

The MELD Score in Advanced Liver Disease: Association with Clinical Portal Hypertension and Mortality

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Background: The Model for End-Stage Liver Disease (MELD) score is a measure of chronic liver disease severity. Patients awaiting transplantation are assessed using this score. However, it has recently been suggested that changes in MELD score may be as important as the absolute MELD score in predicting short-term survival. However, clinical factors that affect the MELD score are unknown. We sought to identify predictors of mortality for potential transplant patients and examine factors that might predict changes in MELD score.

Materials and Methods: Between January 1, 2002, and July 30, 2004, we retrospectively examined risk factors of 429 adult patients awaiting liver transplantation at the University of California at Los Angeles (UCLA). Analysis of the data was performed using demographics, manifestations of portal hypertension, time between last MELD recorded and event, and laboratory values. Significant factors in univariate analysis were further studied using Cox proportional hazards regression multivariate analysis.

Results: At mean follow-up of 2.15 years (\pm 1.49 years), 71 patients (16.5%) had MELD scores that increased 5-10 points, 22 had changes of 10-15 points, and 14 had changes of 15-20 points. Manifestations of portal hypertension, laboratory values, and etiology of liver disease did not predict changes in MELD score. However, development of hepatic encephalopathy (HR, 3.95; $P = .002$; 95% CI,

1.70 to 9.42) and MELD score (HR, 1.04; $P = .001$; 95% CI, 1.004 to 1.08) were associated with variceal bleeding. Also, MELD score (HR, 1.07; $P < .001$; 95% CI, 1.05 to 1.09), refractory ascites (HR, 2.15; $P = .002$; 95% CI, 1.31 to 3.53), and alcoholic cirrhosis (HR, 0.40; $P = .04$; 95% CI, 0.18 to 0.94) were independent predictors of mortality.

Conclusions: Encephalopathy and MELD score were associated with variceal bleeding. Patients with an elevated MELD score, refractory ascites, and alcoholic cirrhosis had increased mortality while on the liver transplant list. No factors predicting changes in the MELD score were identified.

Key words: MELD, Liver transplantation, Outcome

Patients awaiting transplantation are assessed using the Model for End-Stage Liver Disease (MELD) score [1-3]. The MELD score reflects liver disease severity, with higher values indicating worse disease [4, 5]. The MELD score is believed to be a more objective and better predictor of short-term survival than the Child-Pugh classification system [6]. The addition of portal hypertension manifestations to the MELD does not appear to affect its predictive ability.

Factors associated with changes in MELD scores are not well understood. Knowledge of these factors might be important to the timing of transplantation and might predict survival independent of the absolute score. In a retrospective study of 760 patients on a liver transplant waiting list, Merion and coworkers demonstrated a 3-fold greater mortality risk when MELD score increased by 5 units [7]. Moreover, each MELD unit was associated with a 22% increase in risk of death on the wait list. However, a recent study was unable to confirm the impact of changes in MELD score on mortality [8]. Bambha and colleagues studied survival in 861 patients on a liver transplant wait list prior to using the MELD and found that according

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to multivariate analysis, changes in MELD were predictive of death only within 4 days of the event [8]. It remains unclear whether the MELD score is sensitive to manifestations of clinical decompensation, and at what rate it changes in patients awaiting liver transplantation [9].

Because of the uncertainty regarding factors associated with MELD score changes and the controversy regarding the impact of MELD score changes on mortality, we sought to further study these issues in our institution. The results would help us to better educate providers and patients about the timing and likelihood of transplantation, as well as the prognosis.

Materials and Methods

Adult patients awaiting liver transplantation at the University of California Los Angeles Medical Center between January 1, 2002, and July 30, 2004, were identified from an administrative transplant database and included in the study. Patients with fulminant hepatic failure or those awaiting retransplantation were excluded.

We collected data regarding patients' age, sex, ethnicity, etiology of liver disease, date listed for transplantation, and transplant date. We also collected creatinine, albumin, sodium, total bilirubin, and international normalized ratio (INR) values. Complications and treatment of portal hypertension were recorded for manifestations including medically responsive and refractory ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatic hydrothorax. We also recorded the time between last MELD score recorded and event. Standard operational definitions were used for hepatorenal syndrome, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatic hydrothorax [10, 11]. Refractory ascites was defined as the inability to mobilize ascitic fluid because maximum doses of diuretics were associated with electrolyte disturbances or adverse effects or maximum doses were ineffective. We also recorded the presence and treatment of pruritus. All data for the current study were collected in accordance with Institutional Review Board requirements. Liver disease severity was assessed using the MELD currently used by the United Network for Organ Sharing. The MELD score was calculated by setting the minimum value of serum bilirubin, creatinine, and INR to 1.0 to preclude negative values. Calculated MELD scores were used

for patients with hepatocellular carcinoma, rather than scores allocated based on exemption.

Follow-up was defined as the time from liver transplant listing date to transplantation, death, or last visit. Categorical variables were expressed as percentages, and continuous variables were expressed as means (\pm standard deviation [SD]). Variables found to be significant in univariate analyses were further studied in a multivariate analysis using Cox proportional hazards regression analysis.

All statistical analyses were performed using STATA 7 software (Stata Corporation, College Station, Tex, USA). *P* values less than .05 were considered significant. Variables found to be significant in multivariate analyses were used to create a receiver operating characteristic graph. The graph depicts the true-positive proportion plotted against the false-positive proportion for the different cutoff values of the decision criterion. The c-statistic is used to evaluate prognostic models. A c-statistic between 0.8 and 0.9 indicates excellent accuracy, while a c-statistic > 0.7 generally is considered a useful test result [12]. A c-statistic less than 0.7 suggests a test is not clinically useful.

Results

Demographics

We identified 286 men and 143 women awaiting liver transplantation during the study. The mean age of the cohort was 53.92 years (± 13.52 years). The median number of MELD scores available per patient was 3 (range, 1 to 6). The mean MELD score was 16.29 (± 10.06). The distribution of MELD scores is shown in Figure 1. Mean follow-up was 2.15 years (± 1.49 years). The mean albumin, sodium, and platelet counts were 2.93 g/dL (± 2.01 g/dL), 134.7 mmol/L (± 5.39 mmol/L), and $74.1 \times 10^9/L$ ($\pm 48.3 \times 10^9/L/\mu L$),

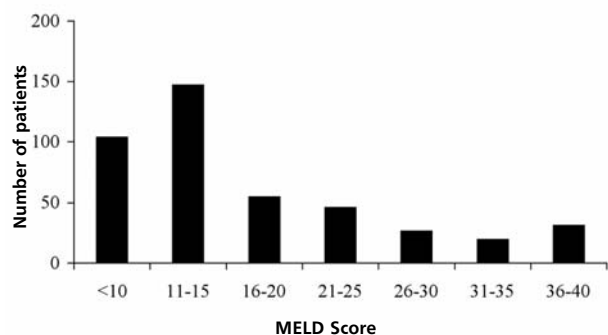


Figure 1. Distribution of initial Model for End-Stage Liver Disease (MELD) scores.

respectively. During follow-up, 131 patients were transplanted, and 79 died. Hepatitis C was the most common etiology of liver disease in our cohort (Table 1).

Table 1. Clinical characteristics of study population

Age (years)	53.92 (\pm 13.52)
Gender	
Male/female	286/143
Ethnicity, number (%)	
Non-Hispanic white	196 (46)
Hispanic	150 (35)
African American	15 (4)
Asian	45 (11)
Other	23 (5)
Etiology of liver disease, number (%)	
Hepatitis C	268 (63)
Alcohol	70 (16)
Hepatitis B	38 (9)
Cholestatic disease	34 (8)
Hepatitis B and C	10 (2)
Other*	9 (2)

* Others include congenital hepatic fibrosis, iron overload, Wilson's disease, tyrosinemia.

At initial presentation to UCLA, ascites was present in 303 patients, hepatic encephalopathy in 110, gastroesophageal variceal bleeding in 126, spontaneous bacterial peritonitis in 41, and hepatic hydrothorax in 17. Complications that developed while on the wait list included encephalopathy in 57 patients, variceal bleeding in 26, and hepatic hydrothorax in 15. The mean time for a change of 5 MELD points was 1.88 months (\pm 4.16 months).

Predictors of Changes in MELD Score

Seventy-one patients (16.5%) had MELD scores that increased by 5-10 points; 22 had changes of 10-15 points; and 14 had changes of 15-20 points. Laboratory values, etiology of liver disease, and clinical manifestation of portal hypertension were not associated with MELD score increase of at least 5 points. Multivariate analysis did not identify any variables associated with MELD score changes.

Predictors of Decompensation

Univariate analysis identified initial MELD score, albumin, platelets, alcoholic cirrhosis and hepatitis C cirrhosis, hepatocellular carcinoma, spontaneous bacterial peritonitis, and any magnitude of change in MELD score as possible significant predictors of decompensation. The development of hepatic encephalopathy (HR, 3.95; P = .002; 95% CI, 1.70 to 9.42) and the MELD score (HR, 1.04; P = .001; 95% CI, 1.004 to 1.08) were associated with variceal bleeding. None of the study variables were associated with the

development of ascites and/or hepatic encephalopathy, including changes in MELD score.

Predictors of Mortality

On univariate analysis, baseline MELD score, variceal bleeding on the wait list, alcoholic cirrhosis, alcohol and hepatitis C cirrhosis, hepatic encephalopathy while on wait list, refractory ascites, and MELD score changes were significantly associated with mortality. In multivariate analysis, the MELD score (HR, 1.07; P = .000; 95% CI, 1.05 to 1.09), refractory ascites (HR, 2.15; P = .002; 95% CI, 1.31 to 3.53), and a history of alcoholic cirrhosis as an etiology of liver disease (HR; 0.40, P = .04; CI, 0.18 to 0.94) were independent predictors of mortality. The C-statistic for predicting mortality using the MELD score alone was 66%.

Discussion

Since February 2002, liver allocation policy in the United States has been based on the MELD score. Initially, the MELD was designed to evaluate the mortality risk for patients undergoing a transjugular intrahepatic portosystemic shunt procedure and proved to be an accurate predictor of mortality in this group. Baseline MELD score has been shown also to be an accurate predictor of 3-month mortality on the wait list in patients with end-stage liver disease, and it was suggested that the accuracy may extend to up to 1 year [12].

Managing complications of end-stage liver disease for patients on the wait list is challenging and requires a multidisciplinary approach. Since patients present at different stages in the course of their liver disease, it is difficult to predict the rate of progression to severe decompensation. At the time of the initial evaluation for liver transplantation, the prospective recipient is given a baseline MELD score based on current INR, creatinine and total bilirubin, which is intended to reflect the severity of liver disease and urgency for transplantation. Although baseline MELD scores have been found to be significantly associated with wait list mortality, a single MELD score at the time of placement on the wait list can accurately reflect mortality risk while on the wait list.

The results of our study are consistent with previous reports demonstrating that MELD score predicts survival in patients with chronic liver disease [4, 5]. In addition, our results show that risk of death is twice as high in patients with refractory ascites compared with those without refractory ascites. The clinical

significance of medically responsive and refractory ascites has not been well studied under the current method of organ allocation. During the MELD validation studies, stratification of ascites into medically responsive and refractory categories was not reported [5]. Indeed, refractory ascites has been proposed to represent one extreme of the ascites continuum in the Child-Pugh classification. Previous reports have indicated a 50% patient survival rate in patients with refractory ascites [13]. In our study, serum sodium was not associated with increased mortality. This contrasts with previous recent reports that the addition of serum sodium into MELD is a better predictor of survival than is the MELD score alone [14, 15]. Serum sodium is often seen as a surrogate marker for ascites [16, 17]. In the widely accepted vasodilatation hypothesis for ascites formation, ascites (in particular refractory ascites) is one of the major manifestations of portal hypertension. Serum sodium falls because of circulatory dilution. Future studies are needed to assess the independent effect of serum sodium on mortality. Spontaneous bacterial peritonitis was not associated with increased mortality, likely because of the use of volume expanders during the infection and the introduction of secondary prophylaxis. However, these data were not assessed in the present study.

Our results do differ from a recent publication by Merion and coworkers that showed that a change of MELD score of at least 5 points was associated with increased mortality, and delta MELD was proposed as a tiebreaker for patients with similar MELD scores [7]. However, the MELD score was developed in patients who were hemodynamically stable, and reversible conditions were corrected [18]. Changes in MELD score may reflect increased mortality from a reversible condition, such as sepsis, that may be unrelated to the underlying liver disease.

The effect of disease etiology is controversial. In the original MELD study, etiology of liver disease was believed to predict survival [18]. One of the limitations of our study was that the cause of death was not assessed. This may assist in further exploring the discrepancy between our results and other published studies. Also, we did not identify predictors of MELD score changes. Nearly half of our patients had a change of MELD of at least 5 points. Clinical manifestations of portal hypertension were not associated with changes in MELD, which further suggests the value of MELD in predicting disease severity but not necessarily portal hypertension. Indeed, in published validation studies of MELD, clinical manifestations of

portal hypertension did not substantially improve the predictability of survival, suggesting that mortality is associated with liver disease severity and not manifestations of portal hypertension [19].

The combination of MELD score, refractory ascites, and disease etiology was considered useful in predicting survival. However, the c-statistic for MELD score alone was lower in our study than elsewhere [5]. An explanation for this difference may be the time frame chosen in our study. The MELD score was developed assessing 3-month survival [18]. However, when the time frame has been extended beyond 3 months, the ability of MELD to predict survival declines [10, 19, 20]. Another limitation may have been the inclusion of patients with hepatocellular carcinoma, who may have been transplanted with additional MELD exemption scores, rather than their biological calculated MELD score. In fact, our c-statistic was similar to that found in another large study where the mean follow-up was 5.2 years [20]. Nevertheless, the MELD was independently associated with wait list survival in our study, and the addition of refractory ascites and disease etiology enhanced its relationship. We could not report 3-month mortality data because of a lack of sufficient events during this time frame. Adequate 3-month mortality data would be best studied in a prospective study.

Patients with elevated MELD scores, refractory ascites, and alcoholic cirrhosis had increased mortality while on the liver transplant wait list. However, neither these nor other studied factors in our study predicted changes in the MELD score. Additional long-term studies are needed to identify factors that predict MELD score changes.

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