The Impact of Organ Allocation Strategies on Liver Transplantation

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Organ allocation is based upon the prioritization of patients on the liver transplant waiting list (1). The purpose of this grand rounds is to review the history of organ allocation, including the United Network for Organ Sharing (UNOS) listing system, the development of the Model of End Stage Liver Disease (MELD) system, MELD exceptions, recent updates on limitations of the MELD and etiology specific liver disease scoring systems.

The immense magnitude of liver transplantation within the United States continues to escalate. On January 1, 2001, the United Network for Organ Sharing (UNOS) had 14,261 patients on the liver transplant waiting list: 14 - status 1, 63 - status 2a, 3,027 - status 2b and 11,157 - status 3. 8.2% of patients died on the liver transplant waiting list in 2000 (2). During 2001, there were 5108 cadaveric liver transplantations performed in the USA (with total population of 285 million) (3,4). UNOS data from 2001 documented that 2,003 patients who were listed for liver transplantation died while waiting and 494 were removed from the waiting list as too sick to transplant (5). Therefore, in essence only 5108/7608 (68%) patients received life saving liver transplants while 32% did not. The number of these adverse outcomes has increased by nearly 300% over the course of the past decade. In contrast to the number of transplantations, the number of cadaveric organs available on an annual basis has only increased by 25% in the past decade (6). The need for liver transplants will continue to increase (7). Some investigators have estimated that liver transplants may quintuple from 5,157 in 2003 to 27,229 in 2015 while the rate of organ donations will remain stable (8).

As of 1/2003, 17,200 patients were listed with UNOS as candidates for liver transplantation. Of these, more than 10,000 had been listed within the past year (9). This rate of new liver transplant registrations represent a doubling in comparison to the number of annual new registrations that occurred a decade ago. This marked increase in the number of patients awaiting liver transplantation is a consequence of a number of factors, the rise in cases of HCV associated cirrhosis, the increasing recognition of the benefit of liver transplantation and improved care of patients with end stage liver disease (ESLD) allowing patients to survive their index hospitalization (3,7,10).

In comparison, Canada and "Scandanavia" have approximately 1/10th the population and number of transplant centers: 31 million and 7 transplant centers vs 24 million and 11 transplant centers, respectively (11-13). Both groups performed much lower number of liver transplants (LT) per million population (177- Canada and 175- Scandanavia) (11-13). In Scandanavia, 6% patients died while waiting for transplant and 8% were withdrawn. 20% were still awaiting transplant. Importantly, the average time from placement to transplantation was only 4 months in Canada. These disparities may reflect the patient population, availability of resources within health care systems, and organ donations.

HISTORY

Before the 1980's, organ allocation was based largely on word of mouth. In the early 1980's several public appeals for organs were made on behalf of individuals by the news media. Congress realized that there needed to be an organized national system to ensure a more equitable distribution of organs. In 1983, Congress mandated establishment of a task force to look into the problem. The Department of Health and Human Services (DHSS) assembled a 25 member task force which recommended that an organ transplant network be established. In1984, Congress passed the National Organ Transplant Act (NOTA) that mandated the establishment of an Organ Procurement and Transplant Network (OPTN), which was to be run by the transplant community with oversight from Department of Health and Humans Services (14). In 1986, the United Network for Organ Sharing

(UNOS) was awarded this contract and has held the contract for the past 17 years (14). In order to understand the next few years, a number of terms need to be defined as outlined in table 1 (1).

Table 1
Definitions -
Urgency - the risk of LT candidate's death without transplant
Utility - the chances a candidate will survive liver transplant
Organ allocation - Prioritization of patients on the transplant waiting list. Estimation of the prognosis of patient, ie survival
Distribution - Prioritization of liver transplant centers in relation to the location of the cadaveric donor
Minimal listing criteria - Predetermined limits of estimated severity of disease to be placed on the LT waiting list

Because of concerns regarding organ allocation, the importance of waiting time and geographic inequality, in 1998, DHHS issued the Final Rule. The Final Rule stated that: organs should be allocated to LT candidates in the order of Medical Urgency; the role of waiting times should be minimized; and attempts should be made to avoid futile transplants (15).

Importantly, the Final Rule prompted investigators to initiate a number of proposals defining "medical urgency"(patient's risk of death within the next 3 months) (15). Various mathematical models, including Child-Turcotte-Pugh (CTP) classification, the Model of End Stage Liver Disease (MELD) classification, and specific disease states including Primary Biliary Cirrhosis (PBC), Primary Sclerosing Cholangitis (PSC), Viral Hepatitis and Hepatocellular Carcinoma (HCC) have all assessed medical urgency (16-21). Models have been developed to assess survival after transplantation, in order to assess the "usefulness" of the transplant and guard against the "futile" transplants (15). One of the first attempt at organ allocation was the UNOS Listing criteria.

UNOS LISTING CRITERIA

UNOS utilized 3 criteria in listing a patient for liver transplantation: Child-Turcotte-Pugh, ABO blood type, and overall waiting time. The UNOS criteria included Status 1, Status 2a, Status 2b and Status 3 patients. Status 1 were patients with acute fulminant hepatic failure or patients with primary graft dysfunction or hepatic artery thrombosis occurring within the first week post transplantation or pediatric patients who decompensated and required continuous care in the intensive care. Status 1 patients received priority for liver allocation over all patients with chronic liver disease. Status 2a-3 are outlined below (table 2)(22).

Table 2
United Network for Organ Sharing Status Criteria for Patients with Chronic Liver Disease

Status 1	Acute Fulminant Hepatic failure, patients with primary graft dysfunction or hepatic artery thrombosis occurring within the 1st week post transplantation or pediatric patients who decompensate and require ICU care
Status 2a	CTP ≥ 10, ICU care and estimated < 7days to live
Status 2b	CTP score ≥ 10 or ≥ 7 associated with refractory complications of portal hypertension or HCC meeting the following criteria; 1 lesion<5 cm or ≤ 3 lesions all < 3 cm each and no evidence of metastatic disease
Stage 3	CTP≥ 7 minimal listing

An integral part of the UNOS listing status was the Child-Turcotte-Pugh (CTP) classification which had been used since minimal listing criteria were first defined in 1998 as an index of severity for patients with End Stage Liver Disease (ESLD). Historically, the purpose of the CTP classification was to assess the operative risk of patients with ESLD with variceal bleeding undergoing portosystemic shunt surgery (23). In 1973, Pugh et al used a modified version of the Child-Turcotte version of this severity index in describing the outcome of patients undergoing surgical ligation of esophageal varices (24). Pugh assigned a score ranging from 1 to 3 to each of the variables in the classification: ascites, portosystemic encephalopathy (PSE), bilirubin, albumin and prothrombin time. Pugh assigned a score ranging from 1 to 3 to each of the factors in the classification. CTP classes A, B and C were calculated by totaling the sum of individual scores (table 3).

Table 3 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 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

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

The liver transplant community met in February 1997 at the NIH to formulate specific criteria based on minimal listing criteria already developed by the UNOS Liver and Intestinal Committee **(22)**. The minimal criterion included that patients with chronic liver disease would be suitable for placement on the waiting list when their estimated 1- year survival without transplantation was 90%, which in essence was a CTP score ≥ 7 points or a cirrhotic patient with variceal bleeding or spontaneous bacterial peritonitis. Because of this liberal criteria, many patients remained on the waiting list for an extended period of time.

In addition, the CTP score was variable and subjective and could be maniupated by clinicians. Historically, ascites was determined only by clinical exam but more recently, ascites was determined by ultrasonography increasing the ascites score in certain patients listed for liver transplantation. In current practice, fatigue, forgetfulness and insomnia may qualify as a symptom of PSE, which may be manipulated by sedative medications. Albumin, which was supposed to reflect the state of a patient's nutritional state can be iatrogenically manipulated with infusion of albumin. Prothrombin time can vary from laboratory to laboratory depending on the control measures. Finally, of great importance, additional severity was not assigned to a patient with increasing level of bilirubin. For example, the CTP score allots patients with serum bilirubin values of 3.5 m/dL the same score as those with serum bilirubin levels of 10 mg/dL or even 40 mg/dL (25). This latter limitation was also

referred to as "the ceiling effect (1). All of these subjective variables made the CTP score suspect as far as providing exact prognosis of a patient's short term mortality. Furthemore, the tie breaker for the same CTP score was time on the waiting list and investigators had demonstrated that the waiting time on the list did not correlate with the waiting list mortality (26).

Investigators have assessed whether specific patient populations were "privileged"using this system. The retrospective study was designed to determine if this system benefitted a particular group in prioritization of liver transplant. Investigators reviewed the charts of 2376/9244 patients, who had received a liver transplant (LT) as a status 2a or had been listed as a status 2a in 2000. The strongest patient characteristic that predicted transplantation for a status 2a patient were listing in Western U.S. and shorter duration of registration. Positive predictors included blood type O, college education, coverage with private insurance or HMO/PPO while Laennec's cirrhosis was a negative predictor (27). In essence, the CTP score and the UNOS listing criteria did not designate the patients with the highest "medical urgency."

DEVELOPMENT OF ESLD SURVIVAL MODELS

Because of the inherent complexity of chronic liver disease and problems in CTP score, investigators continued to develop studies to define the critical factors that would predict death in patients with ESLD. As early as 1956, progressive renal failure was recognized as a common preterminal complication in patients with cirrhosis of the liver (28). In 1965 Shear published an article entitled "Renal failure in patients with cirrhosis of the liver: clinical and pathological characteristics (29). Shear reported the poor outcome of cirrhotic patients with renal insufficiency. Renal insufficiency has continued to be recognized as a critical component of ESLD prognosis. Other critical factors were also noted prothrombin time, hypoxemia, cognitive function (30-32). In the 1990's, a two phase prospective cohort study was conducted at 5 teaching hospitals in order to develop and evaluate a model for prediction of death. The important variables included: renal insufficiency, cognitive dysfunction, prothrombin time and mechanical ventilation or hypoxemia. These risk factors stratified 243 cirrhotic patients in phase II into three groups with cumulative incidence of death at 30 days of 12, 40 and 74% (33).

Transjugular intrahepatic portosystemic shunt (TIPS) model

In 2000, a model was developed to predict the outcomes of the transjugular intrahepatic portosystemic shunt (TIPS) procedure in patients with chronic liver disease (34). The TIPS procedure worsened liver function and decreased survival in some patients. In a retrospective study, the survival of 231 patients at 4 medical centers within the United States that underwent elective TIPS was studied to develop statistical models to predict patient survival and identify those patients whose liver related mortality post-TIPS would be 3 months or less. Death related to liver disease occurred in 110 patients, 70 within 3 months. Cox proportional hazards regression identified serum concentration of bilirubin and creatinine, international normalized ratio for prothrombin time (INR) and the cause of the underlying liver disease as predictors of survival in patients undergoing elective TIPS. These variables were used to calculate a risk score for patients undergoing elective TIPS. The model was

$$R = 0.957 \log_e \text{creatinine (mg/dL)} + 0.378 \log_e \text{bilirubin (mg/dL)} + 0.120 \log_e (\text{INR}) + .643 \text{ etiology}) \times 10.$$

For example, a risk score could be calculated for a patient with cirrhosis

$$R = (0.957 \times \log_e 1.9) + (0.378 \times \log_e 4.2) + (1.120 \times \log_e 1.2) + (0.643 \times 1) \times 10 = 2.003.$$

The risk score was applied to a survival equation. A nomogram was published to be used at the bedside whereby the clinician placed the actual values of bilirubin (mg/dL), INR and creatinine (mg/dL) on the chart and connected the lines. The predicted probability of death within 3 months of placement of TIPS could be read off the scale (33).

Furthermore, the model was validated in an independent set of patients that had received an elective TIPS. Specifically, survival of 71 independent TIPS patients from the Netherlands were stratified according to their risk score into two risk groups, namely a high risk group with a median survival less than 3 months ($R > 1.8$) and a low risk group with a median predicted survival more than 3 months ($R < 1.8$). Actual (Kaplan-Meier) and expected survival using the Mayo model were compared. For the low- and high-risk patients, the observed and expected survival were similar ($p=0.88$ and $p= 0.41$, respectively)(34).

Validation of TIPS (MELD) model in broad range of liver disease/severity

In order to determine the generalizability of a model previously created to estimate survival of patients undergoing TIPS procedure, a study was conducted with different patient groups with a broader range of disease severity and etiology. Using the exact same TIPS survival equation and variables, the Model for End-Stage Liver Disease (MELD) score was born. The hypothesis was that survival following TIPS was determined by the severity of the underlying liver disease and that the same model could be used as a prognostic indicator in all patients with advanced chronic liver disease. The measured outcome of their study was whether the model was able to rank patients according to their risk of death in 3 months. The model's validity was tested in 4 independent data sets, including: (1) patients hospitalized for hepatic decompensation (referred to as "hospitalized" patients), (2) ambulatory patients with noncholestatic cirrhosis, (3) patients with primary biliary cirrhosis (PBC), and (4) unselected patients from the 1980s with cirrhosis (referred to as "historical" patients)(35).

The validity of the model was determined using the c-statistic (concordance-equivalent to the area under the receiver operating characteristic graph) (36). In this context, the c-statistic was 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 (ROC) graph depicted the true positive proportion (specificity) plotted against the false positive proportion (sensitivity) 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 valuating prognostic models (37). A c-statistic between 0.8 and 0.9 indicates excellent accuracy while a c-statistic of >0.7 is generally considered a useful test result. Specifically, the curve with the largest area under the curve has the highest accuracy.

Because the MELD was developed in patients undergoing the TIPS procedures , initially, the model usefulness in patients with decompensated cirrhosis not undergoing TIPS (hospitalized) was assessed. All cirrhotic patients hospitalized from 1994-1999 at a single center were identified. There were 129 deaths, 50 of which occurred during the first 3 months (35). The c-statistic for prediction of 3 month survival by the MELD score was 0. 87. The 3 month mortality in CTP class A was 4%, for CTP class B it was 14%, for class C it was 51%. The c-statistic associated with the CTP score of 3 month survival was 0.84.

Next, the MELD score of ambulatory patients with noncholestatic liver disease was determined by retrospective analysis of Italian patients with newly diagnosed cirrhosis (viral etiology). There were 491 patients; 117 patients died, 34 of whom died in the first 3 months. The c-statistic for the MELD scale of 3 month mortality was 0.80. In another group of 316 ambulatory patients with PBC accrued from 1973- 84, 5 and 23 deaths occurred in the first 3 months and 1 year, respectively. The c-statistic for mortality at 3 months or 1 year were 0.87. For the historical cirrhotic patients accrued in the 1980's, the c-statistic was 0.78 and 0.73 for mortality at 3 months and 1 year, respectively. Of interest, individual complications of portal hypertension had minimal impact on the model's prediction. Furthermore, excluding liver disease diagnosis from all groups had minimal effects on the c-statistic. These studies were paramount prior to determining the utility of the model for the prediction of mortality of patients on the transplant waiting list.

Freeman Model

Other "Liver Disease Severity" scoring systems were being developed for the patients, especially those patients on the liver transplant waiting list. Freeman et al from the New England area developed a scoring system in order to predict death in patients awaiting transplant (38). Because of the inherent problems with the CTP score and waiting listing, transplant centers in New England adopted a new definition for 2a and then constructed a continuous score for the 2b definition that emphasized medical severity in late 1990's. The continuous score consisted of the following: Revised strict status 2a criteria including CTP>12, admitted and ICU confined and ≥ 1 of the following; intubated and on a ventilator, serum creatinine >2.4 and U_{Na}<400 or Urine output<400cc/day or on dialysis or gastrointestinal bleed with requirement of >1 unit/D PRBC or refractory ascites. Revised status 2b included the following: serum creatinine > 2, refractory ascites, gastrointestinal bleed, Stage I or II hepatocellular carcinoma (HCC), hepatopulmonary syndrome, familial amyloidosis or recurrent cholangitis. 67 livers were allocated from 8/00 through 1/01 (before the new system) and 75 livers were allocated 3/01-9/01 (after the new system). There was a significant reduction in the number of transplantations performed for patients listed as status 1a and an increase in the number of patients listed as status 2b who received transplantation. Most dramatically there was a 37.1 % reduction in overall deaths on the waiting list: from 94 deaths in period 1 to 62 deaths in period 2. These studies confirmed that a continuous medical severity score would be helpful in reducing mortality on a liver transplant waiting list.

MELD and LT Waiting List

In January 2003, a study was published that determined the MELD's ability to predict 3 month mortality of a patient on LT waiting list. The investigators were concerned about the subjectivity of the UNOS waiting time, the small number of categories of disease in the UNOS listing system **(39)** and the subjectivity of the CTP score. Specifically, the investigators assessed the MELD score's ability to correctly rank order patients according to risk of death while on the waiting list. The analysis was performed by measuring the c-statistic equivalent to the area under ROC (36). The outcome assessed was the 3 month mortality of patients on the liver transplant waiting list. The mathematical equation (table 4) employed to calculate these scores for patients with chronic liver disease was:

Table 4

MELD Calculation
MELD score = .957 X $\log_e$ Creatinine (mg/dL)
+.378 X $\log_e$ bilirubin (mg/dL)
+.120 X $\log_e$(INR) X 10
+ .643(etiology of the disease) - subsequently removed from the scoring system
Web.calculator available at www. optn.org/resources.

The mean age of the study cohort was 50.7 years and 2/3 of the patients were men. The cohort consisted of 70.1% White,14% Hispanics and 9.1% African American. The most common disease for ESLD was hepatitis C (34%) followed by alcoholic liver disease (27.3%). In this study cohort, 536 patients were initially listed on the OPTN list as status 2a and 2,901 were listed as status 2b. Of the patients listed at 2a status, 144/536 patients died whereas 258 of 2901 patient listed at status 2b died (9.2%). 95 patients were removed from the list (39).

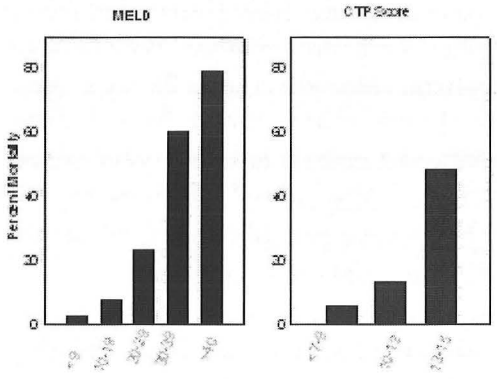


Fig. 1

The mean MELD score of the 2a status patients was 28 vs 18.3 for the status 2b patients. Patients who died had higher serum creatinine levels, INR and serum bilirubin. Comparing 1859 patients who survived with 1452 who either died or needed transplant, there was a statistical difference between creatinine, bilirubin, INR and MELD but no statistical differences in CTP scores. As demonstrated in panel A of figure 1, mortality increased in proportion to the increase in the MELD score. Patients with a MELD score of <9 experienced a 2.9% mortality at 3 months, whereas patients with a MELD score > 40 had a 79.3% mortality. As shown in panel B, the mortality also increased with CTP score. With less categories, varying severities of liver disease were isolated into 1 category with an overall 3 month mortality of 40%. Patients who had CTP scores of 11 had MELD scores ranging from 8-46. The relationship between the MELD score and estimated 3 month mortality in patients with chronic liver disease appears to be a linear relationship between 20 and 40, dropping from an 80 to 20 percent survival rate. Importantly, the c-statistic with a 3 month mortality as the end point, the area under the ROC curve for the MELD score was 0.83 compared with 0.76 for the CTP score (39).

MELD EXCEPTIONS

A number of special conditions were recognized by the transplant community as meriting elevation of the candidate up the wait list beyond the level accorded by their MELD score (40). Adjustments were made to accommodate patients with hepatocellular carcinoma and other diagnoses,

such as hepatopulmonary syndrome and metabolic liver diseases because these patients have risks of their condition progressing beyond the stage favorable for transplants (risks that are unrelated to laboratory test). A regional peer review system was included in the new allocation plan to apply for increases in MELD scores for these cases (41). These conditions and their corresponding adjusted MELD scores are outlined in table 5. **Table 5**

MELD Exceptions	
HCC Milan criteria stage T1	20 points
HCC Milan criteria stage T2	24 points
Hepatopulmonary syndrome	24 points
Familial amyloidotic polyneuropathy	24 points
Primary oxaluria	24 points
Additional special requests may be entertained on case by case basis by UNOS Regional Review Boards	

Recent studies have shown that HCC tumor size (<5 cm) or the number of tumor nodules (up to 3 lesions< 3 cm) are important with regard to prognosis and recurrent disease (25). Further studies based on these selection criteria for HCC have shown that patient survival and graft survival are similar to survival with other chronic liver disease. A recent study showed that patients who fulfill the aforementioned criteria have a 3 year survival of 83% compared with a 3-year survival of 18% of patients undergoing partial hepatectomy (42). Other studies suggested that HCC tumor nodules ≤6.5cm had similar transplant survival rates and should be included in the HCC transplant criteria (18). With HCC survival rates continuing to improve, changes were made to the UNOS allocation policy with the initiation of MELD. Importantly, a biopsy for the diagnosis of hepatocellular carcinoma (HCC) was not required. Consistent radiologic finding with a nodule > 1 cm or an AFP > 200 and no extrahepatic disease was required (40). For the initial assessment before listing, patients must have a chest computed tomography and bone scans that rule out the presence of metastatic lesions and at least one of the following: a tumor >1 cm in size with a blush corresponding to area of suspicion seen on the imaging studies, an alpha-fetoprotein level>200,an arteriogram confirming a tumor, a biopsy confirming HCC, chemoembolization of the lesion and radiofrequency, cryoablation or chemical ablation of the lesion (40). Initially a T1 lesion (single lesion <1.9cm) was given 24 points (consistent with a 15% probability of death in 3 months) and then lowered to 20 points. T2 lesion with one lesion 2-5 cm or 2-3 lesions all <3 cm was initially given 29 points (consistent with a 30% probability of death) and then lowered to 24 points. Patients with Milan criteria stage T1 and T2 HCC (43) were permitted a further 10% increase in their adjusted MELD score if they remain transplanted for more than 3 months at their original score. Furthermore, other conditions, such as hepatopulmonary syndrome and familial amyloidotic polyneuropathy also increased the MELD score.

RECERTIFICATION SCHEDULES

Since the MELD scoring system has critical components that fluctuate, UNOS has implemented the schedule for each of the MELD categories to be recalculated to insure that an up-to-date MELD score is available on a timely basis and continues to reflect medical urgency (40). As illustrated in table 6, the patients with the highest MELD need laboratory values more often than those

with lower MELD scores. As suggested by investigators the change in MELD over time (ΔMELD) may help discern survival rates (44,45). The plan dictated that a patient would be "recertified" for liver transplant based on his current MELD score.

Table 6

Recertification schedule for MELD Scores		
Status 1	every 7 days	Lab≤ 48 hours old
MELD≥ 25	every 7 days	Lab≤ 48 hours old
Score≤ 24 but > 18	every 1 month	Lab ≤ 7days old
Scores≤ 18 but ≥11	every 3 months	Lab ≤ 14 days old
Scores ≤ 10 but >0	every 12 months	Lab ≤ 30 days old

MELD LIMITATIONS

There have been a number of concerns regarding the use of the MELD model as the only criteria for assessing medical urgency for liver transplantation. First, creatinine a critical factor in the model, can be manipulated by volume status (46). Fluctuations in serum creatinine tend to occur in people with far advanced liver disease, who develop complications such as sepsis or spontaneous bacterial peritonitis (46). Therefore, elevations in creatinine may falsely elevate or lower the MELD score. Repeated MELD scores for each patient may help exclude clinically significant variations in creatinine and in the MELD score. In addition, the ΔMELD may be an additional predictive factor of adverse outcomes (44,45).

Other investigators have raised the concern that MELD score may not be useful in patients with CTP<10. Investigators examined the UNOS data, including patients listed at status 2a as well as status 3 patients, many of which had CTP <10. UNOS conventions were followed, which set a maximum value cap for serum creatinine of 4 mg/dL and minimum values for creatinine, INR, and bilirubin of 1. Complete concurrent data were available for 6958 patients, of whom 306 died within 90 days and 706 were withdrawn or underwent transplantation within 90 days. CTP score was similar to the MELD as a predictor of short-term survival. The c-statistic for CTP and MELD were 0.766 ± 0.032 and 0.759 ± 0.034, respectively. The data set was expanded to include patients whose data were received over a span of 30 days, the population increased to 8445, with 394 early deaths. The c-statistics for CTP and MELD scores as predictors of 90-day mortality were nearly identical (0.793 ± 0.028 vs. 0.789 ± 0.028, respectively)(47). This study suggests that the MELD may not be superior in predicting 3 month mortality in patients with low CTP scores.

Investigators have suggested that survival rates may drop and an increase in the number of futile transplants may be performed. Others have stated that HCC may be transplanted at an increasing rate or that tumor size criteria is too stringent (18,48). Specifically, MELD may provide too much advantage to sicker patients which could potentially lead to an increase in early post transplant deaths

resulting in a fear that a donor liver might be wasted. Other patients with primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC) may be at a disadvantage (37,49).

Regional variation in the disparities between supply and demand continues to create controversy. Currently, up to 40% of the variation in the MELD scores at the time of transplantation may be explained by the region in which the patient is listed for transplantation. MELD stratification system would not improve the regional variation nor the overall organ shortages (50).

POST- MELD IMPLEMENTATION AND VALIDATION STUDIES.

Validation of MELD Scoring System

The MELD score has been applied in a number of European transplant centers in order to determine whether the MELD score ranks liver recipients according to the severity of liver disease and correctly assesses their mortality risk on the waiting list for LT (51, 52). Specifically, the studies examined whether the MELD score could be applied to patients with various medical, social, and ethnic backgrounds. In a European cohort of cirrhotic patients, 6 month and 1-year mortality were not statistically different between the MELD and the CTP score. However, the MELD scores did correlate with a residual liver function measure, which was evaluated by means of a liver blood flow-dependent parameter of liver function, monoethylglycinexylidide test (MEGX test) (51). In cirrhotic patients, the MEGX test has previously shown to predict pretransplant survival and to be useful in assessing priority for LT (53,54). The study demonstrated that an increase in the MELD score was associated with a decrease in residual liver function (50).

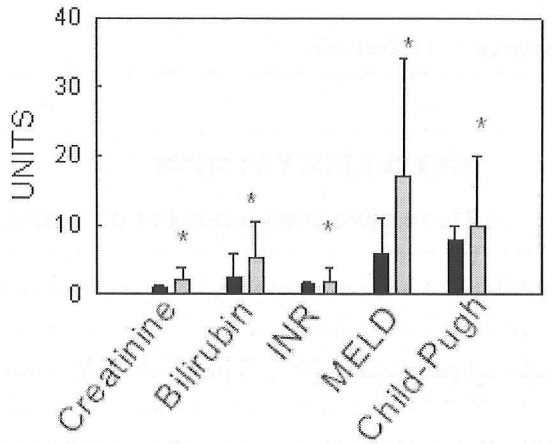


Fig.2

Unlike the 6 and 12 month mortality (51), the 3-month mortality predictive value of the MELD was better than CTP score in a cohort of 145 cirrhotic patients (55). 13 patients died. MELD score and its parameters, as well as Child-Pugh scores were significantly higher among patients who died as compared with patients who survived during the 3 months. Statistical differences were Creatinine p=0.0003, Bilirubin p=0.004, INR p=0.0002, MELD p=0.0001; and Child-Pugh p=.002 (figure 2). Furthermore, ROC curves were used to find both the MELD and Child-Pugh scores with the best sensitivity and sensibility in assessing 3-month survival. A MELD score cut-off of 9 had 100% sensitivity (100–100, 95% confidence interval) and 81% specificity (73–87, 95% confidence interval), while a Child-Pugh score of 9 had 62% sensitivity (32–86, 95% confidence interval) and 77% specificity (69–84, 95% confidence interval) in assessing 3-month survival. Comparison of ROC curves showed a statistically significant difference between the c-statistic for MELD score (0.947) versus the CTP (0.757) (53).

Conversely, the University of Barcelona retrospectively compared 2 groups of patients who died on waiting list and those who successfully underwent LT during the same time period. 4 scores

at the time of entering the waiting list and just before LT or death were evaluated. The evaluated scores included: CTP, MELD, Freeman, Guardiola (model to predict survival of patients with refractory ascites treated by peritoneovenous shunt, based on CTP, Nonalcoholic etiology, low ascites fluid protein and history of SBP). The mortality on the waiting list was 15.9%. All studied scores, except Freeman score were higher in those who died on the waiting list: (MELD 17.4 Child 9.9 Freeman 9.7 Guardiola 2.6). C-statistics of all scores were similar (MELD 0.75, CTP 0.78, Freeman 0.65 and Guardiola 0.79). None of the studies scores had an excellent accuracy in predicting prognosis of patients on waiting list for LT in Spain, which has a high proportion of HCC (56).

Early Post-MELD Trends

Freeman reported that early results comparing the first 6 months of the new system (2/27/02-8/30/02, era 2) with the corresponding time period 1 year earlier (era 1) demonstrated that fewer patients were registered, fewer patients died or were removed from the list for being " too sick" and more cadaveric liver transplants were performed (41). A higher proportion of transplant recipients with HCC (21.5%) were transplanted under the new system compared with 8% previously. Most of the liver transplants for HCC under the new system occurred within 90 days of initial application for the HCC status. All areas within the U.S. saw increases in the number of cadaveric transplants and reduction in the number of deaths on the waiting list and these changes were not different among diagnostic, ethnic, blood type or gender groups. There was a slight reduction in the number of relist and retransplants but an increase in the number of combined liver kidney transplants under the new system (41).

MELD and Post Transplant Survival/Resource Utilization

Studies suggested that renal insufficiency at the time of transplantation was predictive of lower post liver transplantation survival. Primary graft nonfunction and 30-day mortality rates were higher and 1-, 2-, and 5-year graft and patient survival rates were lower in patients with moderate or severe renal failure (54). CCr less than 40 mL/min was associated with significantly lower short-term and long-term graft and patient survival rates (57). Therefore MELD's reliance on creatinine has been a concern in insuring the "usefulness" of the transplant.

In an early multicenter data base including 2 large transplants centers 1185 patients in 4 diagnostic categories (viral hepatitis 30%, alcoholic liver disease 15%, cholestatic disease 31% and other liver disease 24%) was reviewed in order to assess post liver transplant outcome. Outcomes included graft and patient survival at 3 months, intraoperative blood transfusion requirement and length of intensive care unit and hospital stay. The outcomes were found to become worse as the pretransplant MELD score increased. The model's prediction of mortality within 3 months following liver transplant, expressed as the c-statistic was only 0.62, raising the question of the MELD's ability to predict post-LT survival. (58).

In another study, MELD's abilities to predict post-transplantation outcome was determined at a single center. In order to determine outcome in the first 2 years post-LT, 669 consecutive LT patients transplanted between 12/93-10/99 were evaluated retrospectively at a single center. Patients were stratified according to MELD score <15, 15 - 24, and ≥ 25. As suggested by the previous abstract, post-transplantation survival at 3, 6, 12, 18 and 24 months was significantly lower in the groups with a higher MELD score. Importantly, the difference was significant for hepatitis C and

noncholestatic liver diseases, but not cholestatic diseases. In patients with a MELD score between 15 and 24, survival was significantly greater with cholestatic diseases and lower in patients with hepatitis C. Pretransplantation MELD score was inversely correlated with survival in the first 2 years after liver transplantation. There was a survival advantage for patients with cholestatic diseases compared with those with hepatitis C (59).

In another center, a retrospective analysis of 1-year patient survival in 404 adult LT transplanted from 1998-2001 was evaluated. The hazard rates of patient survival according to the MELD strata and UNOS statuses were assessed by Cox regression analysis. The difference in survival for MELD strata and UNOS status were compared. There was a significant difference in 1-year patient survival ($p=0.0006$) using different MELD strata, whereas there was a trend according to UNOS status ($p=.051$). Increased rate of death was observed in recipients of LT with higher MELD scores (> 36, hazard ratio 3.9; 95% CI 1.55, 10.27) and more urgent UNOS status (2A; hazard ratio, 1.99; 95% CI 1.07, 3.7). In essence, this study reported that the MELD stratum is better associated with 1-year patient survival in liver transplant recipients than UNOS statuses and patient survival was worse with higher MELD scores (60). In contrast to this study, other investigators from a different center compared the ability of the MELD and CTP score to predict post LT post OLT in status 2a patients during the time period 8/98-11/00. 42 consecutive adult patients undergoing a LT at a single center were evaluated. The study population had a median age of 53 years; median MELD of 24.6 and mean CTP score of 12. The overall 1 year survival rate was 91%. Neither the MELD nor the CTP score was predictive of survival post LT (61). Though a small study, the findings may reflect regional and center variations in survival.

In a recent abstract presented at AASLD, charts from 3,745 patients from the UNOS data base who underwent LT were reviewed. The MELD score ranged from <10 297 patients; 10-19 1,357 patients; 20-29 699 patients and >30 392 patients. Relative risks of graft failure within 3 months increased above a MELD of 25 (MELD 25 - RR1; MELD 30 - RR1.2; MELD 35 RR1.6; MELD 40 RR2.1. Therefore, a MELD score > 25 was associated with an increased risk of graft loss/ failure (62).

There has been limited data to evaluate the effect of the MELD system on LT associated resource utilization. Patients undergoing LT at a single center in the 6 months following MELD implementation were compared to those undergoing LT in the immediate preceding 9 month period (63). 62 underwent LT post MELD and 62 underwent LT prior to MELD. The average MELD scores were 25.9 vs 24.1, respectively. Overall length of stay (LOS) was similar in the two groups. However, pre-LT LOS in ICU was higher in the pre MELD group. The MELD score was significantly correlated with post-LT LOS with serum bilirubin and creatinine showing the strongest correlation. Therefore, cost savings post-MELD are attributable to the elimination of the pre-LT ICU stay, previously an integral component of prioritization for organ allocation.

MELD and Exceptions Including Hepatocellular Carcinoma

The use of the revised MELD scoring system to establish the medical urgency of hepatocelluar carcinoma (HCC) raised a number of concerns. These concerns included that more patients with HCC would be transplanted and that there may be a poor correlation between preoperative stage and final liver pathology. Conversely, the dropout rate due to HCC because of the increased MELD score was expected to drop. As anticipated, directly after the implementation of the MELD, the number

of patients with HCC who underwent transplantation in the 6 months before MELD and the 6 months after MELD were 230 vs 513 nationally (64). Furthermore, between 2/2002 and 11/2002 there were 1957 exceptional case request for patients believed to not be adequately served by the MELD scoring system. These exceptional cases included (HCC - 1193/1278 requests granted; Familial amyloidosis -14/16 request granted; hepatopulmonary syndrome (HPS) -78/89 and other specified indications 366/541)(64). As described by the current MELD allocation system, the regional review board evaluated all of these exceptional case requests. MELD exceptional cases including HCC consisted of approximately 25% of all transplants and there was a 100% increase post MELD of patients receiving livers for HCC. These statistics indicated that a high proportion of liver transplantations were comprised of the MELD exceptional cases.

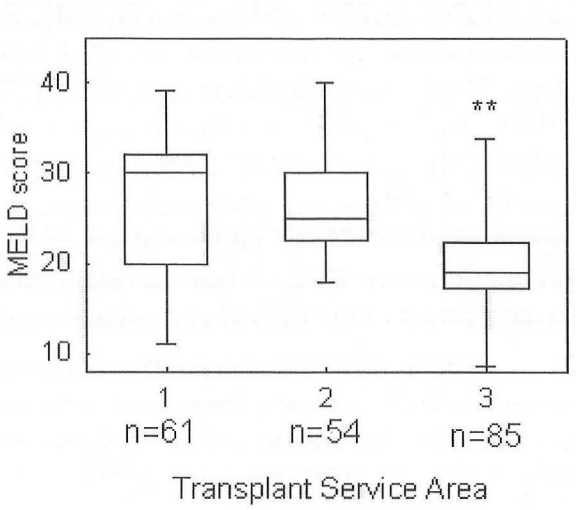
In addition to the high number of transplantations that occur because of the additional points received by HCC patients, there was a concern that these patients may not be staged correctly preoperatively. In order to address this concern, a group of investigators reviewed the charts of 979 adult patients with HCC representing 23% of the total LT in the post-MELD era (65). Of these, 82% were listed as stage 2 and 16% met stage 1 criteria. As anticipated, the dropout rate was very low with 4.1% and 7.9% (stage 1 and 2, respectively). Of the final 666 reports reviewed, 51% had lesions that were consistent with preoperative stage request. Microvascular invasion was seen in 7% of cases. Only 46% had HCC lesions meeting the Milan criteria with 10% having no lesion, benign or malignant. Explant pathologic stage distributions were: Stage 0 - 23%; Stage 1- 8%; Stage 2 - 37%; stage 3 - 10%; Stage 4a - 8% and stage 4b - 12% In combination, 30% of the LT patients had stage 3 and 4 HCC. These findings suggest that preoperative staging needs to be refined and that post liver transplant survival with stage 3/4 need to be further defined.

MELD and Geographic Disparities

The MELD is also not designed to address any geographic disparities but rather within regions to insure that patients are listed in a medical urgency priority. Importantly, there may be other factors that will determine whether a patient receives a LT in a specific area and various plans have been outlined to improve organ allocation nationally, including restructuring organ distribution boundaries (66).

In one study, investigators hypothesized that certain regions, with a high supply of organs/centers, would perform LT at lower MELD scores. The United States is divided into 11 distinct regions (UNOS region), determined by UNOS. Investigators reviewed charts from 1 UNOS region with 3 distinct geographic areas. Within 1 UNOS region, there were different characteristics of each transplant service area (TSA). TSA 1 had 1 organ procurement organization (OPO) and 5 LT centers; TSA 2 has 1 OPO and 2 LT centers; TSA 3 had 1 OPO and 2 LT centers and 1 OPO with 1 LT center. In essence, TSA3 had more OPO per LT centers. The UNOS region patients who received a cadaveric liver had higher median MELD scores than cadaveric liver recipients in the US (26 vs 24). When comparing the TSA's, the TSA with competing liver transplant programs performed transplants on patients at a significantly higher MELD than the TSA dominated by single center (27.3 vs 26.6 vs 21.3) (64). Specifically, OPTN data showed that transplant centers within TSA 3 performed cadaveric liver transplants at a lower average disease severity than TSA 1 or 2 (figure 3)(64). This disparity held even when transplantation for HCC were excluded. Among the 5 centers in TSA 1, the distribution of MELD scores were weighted more heavily toward patients with higher MELD. Within TSA 1,

more than 2/3 of all LT were performed in patients with MELD of 29 or greater. Furthermore, implementation of the MELD resulted in a substantial increase in the number of transplantation performed for HCC and MELD exceptions for all reasons were more common in TSA's with multiple centers. Data suggest that competition among centers in an OPO also might factor into the decision of whether to list or perform transplantation. LT centers with competitions performed transplantation on patients at higher MELD scores than centers without competition.



MELD and Retransplantation

Survival following secondary transplantation has been shown to diminish as level of urgency increases. Numerous authors have argued that in the face of poor outcome and limited resources, the most urgently ill patient should be balanced against the duty to allocate scare resources to those who are most likely to benefit from them. Thus, an allocation system attuned to efficacy concerns might give priority to a transplantation candidate who has a high post-tranplantation survival rate as opposed to a higher pre-transplantation mortality (67). Since it has been proposed that an expected 1 year survival rate of less than 40% in re-LT patient would be an unreasonable use of a donor organ when a primary LT recipient would be anticipated to have at least double the survival rate (68).

The objectives of a recent study were to determine the validity of a recently developed UNOS multivariate model using an independent cohort of patients undergoing re-LT outside the U.S. The study was to determine whether incorporation of other variables that were incomplete in the UNOS registry would provide additional prognostic information, to develop new models and to evaluate validity of the MELD in patients undergoing re-LT.

281 patients undergoing re-LT (between 1986 and 1999) at 6 foreign transplant centers comprised the validation cohort. In the patients for whom the INR was available, MELD correlated with outcome following re-LT; the median MELD scores for patients surviving at least 90 days compared with those dying within 90 days were 20.75 versus 25.9, respectively (p.004). Utilizing both patient cohorts (n = 979), a new model, based on recipient age, total serum bilirubin, creatinine, and interval to re-OLT, was developed. The risk scores for the final model were derived using the following equation:

$$R=10 \times (0.236 \text{ (recipient age)} + .125 \text{ (square root bilirubin)} + 438 \text{ Log}_e \text{ (creatinine)} - 0.234 \text{ (interval to re-OLT)}.$$

Using the c-statistic with 30-day, 90-day, 1-year, and 3-year mortality as the end points, the area under the ROC curves for the new model was found to be comparable or slightly better than the MELD (68).

OTHER SCORING SYSTEMS

Primary Biliary Cirrhosis

Though the MELD system appears to be useful for mortality prediction in a broad category of etiologies, others have been developing models for specific liver disease states for 15-20 years. For example, Shaffner et al in 1979 reported elevated bilirubin as a prognostic factor in patients with primary biliary cirrhosis (PBC) (69). In 1983, Klatskin and his group reported the prognostic importance of clinical and histological factors in a symptomatic PBC, indicating the elevation in bilirubin was a critical factor (70). In 1984, Epstein et al suggested a mathematical model for prognosis of patients with PBC (71). In 1988, Roger Williams group reported the use of a prognostic index in evaluation of liver transplantation for (72).

In 1989, Dickson et al described the Mayo PBC survival model (73). Five variables were used: bilirubin, albumin, prothrombin time, age and presence of edema. The mathematical equation utilized was:

$R = 0.871 \log_e$ (bilirubin mg/dL) + -2.53 $\log_e$(albumin gm/dL) +.039 age + 2.38 Log_e (prothrombin time) + 0.859 edema.

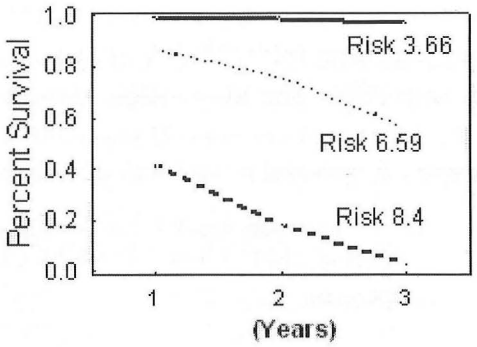


Fig. 4

Figure 4 is an example of survival curves for 3 different R values. Survival decreases with increasing R values. At that time, the investigators suggested that an important application of the model would be the timing of and selection of patients for transplantation. The model was compared to the Yale and European survival models (19,71). The most important difference among the models was the fact that the Mayo model did not require a liver biopsy.

The Mayo PBC prognostic model has been validated in patients from two institutions outside the Mayo clinic (74,75). The Mayo model and its frequent updates are useful to assess survival in PBC patients. Importantly, the model was developed with clinical data collected at the time of referral and cannot be used with certainty on multiple future occasions. Furthermore, albumin and prothrombin time can have substantial variability between different centers. Finally, the age factor index in the models tends to overestimate disease mortality for older patients in a stable condition.

Although the Mayo and the MELD have not been examined in patients on a waiting list, there are 3 studies that address Mayo's PBC and the MELD's scores' ability to predict 3 month survival both pre and post liver transplantation. As previously discussed, the MELD scoring system predicted the ambulatory PBC patients survival at 3 months and 1 year (35). Similarly, post liver transplant patients with cholestatic diseases have higher post LT survival than HCV and other noncholestatic diseases and a higher MELD was not predictive of post transplant mortality (55). Hence, a higher MELD in cholestatic disease such as PBC does not have a poor prognosis after LT in cholestatic disease processes such as PBC.

Mayo risk score for PBC and the CTP score for post-liver transplant outcomes have been compared in a small cohort of patients with PBC (n=43) from a single center in Australia (76). 43 patients were included in this study and 5 patients died while awaiting LT. The mean Mayo risk score at the time of acceptance was 9.6. 11 patients died after LT with all but 2 occurring in the early postoperative course < 3 months. Causes of death included heart disease (8 patients), sepsis (2 patients) and graph malfunction (1 patient). The mean Mayo risk score was significantly greater in the group of patients who died after LT compared with the group of survivors. (8.6 ± 1.4 vs 7.1 ± 1.8, $p<.05$). The mean CTP score of patients who died was significantly greater than that of the survivors (10.8 ± 2 vs 8.5 ± 2.9, $p = 0.03$). The investigators concluded that the 2 scores correlated with one another and with mortality and resource utilization but that the Mayo score was superior at predicting outcome (76).

Primary Sclerosing Cholangitis.

In 1989, Weisner assessed the natural history of primary sclerosing cholangitis (PSC) in a large group of patients with PSC (77). A model was developed as an initial attempt at estimating survival of patients with PSC. The Mayo clinic identified 174 patients who had a diagnosis of PSC between 1970 - 1984. The mean age was 40 years and 66% were male and 71% had associated inflammatory bowel disease. A survival model was developed and the risk equation was:

> $R = 0.06$ age (year) $+ 0.85 \log_e$ (minimum bilirubin mg/dl or 10)- $4.39 \log_e$ (minimum hemoglobin g/dl or 12) $+0.51$ x biopsy stage $+1.59$ X indicator for inflammatory bowel disease.

Three risk groups groups were identified: Low risk (-9.74 to -5.14); intermediate (-5.12 to -3.12) and high (-3.23 to 0.43) (77). This scoring system has been further refined since 1989 (78,79). In 1992, investigators reported a revised model that included the presence of splenomegaly(78). The new PSC model was

$R = .535$ X ($\log_e$ Bilirubin mg/dL) + .486 X (histological stage) + 0.041 X (age in years) + 0.705 presence of splenomegaly.

In 2000, the investigators reported the most recent version, which included ast, age, bilirubin and albumin (79).

$R = 0.03$ (age in years) $+.54$ X ($\log_e$ Bilirubin mg/dL) + .54 X (AST U/L) + 1.24 X (variceal bleeding (0/1) - 0.84 X albumin.

Though investigators have not compared the MELD to the Mayo PSC survival model, investigators have examined whether the CTP or the Mayo PSC scoring system have similar ability in predicting post liver transplant survival (78,79). Data from 128 patient with PSC, identified from the NIDDK database, were used to calculate patient specific Mayo PSC and CTP score before transplantation. CTP scores were found to be a significantly better predictor of death after liver transplantation than LOS. 21 days or death before discharge and resource utilization were measured by area under the ROC curve. Among patients with PSC undergoing LT, CTP score was a better overall predictor of both survival and economic resource utilization than the Mayo PSC score (80).

Viral Hepatitis

In addition to PBC and PSC, other investigators have attempted to find models that would predict survival in patients with viral hepatitis. In 1988, Williams and Hoofnagle examined the diagnostic and prognostic usefulness of AST /ALT ratio in patients with viral hepatitis (20). They first proposed that this ratio was a prognostic index for survival. Recently, investigators retrospectively studied 99 patient with liver cirrhosis of viral etiology. 71% of the patients were men. Of interest, the AST/ALT ratios and MELD scores showed a significant correlation ($r_s = 0.503$, $p = 0.0001$). In all, 8% and 30% of the patients had died after 3 months and 1 yr of follow-up, respectively. AST/ALT ratios and MELD scores were significantly higher among the patients who died during both 3-month and 1-yr follow-up. For patients with virus-related cirrhosis, the AST/ALT ratio had a prognostic capability that was not significantly different from that of an established prognostic score such as MELD. The investigators suggested that combined assessment of the two parameters increases the medium-term prognostic accuracy (82).

Pediatric Liver Disease Severity Score (PELD)

Most of the prognostic models have been developed for adult patients with cirrhosis. Because of the concern of the inherent differences in pediatric liver disease, a specific prognostic score was derived for pediatric patients. The Studies of Pediatric Liver Transplantation (SPLIT) database with 884 pediatric ESLD patients was utilized in order to determine the variables that would predict death (83,84). 779 of these patients were not in the intensive care. For the purpose of development of a severity index, primary outcome was defined as death, transplant or admission to ICU. 74/779 patients had a primary outcome. Death occurred in 41 children without a transplant and 33 pediatric patients were transferred to an ICU. 14% of children <1 year were dead or transferred to ICU compared to 6.3% > 1 year. Furthermore, children with a height and weight of 2 SD below normal experience a higher incidence of one of the primary outcomes (14.2 % vs 7.2%).

Table 7

PELD Calculation
PELD score =.480 X loge Creatinine (mg/dL)
+1.857 X loge INR
+.687 X log e Albumin (g/DL0
+ .436 if patient age < 1 year
+ .667 if patient has growth failure (< -2SD)

The first model developed (PSS - Pediatric Severity Scale) consisted of serum albumin, total bilirubin, INR and growth failure. The second model (PSSAGE) included all of the above plus age. The final model (PDSS-Pediatric Death Severity Scale Model) was developed to predict death and used age, bilirubin and INR. The best model of prediction of primary outcome was the PSS model. Because age <1 year was a strong predictor of death, the Pediatric Liver group added age <1 year

to the final PELD that would be used in determining medical urgency of children listed for liver transplantation (Table 7).

A comparison between the 3 pediatric severity models and the MELD model was performed by computing the area under the curve for ROC predicting the primary outcomes at 3 months. Using the SPLIT data base, the 3 pediatric severity scores consistently performed better than the MELD (table 8) and the area under the curve of the ROC for the PSSAGE model was at least 10% higher than the MELD score (37).

Table 8 Comparison of Pediatric Liver Disease Severity Scores

	Death or ICU	Death
PSS	.82	.91
PSSAGE	.82	.92
PDSS	.76	.88
MELD	.71	.82

Conclusion

In conclusion, the development of the MELD occurred over many years, beginning in the 1950's when renal insufficiency was recognized as a predictor of poor outcome in terminal liver disease and developing in response to a new procedure that became available in the 1990's, the transjugular intrahepatic portosystemic shunt and finally being validated in a large number of liver patients with a broad spectrum of etiologies. The limitations of the MELD as a perfect "organ allocation system" includes the large number of exceptions that are not covered by the MELD system, including hepatocellular carcinoma. Expectations following MELD incorporation into the UNOS listing system including increase in transplants in patients with HCC, geographic disparities and increased number of poor outcome in patient with high MELD scores have been observed.

As indicated previously, the best allocation system would be to allocate scare resources to those who are most likely to benefit from them. Thus a" perfect" allocation system would insure that the priority for a patient with chronic liver disease would include not only a high pretransplant mortality but a high post-transplantation survival rate. Ideally, one would like to construct a system that allocates organs to those candidates most likely to die without a transplant but also to those most likely to survive with the transplant. It may be necessary to accept an 80% post-transplant survival rate to minimize the pretransplantation mortality rate to achieve the optimal number of livers saved by the entire liver transplant system (85).

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