
When Is a Patient Too Well and When Is a Patient Too Sick For a Liver Transplant?

Robert M. Merion

Key Points

1. Liver transplantation is currently offered as a therapeutic option for patients with a wide range of end-stage liver diseases.
2. Conventional wisdom suggests that patients who receive a liver transplant have a greater expected lifetime when compared to comparable candidates on the waiting list.
3. The model for end-stage liver disease (MELD) scoring system is an excellent predictor of mortality on the waiting list and also predicts mortality after liver transplantation.
4. The combination of waiting list mortality risk and posttransplant mortality risk assessed by MELD and other factors can be used to estimate whether candidates are likely to derive a survival benefit from a liver transplant. (*Liver Transpl* 2004;10:S69–S73.)

In an ideal world, every patient with liver disease whose predicted lifetime with a transplant is longer than his or her lifetime without a transplant would be able to receive an organ transplant at an optimal and timely point in the course of their disease and no waiting list deaths would occur. Transplants would not be performed in circumstances in which the nontransplant option was associated with a longer lifetime, and this statement would hold true for patients throughout the disease severity spectrum.

Of course, we are unlikely to inhabit such a world anytime soon. Donor organs are available in small numbers relative to the pool of candidates and our ability to predict the future lifetimes of individual patients is limited. Liver transplantation is currently offered as a therapeutic option for patients with a wide range of end-stage liver diseases whose outcome is predicted to be fatal, usually at a point when the candidate is still expected to live long enough to survive the uncertain wait for a donor organ. Listing criteria for liver transplantation are currently very broad and delisting criteria have never been promulgated or placed into policy.

The model for end-stage liver disease (MELD) scoring system has emerged as an excellent predictor of mortality on the waiting list^{1,2} and also predicts mortality after liver transplantation.³ The combination of waiting list mortality risk and posttransplant mortality risk assessed by MELD and other factors can be used to estimate whether candidates are likely to derive a survival benefit from a liver transplant.^{4–6} In this essay, I discuss transplant decision-making approaches for liver

transplant candidates, focusing especially on patients at the ends of the risk spectrum.

Predictions of Waiting List Mortality

The development of MELD marked an important milestone in our ability to predict the prognosis of patients with chronic liver disease.^{7,8} Derived from a trio of simple, reproducible, and objective laboratory parameters (serum bilirubin, prothrombin time international normalized ratio, and serum creatinine), MELD provides robust estimates of mortality risk across a broad range of patients.⁸ The initial elaboration of the MELD score was based on a cohort of patients undergoing transjugular intrahepatic portosystemic shunt procedures for portal hypertension.⁷ Later reports showed that MELD was also predictive of liver patients generally, as well as those selected as potential liver transplant candidates.^{2,8} A modification of MELD was developed to account for the needs of pediatric liver transplant candidates (the pediatric end-stage liver disease scoring system), incorporating information on serum albumin and growth failure.^{8,9} In addition to the value of MELD *per se* as a predictor of mortality, the rate of change in MELD has also been shown to be independently associated with mortality risk in wait-listed candidates.¹⁰

Once a patient has been placed on the waiting list, it is of interest to know the likely direction and magnitude of subsequent changes in MELD score (and the associated risk). We studied 18,361 candidates waitlisted between April 1, 2002 and March 31, 2004, and analyzed 60,391 MELD scores while active on the waitlist

Abbreviations: MELD, model for end-stage liver disease.

From the Division of Transplantation, Department of Surgery, University of Michigan, Ann Arbor, MI.

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Address reprint requests to Robert M. Merion, MD, University of Michigan, Department of Surgery, Division of Transplantation, 2926 Taubman Center, Box 0331, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0331. Telephone: 734-936-7336; Fax: 734-998-6620; E-mail: merionb@umich.edu

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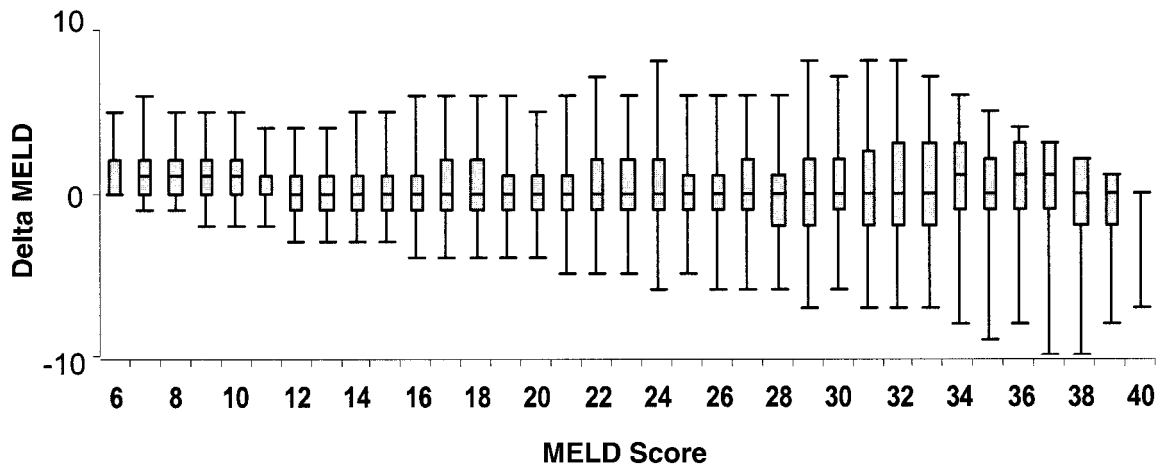


Figure 1. Box plots of change in MELD score compared to current MELD score, by MELD score.

through March 31, 2004. Change in the MELD score at time of next reported score (delta MELD) was calculated by category of MELD, and by the time between the 2 MELD scores. Figure 1 shows that for patients with low MELD scores, progression tends to be modestly upward, but not at a particularly rapid pace. In contrast, patients with high MELD scores tend, on average, to have declining scores.

The mortality risk on the waiting list while a patient has any given MELD score can be reliably estimated (Fig. 2). In addition to MELD, other parameters have been examined to determine whether they add measurably to the assessment of waiting list mortality risk. These factors include additional laboratory values such as serum albumin, as well as more subjective variables such as a history of variceal hemorrhage, ascites, or portosystemic encephalopathy. In an expanded mortality model, Dykstra et al.¹¹ found that while the listed covariates were significant independent predictors,

their contribution to the goodness-of-fit of the model was modest when compared to the original components of MELD. Ruf et al.¹² found that the goodness-of-fit of the mortality prediction using MELD was improved by the addition of serum sodium as an objective surrogate for ascites.

Predictions of Posttransplant Mortality

Some of the components of MELD were found to predict posttransplant mortality almost 20 years ago.^{13,14} In particular, pretransplant renal dysfunction has long been recognized as an important risk factor for posttransplant death.¹⁴ More recently, the other components of the MELD score have also been shown to be predictive of posttransplant mortality. While unadjusted waiting list mortality rates cover a 300-fold range from low to high MELD scores, the range of corresponding posttransplant mortality rates is about 2-fold

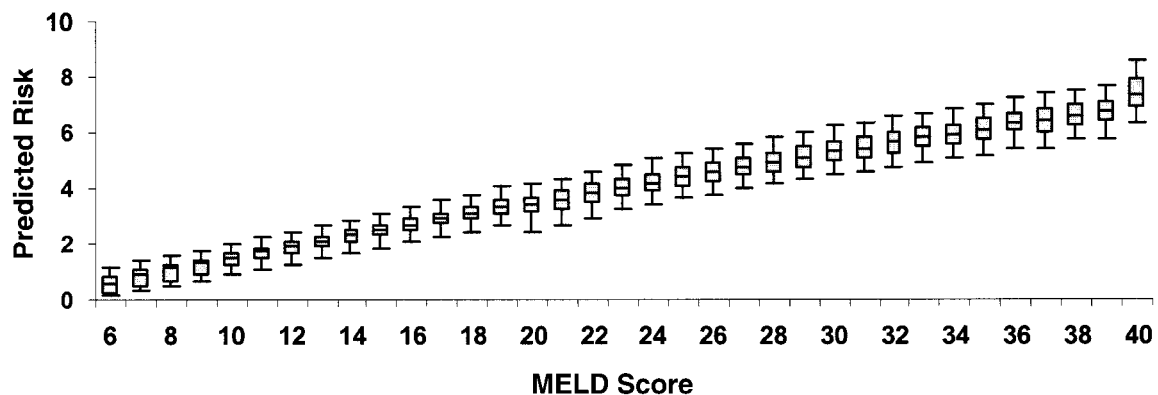


Figure 2. Box plots of mortality risk on the waiting list, by MELD score.

Table 1. Unadjusted Liver Waiting List and Transplant Recipient Mortality Rates by MELD Score Category

MELD	Waiting List Rate per 1,000 PY	Posttransplant Rate Per 1,000 PY
Overall	217.3	183.5
6–11	44.8	163.3
12–14	52.5	127.4
15–17	146.4	164.7
18–20	271.9	174.1
21–23	514.9	178.4
24–26	840.7	176.9
27–29	1,663.8	195.9
30–39	4,634.1	245.5
40+	13,152.7	264.6

(Table 1). More completely specified models of posttransplant mortality are being constructed using the values of variables known at the time of transplantation. Covariates that are significant predictors of posttransplant mortality include age, race, diagnosis, height, and pretransplant serum creatinine; history of prior liver transplant and primary nonfunction of prior liver transplant; history of variceal bleeding, ascites, portal vein thrombosis, and insulin-dependent diabetes mellitus; and the need for pretransplant inotropic support, life support, and intensive care unit or hospital care.

Combining Waiting List Mortality and Posttransplant Mortality Risk to Determine Transplant Survival Benefit

From the viewpoint of a liver transplant candidate, a major question is whether their expected lifetime with a transplant is longer than their expected lifetime without the transplant. Unfortunately, our ability to accurately gauge total lifetimes is quite limited, so instead we rely upon estimates of shorter-term survival. For example, if a patient has a predicted 1-year survival rate of 60% without a transplant and 70% with a transplant, we would say that there is evidence of a net transplant survival benefit. Even an equal survival percentage at 1 year may be associated with a survival benefit if the shapes of the 2 survival curves are different. In this case, one can calculate the area under the 2 survival curves and generate a statistic that represents the difference between the expected number of days lived during a given interval of time with or without a transplant.

Defining “Too Well”

From a survival perspective, a candidate is considered too well to undergo liver transplantation if his or her

expected lifetime is greater in the absence of a transplant. Of course, this definition does not incorporate measures of the patient’s quality of life or burden of disease, each of which might weigh heavily on an individual’s desire to go ahead with a surgical procedure that might actually shorten their life. In practical terms, we have examined the relative mortality risk after liver transplantation compared to the risk of death on the waiting list, given an equivalent time since placement on the waiting list and comparable risk of pretransplant death (e.g., MELD score). Adjusted relative mortality risk is significantly higher for transplanted patients than for waitlisted patients when the MELD score is less than 15, as assessed during 1-year posttransplant follow-up.⁶ Given underlying chronic liver disease, however, it is likely that the risk of death will increase over time in the absence of a transplant. If the MELD score rises to greater than 15, there is no longer a significantly higher risk of death with the transplant and the patient would no longer be considered too well.

Defining “Too Sick”

It is considerably more difficult to identify patients who are too sick for a liver transplant, rendering a transplant futile. Three conceptual bases for a determination of transplant futility may be discussed. The 1st examines the relative mortality risk of the transplant vs. continued residence on the waiting list, a measure of individual relative transplant survival benefit. Patients with MELD scores of 18 and higher derive significant transplant survival benefit, and the magnitude of benefit increases with the score. However, candidates at very high MELD scores are more likely to be placed on inactive status at any given time when compared to candidates who have lower MELD scores (Fig. 3). Comparisons of the relative mortality risk for transplanted patients and waitlisted candidates at the very high end of the MELD score spectrum may tend to overestimate the benefit of transplantation because selection bias in the transplanted group resulting from appropriate physician judgment in clinical practice enriches the waitlisted group for nonsurvivors and the recipient group for survivors. Nonetheless, the measured benefit of transplantation for very sick candidates is unlikely to be nullified by this methodological issue.

Second, the current MELD-based allocation policy caps the score at 40. Thus, patients whose calculated uncapped score is higher than 40 are aggregated with those whose calculated score exactly equals 40. Examination of the subgroup of candidates with MELD scores higher than 40 has revealed that such scores are

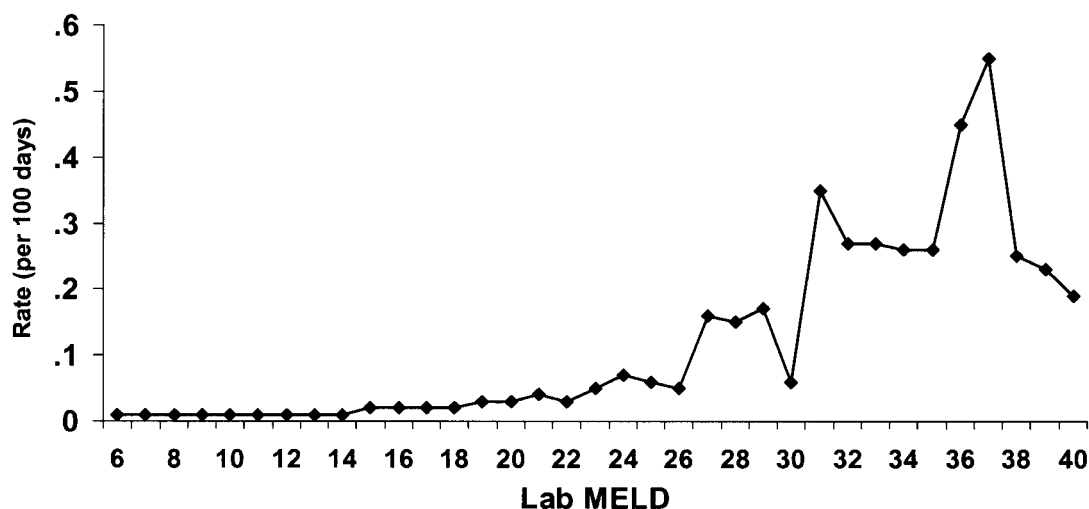


Figure 3. Rate of change to inactive status per 100 days, by MELD score.

not associated with a diminished transplant benefit when compared to those whose scores are exactly 40.

Third, some patients with a transplant survival benefit based on relative waitlist and posttransplant mortality estimates may nonetheless have an absolute posttransplant survival rate that is extremely low. For example, is a 1-year posttransplant survival rate of 30% unacceptable, even if it represents a much better survival prospect for a patient than in the absence of a transplant? This important societal question, with far-reaching consequences for the transplant community, was discussed at a conference on the MELD allocation system held in December 2003.¹⁵ At that meeting, there was consensus that a minimum acceptable predicted absolute posttransplant survival was needed, although the precise method for determining this level was not able to be elaborated.

Summary

Liver transplantation has evolved to the point where the survival benefit of the procedure can now be estimated. The MELD scoring system allows us to estimate pretransplant mortality risk with remarkable precision and provides a good 1st approximation for posttransplant mortality risk. Comparisons of the relative mortality risks on the waiting list and after transplant allow us to determine whether and to what degree patients are well served by undergoing liver transplantation in terms of survival. Additional ongoing work on models of posttransplant mortality risk will result in more accurate measurements of this side of the equation. These advancements will ultimately improve our ability to

allocate organs in a fair and equitable manner and counsel potential liver transplant candidates.

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