were excluded from the analysis. A total of 1,185 patients in 4 diagnostic categories (viral hepatitis 30%, alcoholic liver disease 15%, cholestatic disease 31%, and other liver diseases 24%) met the inclusion criteria. The median MELD score, computed immediately before liver transplantation, was 13. Outcome parameters included graft and patient survival at 3 months, intraoperative blood transfusion requirement, and length of intensive care unit and hospital stay. The outcome parameters were found to become progressively worse as the pretransplant MELD score increased (Table 8). However, because of a number of random deaths, the model's prediction of mortality within 3 months following liver transplant, expressed as the c-statistic, was only 0.62 (confidence interval 0.55 to 0.69). Although these results suggest a

Table 8. Effect of MELD Score on Patient and Graft Survival, Intraoperative Blood Transfusions, Intraoperative Red Blood Cell Transfusions, and ICU and Hospital Days After Liver Transplantation

MELD Score	<10 (n = 392)	10-19 (n = 527)	20-29 (n = 164)	30-39 (n = 63)	>40 (n = 39)
Death (3 mo) (%)	5	6	10	10	26
Graft failure (3 mo) (%)	7	8	14	14	33
RBCs (L)	1.5	2.3	3.5	3.5	3.7
ICU (d)	2	3	4	5	6
Hospital (d)	14	15	17	21	19

Abbreviation: RBCs, red blood cells.

relationship between the MELD score and postoperative patient and graft survival and resource utilization, it also suggests that the MELD model is not able to predict random postoperative deaths which are unrelated to pretransplant liver disease severity. Nevertheless, we believe this study represents an initial step in the process of attempting to optimize the benefit of liver transplantation based on estimating pre- and posttransplant mortality.

Summary

Compared to the CTP score (Table 9), the MELD and PELD models provide the means to more accurately measure liver disease severity and to better predict which patients are at risk of dying on the waiting list. The relation between the MELD score and the risk of 3-month mortality is shown in Fig. 7. Most importantly, by de-emphasizing waiting time these two models will allow organ allocation based on medical urgency, as mandated in the DHHS final rule.

However, while the MELD score is an extremely powerful predictor of the probability of death in patients with chronic liver disease, it does not address one of the guidelines in the final rule, that an organ allocation system should promote the most efficient use of scarce donor resources and should avoid futile transplants. Thus, a future challenge will be to modify the MELD model in order to predict the probability of death with and without a liver transplant and thus to allow further optimization of the timing of this lifesaving procedure. Finally, ongoing studies are needed to further define when the severity of liver disease of a patient has deteriorated to the point that the transplant procedure itself becomes futile. Hopefully, ongoing data collection, as mandated by the Final Rule of HHS, can help us address some of these extremely complex and challenging issues.

Table 9. Comparison of MELD and CTP Models

	MELD	CTP
Reason developed	Shunt outcome	Shunt outcome
Derived	Prospective data	Empiric
Parameters	Objective	Subjective components
Parameter variability	Minimal	Center-to-center variability
Spectrum	Continuous	Ceiling effect, few categories
Validation studies	Yes	No
Allocation emphasis	Disease severity	Waiting time

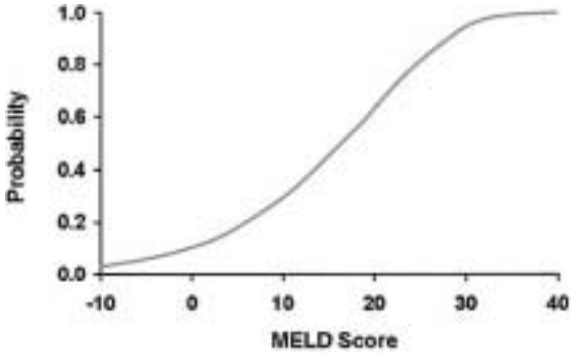

Figure 7. Relationship between the MELD score and estimated 3-month mortality in chronic liver disease patients.

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