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Organ allocation for chronic liver disease: model for end-stage liver disease and beyond

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Abstract

Purpose of review—Implementation of the model for end-stage liver disease (MELD) score has led to a reduction in waiting list registration and waitlist mortality. Prognostic models have been proposed to either refine or improve the current MELD-based liver allocation.

Recent findings—The model for end-stage liver disease – sodium (MELDNa) incorporates serum sodium and has been shown to improve the predictive accuracy of the MELD score. However, laboratory variation and manipulation of serum sodium is a concern. Organ allocation in the United Kingdom is now based on a model that includes serum sodium. An updated MELD score is associated with a lower relative weight for serum creatinine coefficient and a higher relative weight for bilirubin coefficient, although the contribution of reweighting coefficients as compared with addition of variables is unclear. The D-MELD, the arithmetic product of donor age and preoperative MELD, proposes donor–recipient matching; however, inappropriate transplantation of high-risk donors is a concern. Finally, the net benefit model ranks patients according to the net survival benefit that they would derive from the transplant. However, complex statistical models are required and unmeasured characteristics may unduly affect the model.

Summary—Despite their limitations, efforts to improve the current MELD-based organ allocation are encouraging.

Keywords

model for end-stage liver disease – sodium; organ allocation; product of donor age and model for end-stage liver disease; serum sodium; transplant benefit

Introduction

Mathematical models in medicine have been used to help clinicians make diagnoses, determine prognosis, and select the most effective therapy. Somewhat uniquely, the liver transplantation (LTx) community has embraced prognostic models as a tool to allocate donated organs to recipients in the most equitable and efficient fashion. Current criteria for selection of chronic liver disease patients for transplantation are based on the model for end-stage liver disease (MELD) score. Recently, alternate mathematical models have been put forth to either modify the MELD score (by adding variables or updating coefficients) or replace the MELD score with a net benefit model of organ allocation (Table 1). In the

following sections, we summarize the advantages and limitations of select proposals that deal with management of liver transplant candidates and organ allocation.

Model for end-stage liver disease

MELD was originally developed to predict survival in 285 patients undergoing elective placement of transjugular intrahepatic portosystemic shunts [1]. The model was subsequently validated as a predictor of survival in several cohorts of patients with varying levels of severity of hepatic dysfunction as well as patients of geographically and temporally diverse origins [2]. The score incorporates three widely available laboratory data including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The score can be calculated on handheld computing devices and is available at various Web sites, including our own – www.mayoclinic.org/MELD.

The implementation of MELD in 2002 led to an immediate reduction in LTx waiting list registrations for the first time in history of LTx (12% decrease in 2002) [3] as well as reduction in mortality on the waiting list [4]. For example, the number of deaths on the waiting list decreased from 2046 in 2001 to 1364 in 2005 and the death rate decreased from 910 per 1000 patient-years to 743 per 1000 patient-years. Although this reduction in mortality is in part attributable to a modest increase in available organs (4671 in 2001 vs. 5160 in 2005), there is a general consensus that MELD has made a significant contribution to reducing the LTx waitlist mortality [5]. Following the successful implementation of the MELD-based allocation policy in the United States, transplant authorities in other parts of the world have adopted the MELD score in its original form or in some variation for organ allocation.

In addition to being used as a standard for organ allocation, MELD has been used as a practical patient management tool. Such application includes patient selection for the transjugular intrahepatic portosystemic shunt procedure, short-term survival prediction for complications of liver disease [6-9], and risk stratification for nontransplant surgery [10,11]. Although MELD was initially validated for prediction of short-term (e.g., 3 months) survival, it has been shown to be also useful for long-term prediction of survival in patients with cirrhosis [12,13] and those with hepatocellular carcinoma [14]. Finally, MELD has been shown to be helpful in managing patients with conditions other than end-stage liver disease [12,15-19].

There are, however, limitations to utilizing the MELD score. For example, the current INR system has been optimized for patients who are on anticoagulation and the extent to which INR accurately represents coagulation status in patients with cirrhosis is unknown. Empirically, INR's role in predicting survival in patients with liver disease has been demonstrated repeatedly, especially when used to calculate the MELD score. Similarly, serum creatinine is typically measured by a colorimetric Jaffe method, which is less accurate than enzymatic methods. The former is affected by a high level of serum bilirubin (e.g., >25 mg/dl) because the yellow discoloration of the serum in severely icteric patients interferes with the spectrophotometric measurement. Another concern has been that the severity of liver disease in patients with relatively minimal biochemical perturbation but with intractable complications of portal hypertension such as ascites and hepatic encephalopathy may be underestimated by MELD. Our initial data indicated that these complications do not add substantially to the predictive accuracy of MELD. Subsequent data largely confirm the conclusion, although presence of moderate to severe encephalopathy may worsen the prognosis given the same MELD score. Others are concerned about patients with refractory ascites who are at risk of significant complications such as spontaneous bacterial peritonitis

and hepatorenal syndrome, yet may be assigned a low MELD score. In part addressing some of these concerns, alternate proposals have been put forth to modify the MELD score.

Model for end-stage liver disease – sodium

Hyponatremia is associated with neurologic dysfunction, refractory ascites, higher risk for development of the hepatorenal syndrome, and death from liver disease [20•,21•]. Given the important prognostic value of sodium, its role has been evaluated as an adjunct to the MELD score in organ allocation. Data from the Organ Procurement and Transplantation Network (OPTN) database was used to measure the effect of the MELD score, the serum sodium concentration, and the interaction between the two in predicting mortality among patients on a waiting list for liver transplantation [22••].

Serum sodium was associated with a higher risk of mortality independent of the MELD score in patients listed for orthotopic liver transplantation (1.05 per 1-unit decrease in the serum sodium concentration for values between 125 and 140 mmol/l; $P < 0.001$) [22••]. This effect was greater in patients with a lower MELD score. According to the analysis, there were 477 deaths within 3 months on the waiting list in 2006. For 110 patients (23%), the difference between the MELDNa and MELD scores was large enough to have affected allocation priority. About 7% of the deaths on the waiting list could have been prevented by using MELDNa rather than MELD.

There are, however, concerns with using a MELDNa-based allocation policy. Serum sodium like the other components of the MELD score may be subject to laboratory variation. Further, manipulation and amelioration of sodium by the use of vaptans (vasopressin receptor antagonists) or other conservative methods such as fluid restriction may potentially circumvent the objective nature of the scoring system [23]. Finally, whether transplanting patients with hyponatremia would simply shift the mortality from the waiting list to posttransplant is also a concern.

The latter concern was recently evaluated. In an analysis of two multicenter databases (2175 primary LTx between 1990 and 2000), serum sodium did not have a detrimental impact on survival 90 days after LTx (hazard ratio = 1.00; $P = 0.99$), suggesting that incorporating serum sodium in the organ allocation process may not adversely affect the overall outcome after LTx [24]. This finding needs to be confirmed using data submitted to the OPTN; however, reporting of sodium has only been recently available at a national level.

United Kingdom model for end-stage liver disease

The importance of serum sodium in estimating waitlist mortality has been also recognized in other countries. Since 1996, listing for transplantation in the United Kingdom was based on the following principles: selecting patients if the expected survival without transplantation was 1 year or less or liver disease that was associated with an unacceptable quality of life and expecting that patients would have an at least 50% survival at 5 years with acceptable quality of life [25•]. However, the subjective nature of determining long-term benefit and utilization of the Child–Pugh score, which is subject to manipulation, led to reconsideration of the policy [26]. In 2008, a new scoring system for selecting patients with chronic liver disease for listing for LTx was incorporated at the national level [25•]. The United Kingdom MELD (UKELD) score is derived from the patient's serum sodium, creatinine and bilirubin, and INR. It was developed by an analysis of 1103 patients and validated in an independent prospective cohort of 452 patients. Minimal listing criteria require that the patient should have a projected 1-year liver disease mortality without transplantation of more than 9%. This is predicted by a UKELD score of 49 or greater. A UKELD score of 60 is predictive of a 50% 1-year survival. Given this recent adoption, further independent validation and

refinement is anticipated. The ultimate goal in the United Kingdom is to develop an allocation model that takes into account the net benefit of transplant.

Reweighting of model for end-stage liver disease score components

Implementation of the MELD score has led to a higher proportion of patients with renal insufficiency undergoing LTx. Sharma *et al.* [27•] examined whether reweighting the components of the MELD score using a contemporary cohort of patients being evaluated for LTx would better predict waiting list mortality.

Waitlist data from the OPTN (38899 adults between 2001 and 2006) was utilized and the coefficients for the MELD components were re-estimated using a time-dependent Cox regression model. In contrast to the MELD, the reweighted MELD did not set upper and lower limit bounds on the coefficients of each of the components. Further, the log of 1+coefficient, rather than the coefficient, was created to keep the coefficients positive.

The updated MELD formula was associated with a lower relative weight for serum creatinine coefficient and a higher relative weight for bilirubin coefficient. According to the authors, this suggests that patients with impaired renal function but preserved liver function may have lower mortality than those with worse liver disease and relatively better renal function. The index of concordance (*c* statistic) for existing and reweighted MELD scores in predicting 90-day mortality was 0.75 and 0.77, respectively. The impact of using the reweighted MELD was greater in patients with a higher MELD score (≥ 20).

Whether addition of a variable, such as serum sodium, as compared with reweighting components of the MELD score better predicts waitlist mortality was recently evaluated [28]. Waitlist data from the OPTN (13 964 adults between 2005 and 2006) was used to evaluate the ability of MELD, reweighted MELD, and MELDNa to accurately predict waitlist mortality. Of all the models considered, MELDNa remained the strongest predictor of waitlist mortality (concordance 0.865) as compared with MELD (*c* = 0.848) and reweighted MELD (*c* = 0.84). Whether a combination of reweighting the MELD score elements and adding serum sodium performs better than current MELD-based organ allocation remains to be seen. Regardless, current progress in creating a more accurate model for identifying waiting list mortality is encouraging.

Donor-recipient matching: product of donor age and model for end-stage liver disease

In the face of increasing use of 'extended criteria' or high-risk donors, identifying the right set of donor and recipient matching characteristics that would portend a better outcome after LTx may be important. Donor and recipient matching occurs at the time of organ procurement and transplantation with a substantial degree of selection going into accepting an organ. This subjective decision is, however, hard to quantify. Given the importance of advanced donor age and graft quality, the arithmetic product of donor age and preoperative MELD (D-MELD) was recently evaluated as a predictive model [29•].

Data from the OPTN was used to derive (17 942 adults between 2003 and 2006) and subsequently validate (2007 data) D-MELD. The scores ranged from 40 to 3400 (median score = 704). A decline in survival was noted with increasing values of D-MELD. Graft survival at 1 year was 91.8% for scores less than 400 but 73.4% for scores greater than 2000. A score of 1600 or higher was associated with a higher 4-year mortality for subgroups of patients with MELD 30 or more (63.8 vs. 71.3%), donor age 60 or older (56.7 vs. 68.3%), and transplantation for hepatitis C (54.4 vs. 72.9%).

Although using a D-MELD cap of 1600 would be attractive to limit high-risk donor–recipient matches, potential limitations, as the authors themselves point out, must be kept in mind. First, the group most likely to benefit would be waitlisted patients with a moderate MELD score. Misuse of a D-MELD-based policy could lead to transplantation of donors at high risk, that is, advanced donor age, into recipients with lower MELD scores as long as the composite score is below 1600. As shown previously, transplanting high-risk donor organs into patients with low MELD scores (≤ 20) is associated with poor posttransplant survival (hazard ratio 1.02 per year; $P < 0.005$) [30••]. Second, finding suitable donors for patients with high MELD scores may be difficult and potentially lead to higher waitlist mortality in this susceptible group.

Net benefit model

An organ allocation process based on survival benefit has been advocated by the Scientific Registry of Transplant Recipients [31••]. Mechanistically, a survival benefit represents the balance between 5-year waiting list mortality and post-LTx mortality. Separate models are created to predict waitlist and posttransplant survival. With these models, the difference between survival predicted with and without LTx can be calculated as the predicted benefit of transplantation. For example, a patient with a survival net benefit of 2 years (area between a posttransplant survival curve and a waitlist survival curve) would be expected to live an extra 2 years with a transplant as compared with not receiving a transplant. Hence, patients are ranked according to the net survival benefit that they would derive from the transplant.

All patients undergoing deceased donor LTx between September 2001 and December 2007 were followed from time of transplant to either death, loss to follow-up, or retransplant. A Cox proportional hazards regression analysis was utilized to derive a posttransplant survival model consisting of donor and recipient characteristics. The concordance statistic, a measure of how accurately the model would be able to predict who would die between two individuals, was 0.63. A waitlist survival model was created by considering 10 cross-sections of patients on the waiting list between 2002 and 2006. Cox regression analysis was utilized to create a wait list survival model ($c = 0.74$) utilizing recipient characteristics as well as adjusting for time spent on waiting list. After generating the separate survival curves, the net transplant benefit was derived. Using a liver simulated allocation model, utilization of the benefits model would result in 2223 life years saved, 80 fewer transplants, and 102 fewer deaths.

There are a few concerns of implementing the benefit model in its current form. First, there is an exponential increase in waiting list mortality with increasing MELD scores. In contrast, pre-LTx MELD score has much smaller influence on mortality after LTx. For example, as compared with mortality risk with a MELD of 6–11, the mortality risk at a MELD of 40 is 300-fold higher on the waiting list and 1.5-fold higher after transplantation [32]. Thus, allocating organs to the patient with the highest MELD score would reduce the waitlist mortality while affecting the transplant outcome modestly at best. Out of the 102 deaths saved, 83 of those deaths would be avoided on the waiting list. How this compares to the reduction in waitlist mortality offered by a MELDNa proposed system remains to be seen. Next, to implement such a system, complex statistical modeling is required, based on numerous donor and recipient characteristics; despite the inclusion of these factors, the concordance is between 0.63 and 0.74. Further, unmeasured characteristics such as center of transplantation or socioeconomic and insurance status of the recipient may have effects on the benefit that are not easily quantified by statistical modeling [33]. Finally, not all patients with a diagnosis would have equal priority for a given MELD score. Lucey *et al.* [34] recently showed that the survival benefit of transplantation was significantly decreased

among HCV-positive compared with HCV-negative recipients at intermediate ranges of MELD (9–29) as compared with higher ranges of MELD.

Conclusion

Implementation of the MELD score has led to a reduction in waiting list registration and waitlist mortality. Further, the score is useful in patient management, as it is an accurate gauge of severity of liver disease. Despite its limitations, its application is accepted and easily comprehended by the transplant community and the patients that it serves. Whether a future beyond MELD lies in updating the coefficients, adding terms that are better determinants of liver and renal function, focusing on better donor–recipient matching, or replacing the current equity-based system with a utility-based system remains to be seen.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 289–290).

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Table 1

Current and proposed mathematical models for organ allocation

Model	Equation	Notes
MELD	$9.57 \times \log_e(\text{creatinine, mg/dl}) + 3.78 \times \log_e(\text{total bilirubin, mg/dl}) + 11.2 \times \log_e(\text{INR}) + 6.43$	Lower limits of the individual components are bound by 1 and creatinine is capped at 4 mg/dl
MELDNa	$\text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$	Serum sodium concentration is bound between 125 and 140 mmol/l
UKELD	$5 \times [1.5 \times \log_e(\text{INR}) + 0.3 \times \log_e(\text{creatinine, } \mu\text{mol/l}) + 0.6 \times \log_e(\text{bilirubin, } \mu\text{mol/l}) - 13 \times \log_e(\text{serum sodium, mmol/l}) + 70]$	Minimal listing criteria: projected 1 year liver disease mortality without transplantation of >9% (UKELD ≥ 49)
Re-weighted MELD	$1.266 \log_e(1 + \text{creatinine, mg/dl}) + 0.939 \log_e(1 + \text{bilirubin, mg/dl}) + 1.658 \log_e(1 + \text{INR})$	No set upper and lower limit bounds on the coefficients of each of the components
D-MELD	The arithmetic product of donor age and preoperative MELD	The scores range from 40 to 3400
Net Benefit Model	Separate models are created to predict waitlist and posttransplant survival [31••]. Difference between survival predicted with and without LTx can be calculated as the predicted benefit of transplantation	Patients are ranked according to the net survival benefit that they would derive from the transplant

INR, international normalized ratio; LTx, liver transplantation; MELD, model for end-stage liver disease; Na, serum sodium; UKELD, United Kingdom MELD.