The Model for End-Stage Liver Disease (MELD)

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The Model for End-stage Liver Disease (MELD) was initially created to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts. The MELD which uses only objective variables was validated subsequently as an accurate predictor of survival among different populations of patients with advanced liver disease. The major use of the MELD score has been in allocation of organs for liver transplantation. However, the MELD score has also been shown to predict survival in patients with cirrhosis who have infections, variceal bleeding, as well as in patients with fulminant hepatic failure and alcoholic hepatitis. MELD may be used in selection of patients for surgery other than liver transplantation and in determining optimal treatment for patients with hepatocellular carcinoma who are not candidates for liver transplantation. Despite the many advantages of the MELD score, there are approximately 15%-20% of patients whose survival cannot be accurately predicted by the MELD score. It is possible that the addition of variables that are better determinants of liver and renal function may improve the predictive accuracy of the model. Efforts at further refinement and validation of the MELD score will continue. (HEPATOLOGY 2007;45:797-805.)

February 27, 2007 marked the fifth anniversary of the Model for End-Stage Liver Disease (MELD) becoming the standard by which priorities in donor liver allocation were determined. Since the score was first derived in a relatively small number of patients undergoing the transjugular intrahepatic portosystemic shunts (TIPS) procedure, it has been validated in many different populations of patients with liver disease. Within a relatively short period of time, MELD became a common metric by which the severity of liver disease could be accurately described.

In this paper, we review the initial development and validation of the MELD score, its application in organ allocation and management of patients with a variety of liver conditions, its strengths and limitation, and current and future efforts to refine and improve it further.

Creation and Validation of MELD

MELD was initially created to predict survival following elective placement of TIPS.[1] The model was subsequently validated as a predictor of survival in several cohorts of patients with varying levels of liver disease severity (e.g., hospitalized and ambulatory patients), as well as patients of geographically and temporally diverse origin.[2] The survival model was initially termed the "Mayo End-Stage Liver Disease" or "MELD" model to acknowledge the affiliation of the investigators who created the model. During discussions leading to the establishment of MELD as the basis for prioritization of organs for liver transplantation,[3,4] we changed the name to "Model for End-Stage Liver Disease" which maintained the acronym "MELD", but removed the association with a particular institution, a process that was thought would lead to wider acceptance of the model.

MELD incorporates 3 widely available laboratory variables including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The original mathematical formula for MELD is: $\text{MELD} = 9.57 \times \log_e(\text{creatinine}) + 3.78 \times \text{Log}_e(\text{total bilirubin}) + 11.2 \times \text{Log}_e(\text{INR}) + 6.43$.

The score can be calculated on handheld computing devices, and is available at *www.mayoclinic.org/gi-rst/mayomodel5.html*. When the model was initially created the etiology of cirrhosis was also included. In the TIPS

Abbreviations: ASA, American Society of Anesthesiologists; CTP, hild-Turcotte-Pugh; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis; SOFA, Sequential Organ Failure; TIPS, transjugular intrahepatic portosystemic shunts; UNOS, United Network of Organ Sharing.

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population, the etiology of liver disease was important in that patients with alcoholic liver disease and cholestatic liver disease undergoing TIPS procedures had a better survival than those patients with viral hepatitis-related or other causes of cirrhosis.

In subsequent studies, we confirmed that the etiology of cirrhosis was a less important variable in determining survival in other patient cohorts with end-stage liver disease. Therefore, etiology of liver disease was removed as a variable from the model while still preserving its accuracy.[5] The advantage of dropping etiology of cirrhosis as a variable was that the subjective element in determining etiology was removed, and the model could be based purely on objective laboratory variables.

MELD has been validated as a predictor of survival in independent groups of patients with a wide variety of liver diseases.[5,6] In these studies, the accuracy of MELD was evaluated by its ability to rank patients according to risk for mortality determined by the "concordance statistic" or the "c" statistic. For example, a c-statistic of 0.7 indicates that patients with a higher MELD score will die earlier than patients with a lower MELD score 7 of 10 times. A c-statistic of 0.7 is thought to have reasonable clinical utility, while a c-statistic of $\geq$0.8 in a prediction model lends strong support to its accuracy. Most studies that evaluated MELD to rank patients according to their risk of mortality have yielded "c"-statistics upwards of 0.8, and usually superior to the Child-Turcotte-Pugh (CTP) class. Addition of complications such as ascites, encephalopathy, variceal bleed, and SPB do not improve MELD significantly; quantitative tests of liver function are also not superior to MELD in predicting survival.[7]

Application of MELD

MELD in Liver Transplantation

Prior to February 27, 2002, patients were prioritized for receiving organs for liver transplantation based on their United Network of Organ Sharing (UNOS) status, a reflection of their CTP score. Given that the waiting list for liver transplantation approached 20,000 patients, and there were only 3 categories on the waiting list for patients with cirrhosis, namely Status 2A, Status 2B, and Status 3, time spent on the waiting list became the major determinant of who would receive a liver transplant. Therefore, this policy placed at a disadvantage patients who were at a high risk for mortality but who were listed late in their disease course and had not accrued enough waiting time.

In 1998, the Institute of Medicine decreed that a new allocation policy be put in place based on objective variables and which de-emphasized waiting time, that is, the "sickest first" policy. This led to MELD which is based on objective variables and could accurately rank patients with cirrhosis according to risk of mortality, replacing the then current CTP-based organ allocation system.[3,4,8] In applying MELD to organ allocation, UNOS made several changes to how the MELD score was to be calculated. The lower limit for serum creatinine, serum bilirubin, and INR was fixed at 1 so that there would be no negative scores; the upper limit of serum creatinine was capped at 4 mg/dl.

Implementation of MELD led to an immediate reduction in liver transplant waiting list registrations for the first time in history of liver transplantation (12% decrease in 2002)[4] because accrual of waiting time was no longer necessary. Accurate prediction of short-term mortality in the vast majority (83%-87%) of wait-listed candidates[9] led to a reduction of almost 15% in the mortality on the waiting list.[10] The number of deaths of patients on the wait list increased up to 2001 (Fig. 1); since implementation of MELD in 2002, the number of deaths showed a substantial decrease from 2046 in 2001 to 1364 in 2005. Although this reduction in mortality is in part attributable to a modest increase in available organs (4,671 in 2001 versus 5,160 in 2005), there is a wide consensus that MELD has made a significant contribution to reducing the mortality on the waiting list.[11] A recent analysis showed that the reduction in mortality occurred only among patients with chronic liver disease (in whom MELD is used to allocate organs), but not among patients with fulminant liver disease in status 1 (in whom MELD is not used), suggesting that at least part of the decrease in waitlist mortality may be attributed to MELD-based organ allocation.[12] Moreover, the median waiting time to liver transplantation decreased from 656 days to 416 days in the MELD era.[13] Several countries have replaced the CTP score with MELD to rank patients according to

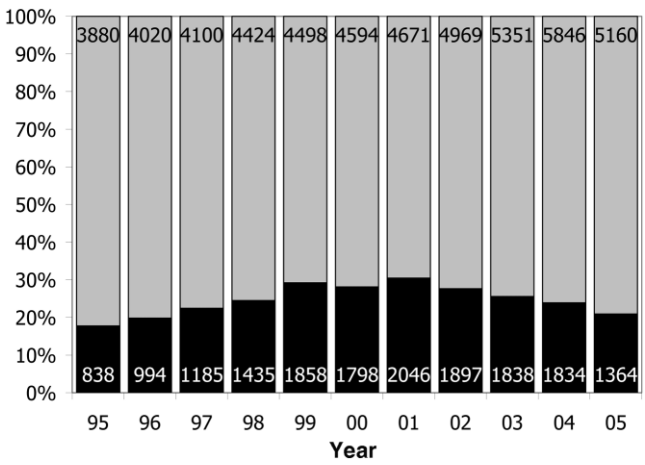

Fig. 1. The number and ratio of LTx (liver transplant) candidates removed from the waiting list due to transplantation (gray) and death (black) in the United States.

mortality risk.[14] In a study from Australia, clinical judgment, which is often used in centers to determine which patient should rank higher on a waiting list for mortality, has been proven to be inferior to the MELD score in determining survival.[15]

In contrast to the clear benefit of accurately estimating mortality on the waiting list, MELD has not been found to be as useful in predicting mortality following liver transplantation.[16-19] Mortality in the post transplantation period is related not only to the degree of liver dysfunction prior to transplantation, but to other factors, such as donor characteristics, experience of the transplantation team, and random postoperative complications which cannot be predicted. Moreover, patient selection by physicians will tend to negate the effect of pre-transplant MELD on post transplant survival. Consequently, almost all models which attempt to determine post transplant survival are not clinically useful. Thus, MELD score before liver transplant is not predictive of post liver transplant outcome because of relatively poor correlation between pre-transplant disease severity and post transplant outcome.

Likewise, in small studies on living donor liver transplantation, pre-transplant MELD scores had little impact on post transplant survival.[20] There have been proposals that organ allocation take into account donor and recipient factors simultaneously such that marginal grafts not be used for patients with high MELD scores in the hopes to improve post liver transplantation outcome.[21,22] Similarly, in patients with MELD scores $\leq$14, mortality with transplantation was found to be higher than that of patients with the same MELD score not transplanted.[23] One must exercise caution, however, in interpreting these results, because they are simply observational (as opposed to randomized) data.

To the degree that disease severity before liver transplantation affects post transplantation morbidity and complications, healthcare resources used correlate with pre-transplantation MELD score. At the level of individual patient, resource utilization, as judged by days in intensive care, red cell transfusions, and duration of hospitalization was higher with higher pre-transplant MELD scores.[24,25] On the other hand, on an aggregate level, MELD-based organ allocation has not increased healthcare resource utilization. Based on a nationally representative hospital utilization database, we have shown that resources used did not increase since MELD was implemented.[26] Thus, MELD-based allocation consistently directs organs to the sickest patients so that those patients in the previous era who had high MELD but insufficient waiting time are undergoing transplantation earlier, reducing the number of "outliers" that incurred astronomical costs to the health care system.

Patients undergoing retransplantation are at a higher risk of mortality after transplantation than those undergoing primary liver transplantation. The 2-year survival after retransplantation is lower than that after primary liver transplantation, with the difference in survival being greatest in patients with MELD $>$25. Moreover, retransplantation more than 2 years after the primary transplantation is associated with poor survival independent of the MELD score.[27] These data notwithstanding, the most immediate question about MELD in allocation for retransplantation is whether the risk of death on waiting list is different between primary and repeated liver transplant candidates. Retransplantation candidates are registered on the waiting list with significantly higher MELD than primary liver transplant candidates (22 versus 14) and thus retransplantation candidates as a whole experienced higher mortality rate on the waiting list.

It is important to note that although the modifications created by UNOS in calculating the MELD score have some rationale, the modifications have been empirical rather than based on validated studies. For instance, the upper value of serum creatinine has been capped at as high as 4 mg/dl, allowing inclusion of patients with intrinsic renal disease. Thus, there has been a higher rate of combined kidney and liver transplants than previously, but without significant change in survival.[28] The need for renal replacement therapy is higher if MELD scores are greater than 24,[29] even though there is a suggestion that the prevalence of chronic renal disease up to 2 years after transplantation has not increased.[30]

Another area which requires more validation is the assignment of MELD scores to patients with hepatocellular carcinoma. The initial recommendation for allocation of 24 MELD points for patients with Stage 2 HCC was found to be too high, and this was later reduced to 22.[31] It remains to be seen whether this reduction in score is more accurately reflective of the patients with hepatocellular carcinoma removed from the waiting list because they exceeded the Milan criteria.

Prediction of Long-term Survival in Patients with Cirrhosis

In a recent systematic review of 118 studies outlining the natural history and prognostic indicators of survival in cirrhosis,[32] MELD and CTP score were recognized as predictors of long-term survival in patients with decompensated cirrhosis. Recently, both MELD and HVPG were shown to be independent predictors of survival. The "c" statistic for predicting survival was 0.71 for the MELD score, and the addition of HVPG and age in-

creased the predictive mortality to 0.76, which was not statistically significant. MELD is an accurate predictor of long-term mortality, even in patients with chronic hepatitis B, with or without cirrhosis.[33] Whereas patients with NASH-related cirrhosis had a lower risk of mortality than patients with HCV-related cirrhosis, even when "decompensated"; MELD was an accurate predictor of survival in both groups of patients.[34]

Application of MELD Beyond ESLD

Variceal Bleeding. Retrospective studies have shown that both MELD and CTP are accurate predictors of survival in patients with variceal bleeding.[35] MELD and hepatocellular carcinoma were better predictors of survival than CTP score in a study of 172 patients with cirrhosis and first variceal bleed, with MELD score discriminating between patients at high risk ($\geq$15) and low risk ($<$15) for mortality.[36] Our own unpublished data confirms the superiority of MELD over the CTP score in determining mortality following a variceal bleed.

Infections in Patients with Cirrhosis. Both studies addressing the predictability of MELD in determining mortality in patients with infections leading to renal failure have demonstrated that the only predictors of survival in these patients were the MELD score, and the type of hepatorenal syndrome; CTP score was not independently predictive of mortality.[37,38] These data would suggest that patients with a high MELD score are either more likely to get infected, or that patients with a high MELD score are more likely to die as a result of spontaneous bacterial peritonitis (SBP) because outpatients with SBP typically have lower MELD scores than inpatients with SBP, and better survival.[39]

Fulminant Hepatic Failure. Among 312 patients with non-acetaminophen-induced FHF in the UNOS database, MELD was a highly significant predictor of 30 day mortality ($P < 0.0001$).[40] Of note, patients with primary graft nonfunction and patients with hepatic artery thrombosis had a lower risk of 30-day mortality than patients with FHF and did not show a significant association between transplantation and survival. On the other hand, patients with FHF experienced the greater benefit with liver transplantation, survival improving from 58% at 30 days without transplantation to 91% with liver transplantation ($P < 0.0001$). This raises the question as to whether MELD should also be used to prioritize candidates with FHF, that is, UNOS Status 1, for liver transplantation.

In a large prospective study from Denmark, the utility of MELD in determining the onset of FHF in patients with acetaminophen-induced liver failure was demonstrated ("c" statistic: 0.92). However, once patients developed FHF, MELD was less accurate in predicting mortality.[41] In a U.S. multicenter study in patients with FHF secondary to hepatitis A, MELD had a "c" statistic of only 0.7 in ranking patients according to mortality risk.[42] These studies would suggest that, in patients with FHF in addition to the MELD score, there are other variables such as the degree of intracranial pressure important in predicting mortality. The U.S. study demonstrated that a model using serum creatinine, serum bilirubin, need for endotracheal intubation, and vasopressor support had a "c" statistic of 0.89. However, there were only 4 deaths, and only 9 of the 29 patients underwent liver transplantation. Therefore, the limited number of endpoints for a 4 variable model (typically, 40 events would be necessary for internal validation of a 4 variable model) is likely to be associated with "model over-fitting", and needs validation in an independent data set before being widely used.

Alcoholic Hepatitis. In all 3 studies that compared the MELD score to the Maddrey score,[43] MELD was a more accurate predictor of mortality.[44-46] This is not surprising because the MELD score has both the variables included in the Maddrey score, namely the prothrombin time and bilirubin but, in addition, has an index of renal dysfunction which is the serum creatinine. The cut-off of the MELD score for determining severe alcoholic hepatitis is $>$21 which is associated with 3-month mortality of 20%, whereas patients with MELD score $\leq$11 have excellent survival.[45]

Other Chronic Liver Diseases. MELD has been shown to be a useful predictor even in patients n whom cirrhosis was not clearly documented. In patients with chronic hepatitis B, MELD and antiviral treatments (lamivudine) were independent predictors of survival.[33] In patients admitted to the Intensive Care Unit, the "Royal Free Model" had similar discrimination ability as the MELD and Sequential Organ Failure (SOFA) score[47] in predicting mortality. All three scores were superior to APACHE II or CTP scores.[48] It must be pointed out that both the Royal Free Model and the SOFA score include variables reflecting multiple system organ failure, and are more likely to "reflect" the dying process rather than being predictors of mortality. Similarly, in patients with acute on chronic liver failure, MELD and hepatic encephalopathy predicted survival,[49] especially when MELD was $\geq$30.[17]

MELD in the Management of Patients with ESLD

Transjugular Intrahepatic Portosystemic Shunts. MELD was originally developed in patients undergoing TIPS and may be used most appropriately to predict probability of survival after the procedure. The indication for TIPS, whether refractory ascites or variceal bleeding, is

not an independent variable determining survival. Emergency TIPS, that is TIPS carried out in a patient actively bleeding in spite of 2 sessions of endoscopic therapy carried out within 24 hours, is a predictor of mortality, but these patients also usually have a higher MELD score.[1] It is not clear whether TIPS adds additional mortality to that predicted by the MELD score in patients with complications of portal hypertension. That is, it is not clear, for example, whether a patient with a MELD score of 24 undergoing TIPS has a higher mortality than a patient with similar complications and a MELD score of 24 not undergoing TIPS. Nonetheless, TIPS is associated with a higher risk of mortality than seen in patients on the waiting list for liver transplantation with identical MELD scores, at least a small additional risk of procedure-related mortality,[50] and a risk of morbidity as well as additional expense.

The importance of MELD as an independent predictor of death in patients undergoing TIPS has been confirmed by other studies.[38,51] The MELD score within the UNOS region at which patients are likely to receive a transplant may also be used in determining whether a TIPS should be carried out before liver transplantation. For instance, if a patient with a MELD score of 28 and refractory ascites is in a UNOS region where organs are available to patients whose MELD score is 28-30, continued conservative measures rather than TIPS might be recommended. In general, a MELD score of >24 is associated with an increased risk of 3-month post TIPS mortality,[52,53] and consequently, TIPS should be avoided in such patients unless they are candidates for liver transplantation.

The MELD score has been compared to both the Emory score,[35] as well as the CTP score for prediction of long-term survival in patients undergoing TIPS. The "c" statistic for the MELD score was superior to the Emory score but only slightly superior to or no better than the CTP classification in predicting post procedure mortality.[38]

Hepatocellular Carcinoma. In our experience, hepatic resection for HCC can be carried out safely in patients with cirrhosis and MELD score ≤ 8. Neither minor hepatic resections (≤ 3 segment resection) nor major resection (≥ 4 segment) were associated with any mortality 30 days postoperatively if MELD score was ≤ 8. Moreover, patients with HCC smaller than 5 cm in diameter and MELD score ≤ 8, had a 5-year survival of 80%. In patients undergoing ablation therapies for unresectable HCC, patients with MELD score ≤ 10 and CLIP score ≤ 2 had the best outcome. In patients with MELD score ≥ 10 and CLIP ≥ 2 the outcome was poor; therefore, local therapies for HCC should probably be considered only in patients with MELD score ≤ 10 and CLIP score ≤ 2.[54]

Selection of Patients for Surgery Other Than Liver Transplantation. Traditionally, the CTP score has been used to determine risk of postoperative mortality. Additional risk factors for mortality have included serum creatinine concentration, the American Society of Anesthesiologists (ASA) physical status class, and cardiopulmonary comorbidity.[55] However, these variables have not been put together to create a model to quantitate the risk of postoperative mortality.

We have demonstrated that patients with cirrhosis are at low risk of mortality after hepatic resection for hepatocellular carcinoma (HCC) if their MELD score is 8 or less.[56] This MELD cutoff of 8 for carrying out hepatic resection for HCC has been confirmed by a study from Italy.[57] The utility of MELD in determining postoperative mortality has also been confirmed in patients undergoing cardiac surgery,[58] as well as in abdominal operations including cholecystectomy,[59-61] However, MELD was an inaccurate predictor of mortality in patients without cirrhosis undergoing liver resection.[62] In our experience, MELD, the ASA physical status, and age can be used to determine mortality following surgery independent of the procedure performed. We have demonstrated a close relationship between MELD score and mortality, with the relationship persisting both short-term and long-term following surgery, irrespective of the type of surgery being performed. Emergency surgery too was not an independent predictor of mortality independent of the MELD score.[63] The MELD score, ASA physical status, and age may be used in determining whether elective surgical procedures should be carried out before or following liver transplantation.

Strengths and Limitations of MELD

In many ways, MELD is an ideal survival model in comparison to either models/scores used in patients with liver disease (Table 1). Its strengths derive from the robust statistical foundation in its development and the large number and variety of samples in which it was validated. The model is based on only objective variables that are readily obtained. Inclusion of creatinine incorporates a measure of renal function, a well-recognized predictor of survival in patients with liver disease.[64-66] Whereas the usefulness of CTP has been appreciated by clinicians for many decades, it did not have much statistical basis in its development, nor did it undergo as rigorous validation as MELD. It also includes subjective variables such as ascites and encephalopathy. In our initial validation study, the c-statistic associated with the CTP score in the prediction of 3-month survival was 0.84 (95% CI 0.78-0.90), in

Table 1. Liver Disease: Features of Current Definitions/Scores

Condition	Objective Parameters	Subjective Parameters	Parameters Readily Available	Prospectively Designed	Validated	
					Internal	*External*
An Ideal Model	✓	–	✓	✓	✓	✓
FHF	✓	✓	✓	–	–	–
SBP	✓	–	✓	–	–	–
HRS	✓	–	✓	–	–	–
Child-Pugh ("Decompensated Liver Disease")	✓	✓	✓	–	–	✓
MELD	✓	–	✓	(?)✓	✓	✓

comparison to 0.87 for MELD. Thus, the MELD scale is thought to be at least as good as the CTP score in predicting short-term mortality, while it may overcome many limitations of the CTP score, at least for the purpose of prioritization in donor organ allocation.

Several authors pointed out that MELD has not been proven to be superior to the CTP score in patients listed for liver transplantation or in a wider population of patients with cirrhosis.[48,67] When the score designation with regard to ascites and encephalopathy is done consistently from one patient to the next by an experienced observer, the CTP score is probably as accurate and reproducible as MELD.[2] However, one of the drawbacks of the CTP system is that it is much more subject to variability and interpretation than MELD. This was one of the factors that made MELD more attractive as a standard for organ allocation in that it minimizes the possibility of "gaming" the system. Another advantage of MELD over the CTP score is that it has a much wider range of possible scores and has a better precision with which to distinguish patients according to their mortality risk. Finally, even the most vocal skeptics of MELD agree that the serum creatinine is an important contribution of MELD in highlighting the importance of renal function in the assessment of mortality risk in patients with ESLD. A model developed by adding serum creatinine to the CTP score has not been proven to be more accurate than the MELD score.[68]

There are some cautions to be exercised in applying MELD in individual patients. First, one must remember that MELD was created and validated in a cohort of patients who were screened carefully with certain criteria, which included absence of acute, reversible complications, such as bacterial infection or azotemia associated with dehydration. In deriving the TIPS model, we used the prothrombin time and serum creatinine and bilirubin data recorded at the time when reversible factors had been excluded. This approach was taken because we were primarily interested in a measure most accurately reflective of the underlying liver function. Therefore, in patients on the waiting list for liver transplantation, the MELD score should, in principle, be calculated only after acute reversible processes are adequately treated.

Second, the primary role that was asked of MELD was to rank patients according to mortality risk in a relatively homogenous population of registrants on the liver transplant waiting list. Thus, depending on the population to which it is applied, mortality seen in patients with a given MELD score may not necessarily be the same. Similarly, hospitalized patients with cirrhosis who were not candidates for liver transplantation may have a higher mortality than candidates for liver transplantation who are younger and devoid of comorbidity. Thus, it is not possible to provide a universally applicable survival prediction by MELD.

Third, although the objectivity of the variables included in MELD is far superior to previous models, the variables used in the MELD score may be subject to some variability depending on how they are measured. The serum creatinine typically measured by a colorimetric alkaline picric Jaffe method may be less accurate than when the enzymatic method for measuring serum creatinine is used. When the serum bilirubin is above 25 mg/dl, the colorimetric method overestimates the serum creatinine. Accordingly, in patients with serum bilirubin >25 mg/dl the enzymatic method for measuring serum creatinine is recommended. A somewhat related question regarding bilirubin is whether the direct fraction of the serum bilirubin is a more accurate predictor of survival than the total serum bilirubin. In the absence of studies clarifying this issue, the total serum bilirubin remains the preferred index for expressing overall liver function.

The prothrombin time is also subject to variability. The thromboplastins available worldwide have an International Sensitivity Index range from 1-3, the lower numbers indicating a more sensitive thromboplastin. The prothrombin time is more prolonged if a sensitive thromboplastin is used as compared with a less sensitive thromboplastin. The INR for prothrombin time was introduced as a means of decreasing this variability when measuring prothrombin times in patients on warfarin anticoagulation. The accuracy of INR may be decreased as a measure of the coagulation status in patients with liver disease, since there are other abnormalities in the coagulation pathway in those patients. However, its role in predicting

survival in patients with liver disease has been demonstrated repeatedly, especially when used to calculate the MELD score. It is possible that other methods of expressing prothrombin time such as the prothrombin index are more accurate reflectors of liver function, but these methods have yet to be validated as being more accurate than the INR, both as indices of liver function and of coagulation status. In our opinion, of measures of the prothrombin time, the INR is superior to others because of it wide availability as well as the track record as a survival indicator in patients with ESLD.

Finally, some debate continues with regard to patients with intractable complications of portal hypertension such as ascites and hepatic encephalopathy. In our initial evaluation of these complications in conjunction with MELD, it was clear that when the c-statistic was used as the criterion to determine the degree of improvement in the model associated with the addition of these complications, they had only minimal benefit to MELD. However, as shown in the case with hyponatremia (see next section), if these complications occur in a small proportion of patients, addition of them would not increase the model c-statistic materially, because it changes the ranking of only a few patients, even when they may have substantial impact in those few patients. To date, however, we are not aware of data to clearly demonstrate that such is the case, except in the case of hyponatremia. If data strongly supportive of these and other complications add to the prognostic evaluation in patients with ESLD, the transplant community may be faced with a difficult decision whether to re-incorporate these potentially subjective elements back to the organ allocation policy.

Further Refinement and Improvement of MELD

Patients with an increasing MELD score have been thought to have an increased risk of mortality, whereas those with a decreasing MELD score have a lower risk of mortality, even if their MELD scores are identical.[69] Thus, it has been proposed that the change in MELD score, that is ΔMELD, may add prognostic information to the MELD score.[69] Intuitively, a patient whose MELD is increasing rapidly is more likely to have a worse outcome than those with stable MELD. We conducted a study using the time-dependent analysis of the effect of the current MELD score and ΔMELD (defined as the difference between current MELD and the lowest MELD score measured within 30 days prior to current MELD). Although all of these variables were significant in the univariate phase, ΔMELD was no longer significant in the multivariable analysis, especially when acute increases in MELD in the last few days of life were excluded. This analysis highlighted that the current MELD is the most important predictor of survival, regardless how that MELD was reached.[12]

MELD could potentially be improved with more accurate indices of liver function and perhaps better ways of assessing renal function. Recently, several studies have shown that the addition of serum sodium can improve the predictive accuracy of the MELD score.[70-73] Our study, which is based on a multicenter database, shows that there is a linear relationship between serum sodium and mortality after adjusting for MELD. In addition, serum sodium may be particularly relevant in patients with a low MELD score, e.g., MELD < 20.[74] As was alluded to earlier, because of the small proportion affected by hyponatremia, the c-statistics of the model did not change substantially. However, with severe hyponatremia, the risk in mortality increased as much as what would be equivalent to an increase of more than 20 points in MELD. Whereas the impact of serum sodium is quite large, it remains uncertain whether the addition of serum sodium to the MELD score can be used to determine allocation of organs for liver transplantation, especially because of the possible poor post liver transplantation outcome of patients with low serum sodium.[75]

In conclusion, based on its ability to rank patients with cirrhosis according to their short term mortality, MELD has been recognized as a major contribution to the daily practice of hepatology. Successful implementation of MELD-based liver allocation in the United States has been followed by widespread adoption of the system globally, attesting to its validity. In addition to organ allocation, emerging data support MELD as a useful clinical tool in a wide spectrum of disease severity and variety. These achievements notwithstanding, MELD is by no means a perfect system. Users of MELD must be aware of several features and limitations in its application. In the meantime, efforts for further refinement and validation must continue.

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