Longitudinal Assessment of Mortality Risk Among Candidates for Liver Transplantation

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Liver allocation policy recently was modified to use the Model for End-Stage Liver Disease (MELD) for patients with chronic liver disease to stratify potential recipients according to risk for waitlist death. In this study, a retrospective cohort of 760 adult patients with chronic liver disease placed on the liver transplant waitlist between January 1995 and March 2001 and followed up for up to 74 months was studied to assess the ability of the MELD to predict mortality among waitlisted candidates and evaluate the prognostic importance of changes in MELD score over time. Serial MELD scores predicted waitlist mortality significantly better than baseline MELD scores or medical urgency status. Each unit of the 40-point MELD score was associated with a 22% increased risk for waitlist death ($P < .001$), whereas medical urgency status was not a significant independent predictor. For any given MELD score, the magnitude and direction of change in MELD score during the previous 30 days (ΔMELD) was a significant independent mortality predictor. Patients with MELD score increases greater than 5 points over 30 days had a threefold greater waitlist mortality risk than those for whom MELD scores increased more gradually ($P < .0001$). We conclude that mortality risk on the liver transplant waitlist is predicted more accurately by serial MELD score determinations than by medical urgency status or single MELD measurements. ΔMELD score over time reflects progression of liver disease and conveys important additional prognostic information that should be considered in the further evolution of national liver allocation policy. (*Liver Transpl 2003;9:12-18.*)

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Mortality risk assessment for patients with severe liver disease has been studied for almost four decades. Publication of the Child-Turcotte classification in 1964,[1] which described a risk classification system for cirrhotic patients undergoing surgical procedures, and its subsequent modification by Pugh,[2] yielded a practical and predictive index on mortality. Child-Turcotte-Pugh (CTP) score has been used in the United States since 1997 as one criterion to rank candidates awaiting liver transplantation.[3] However, concerns recently have surfaced regarding the wide range of disease severity among patients with chronic liver disease within each of the three broad categories of medical urgency defined by current national liver allocation policy. One criticism of CTP score is its use of such subjective criteria as hepatic encephalopathy and ascites. Given the grave imbalance between the pool of suitable recipients and available cadaveric donors,[4] an objective and more accurate method has been sought for ranking potential candidates according to waitlist mortality risk.

Recent studies have documented the ability of a score based on a continuous disease severity scale to predict 3-month mortality in a cohort of patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures for the treatment of variceal hemorrhage in cirrhotic patients.[5,6] Initially termed the Mayo TIPS Model, the investigators found four statistically significant mortality predictors in a multivariable Cox model. Three were readily obtainable laboratory values: serum bilirubin level, serum creatinine level, and prothrombin time international normalized ratio (INR). The fourth variable was cause of cirrhosis; nonalcoholic noncholestatic causes had increased mortality. A regression equation with coefficients for each of the four variables was constructed.

In their second report, Kamath et al[6] slightly modified their model (now termed the Model for End-Stage Liver Disease [MELD]) and examined several patient populations to assess its generalizability to a range of patients with end-stage liver disease. Although promising, these studies relied on a MELD score determination at a single point in each patient's course and did not directly study a group of patients awaiting liver

transplantation. These studies did not address changes in mortality risk over time or the need to periodically reassess that risk during the longer times required for patients awaiting a donated liver. A recent report examined patients on the liver waitlist with severe disease (status 2a) and found that the MELD was a superior predictor of pretransplantation ventilator requirements and dialysis need compared with the CTP system.[7] Another study found that the MELD was highly predictive of pretransplantation mortality in status 2a patients.[8]

Given that liver allocation policy in the United States is targeted toward providing donated livers to patients with the greatest risk for waitlist mortality, analysis of updated MELD scores and mortality risk during the entire interval that patients are on the waitlist is an important step in the evaluation of the MELD as a basis for liver allocation. This is especially so given the recent institution of MELD-based allocation. In addition to information gained from using serial MELD scores, we hypothesized that the direction and magnitude of recent changes in MELD scores may be independently associated with mortality risk. We conducted the current study of waitlisted liver transplant candidates to examine these issues.

Methods

Study Design and Data Collection

The University of Michigan Institutional Review Board (Ann Arbor, MI) approved the study protocol. All adult liver transplant candidates at the University of Michigan Health System with chronic liver disease who were placed on the national Organ Procurement and Transplantation Network (OPTN) waitlist for the first time between January 1, 1995, and study closure on March 13, 2001, were eligible for inclusion in the study. Patients with acute (fulminant) liver failure were excluded. Institutional databases were queried to acquire a data set consisting of age, sex, race, underlying liver disease, and date of placement on the waitlist.

Medical urgency status designation used the system in effect during the study period. Until July 1, 1997, statuses 2, 3, and 4 were used for candidates with chronic liver disease who required continuous hospitalization, continuous outpatient care, and intermittent outpatient care, respectively. As of July 1, 1997, a semiquantitative system based on CTP score was used. Status 4 patients were reassigned to status 3 (CTP score, 7 to 10). Status 2 was redefined. Status 2b required a CTP score of 10 or greater or 7 points plus specified complications. Status 2a was reserved for patients who developed life-threatening complications, required intensive care unit care, and had a life expectancy of 7 days or less.

Each patient's initial waitlist medical urgency status and all subsequent changes were recorded until the earliest of transplantation, death, or continued presence on the waitlist on March 13, 2001. For patients removed from the waitlist for reasons other than transplantation or death, we used data from medical records supplemented by query of the Social Security Administration Death Master File.[9] Time at risk was extended up to 30 days from waitlist removal (not to exceed the study end date), and deaths within 30 days of removal were counted as waitlist deaths.

MELD Score Calculations

MELD scores were calculated using serum bilirubin level, serum creatinine level, and INR according to Kamath et al[6]:

$$0.957 \times \log(\text{serum creatinine}) + 0.378 \times \log(\text{serum bilirubin}) + 1.120 \times \log(\text{INR})$$

Baseline calculation required all three laboratory components within 14 days of placement on the waitlist. Subsequent MELD calculations were made whenever one or more laboratory components changed. Scores were rounded to the nearest tenth and multiplied by 10. Based on previous studies, the coefficient for disease cause was not used; laboratory inputs and MELD score limits were performed in accordance with the current OPTN liver allocation methods.[10] Serum bilirubin, INR, or serum creatinine values less than 1.0 were set to 1.0 to preclude negative scores. Serum creatinine level was capped at 4.0. MELD scores were capped at 40.

Waitlist Survival Modeling

Odds of 90-day mortality were estimated using logistic regression. The concordance c-statistic (area under the receiver operating characteristic curve [AUC ROC]) also was generated. Time-dependent Cox proportional hazard regression models also were developed to assess mortality risk with censoring at transplantation. Models were adjusted for patient age, sex, race, and year of placement on the waitlist. Diagnosis was not significantly associated with mortality on the waitlist and thus was not included in regression models. Survival estimation was performed using SAS, version 8.00 (SAS Intitute, Cary, NC).[11]

Changes in MELD Score Over 30-Day Intervals

The time-dependent Cox models describe mortality risk associated with a particular MELD score calculated at any time during the patient's residence on the waitlist. However, a patient's MELD score may change over time. To determine whether proximate changes in MELD score influence waitlist mortality independent of the risk associated with the current MELD score itself, the slope of MELD scores during the 30 days before each MELD score was calculated using the least squares method, starting at day 30 on the waitlist (ΔMELD). ΔMELD of zero occurs when the slope of the regression line

Table 1. Demographic Characteristics of 760 University of Michigan Liver Transplant Candidates at Waitlist Placement

Variable	Value
Age (yr)	49.3 ± 9.3
Gender	
Women	304 (40.0)
Men	456 (60.0)
Race	
White	646 (85.0)
Black	52 (6.8)
Asian	11 (1.4)
Other	51 (6.7)
Diagnosis	
Cirrhosis	595 (78.3)
Cholestatic disease	114 (15.0)
Metabolic disorders	25 (3.3)
Cancer	7 (0.9)
Other	19 (2.5)
Medical urgency status at waitlist placement	
Status 2 (old)	20 (2.6)
Status 2b	120 (15.8)
Status 3	612 (80.5)
Status 4 (old)	8 (1.1)
MELD score at waitlist placement	7.1 ± 4.8 (0-29)

NOTE. Values expressed as mean ± SD (range) or number (percent).

describing all MELD scores in the 30-day period is zero. A positive ΔMELD occurs when MELD scores generally are increasing during the 30-day period, whereas a negative ΔMELD occurs when MELD scores generally are decreasing.

Validation of MELD Coefficients

Published parameter estimates for Cox model regression coefficients of the MELD equation (given previously) were compared with those calculated using laboratory values from the current study data set.

Results

Seven hundred sixty adult patients were placed on the waitlist for the first time between January 1, 1995, and March 13, 2001, with follow-up during this same time. Table 1 lists demographic characteristics of the patient population. There was a preponderance of men (60%) and whites (85%). Mean age at baseline was 49 ± 9 years. The majority of patients had cirrhotic liver disease (78%) or cholestatic disorders (15%). During the course of the study, 258 patients (34%) received a liver transplant and 190 patients (25%) died on the waitlist. A total of 8,235 MELD scores were available for the 760 patients (mean, 10.9 ± 11.0 [SD] MELD determinations per patient; interquartile range, 3 to 15).

Validation of MELD Coefficients

Regression coefficients for log values of the three MELD components were statistically significant ($P < .05$) and within the 95% confidence bands for the original published coefficients (Fig. 1).

Odds of 90-Day Mortality (Logistic Regression)

MELD scores 30 days after placement on the waitlist were used to estimate the odds of subsequent 90-day mortality (i.e., death on or before day 120). Compared with a reference group of patients with MELD scores between 0 and 10, survival among patients with higher MELD scores was significantly decreased (Table 2). The AUC ROC for this logistic regression model was 0.85. In a separate model, patients classified as status 2b and (old) status 2 after 30 days on the waitlist were at significantly increased risk for subsequent 90-day mortality compared with the status 3 reference group (Table 2). The AUC ROC for this model (0.77) was lower than for MELD score. Additional 90-day mortality analyses starting 60, 90, and 180 days after placement on the waitlist yielded similar results (data not shown). Too few patients were in status 2a at 30 days after

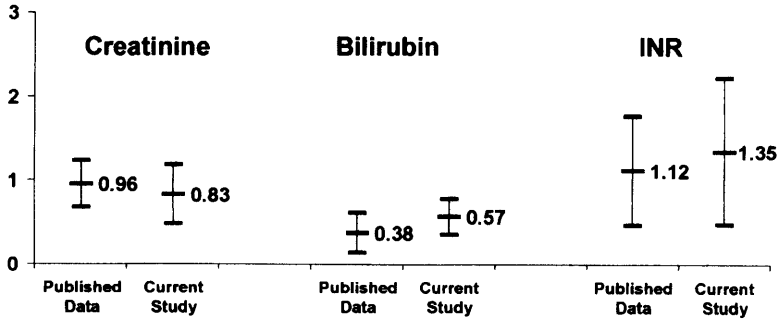

Figure 1. Coefficients for components of the MELD score. Regression coefficients for the log values of components were statistically significant at the $P = .05$ level and within the estimated confidence bands for the original published coefficients (Malinchoc et al[5] and Kamath et al[6]).

Table 2. Probabilities of 90-Day Waitlist Mortality and Mortality Odds Ratios by MELD Score and Waitlist Status

Classification After 30 Days on Waitlist	No. of Patients	90-Day Survival (%)	Mortality Odds Ratio	*P*
Model A				
MELD score				
0-10	430	97.2	1.0	(reference)
11-17	70	80.0	9.1	<.001
18-24	15	53.3	36.8	<.001
25-40	7	14.3	276.8	<.001
Model B				
Status				
3	552	96.7	1.0	(reference)
2b	98	81.6	7.9	<.001
2 (old)	16	75.0	17.9	<.001

NOTE. No patient was in status 2a at day 30 after placement on the waitlist. AUC ROC values for MELD and status were 0.85 and 0.77, respectively.

placement on the waitlist to permit calculation of a risk estimate for this group.

MELD Score and Waitlist Status as Time-Dependent Covariates (Cox Models)

The relative risk (RR) for waitlist death was estimated using two separate Cox models. First, we examined the association of a single baseline MELD score on day 30 with waitlist death. Here, baseline MELD score was a significant mortality predictor (Chi-square, 88.8; RR, 1.15 per unit increase in MELD score; $P < .001$). In the second model, all available MELD scores during the patient's residence on the waitlist were used in a time-dependent Cox model. Compared with baseline MELD score, the time-dependent MELD score was much more predictive of waitlist mortality (Chi-square, 630.6; RR, 1.22 per unit increase in MELD score; $P < .001$). In the time-dependent model, risk for death was associated with updated MELD scores, and each increase of one MELD point was associated with a 22% increase in waitlist mortality.

A separate time-dependent analysis also found that waitlist status was significantly associated with waitlist mortality risk (Table 3). Compared with status 3, status 2b was associated with a fivefold increase in risk, and status 2a, with an RR of 85.2 ($P < .001$).

Finally, MELD score and waitlist status were tested together as time-dependent covariates in a combined Cox regression model. As listed in Table 4, MELD score was highly significant and associated with a waitlist mortality risk of 22% per unit increase in MELD score. Waitlist status provided no significant incremental contribution to risk for death after updated MELD scores were accounted for in the model.

Table 3. Current Waitlist Status as a Predictor of Waitlist Mortality

Current Waitlist Status	Chi-Square	RR	*P*
3		1.0	(reference)
2 (old)	2.3	1.6	.127
2b	54.2	5.1	<.001
2a	120.7	85.2	<.001

NOTE. Waitlist status was used as a time-dependent covariate in a Cox regression analysis of waitlist mortality. The most clinically stable patients (status 3) were defined as the reference group.

Table 4. Current MELD Score and Waitlist Status As Time-Dependent Covariates

Covariate	Chi-Square	RR	*P*
MELD	545.05	1.22	<.001
Status 2a	0.02	0.94	.885
Status 2b	0.08	0.93	.782
Status 2 (old)	0.03	0.95	.858

NOTE. Current MELD score is a significant predictor of waitlist mortality. Medical urgency status is not a significant mortality predictor with MELD score included in the model.

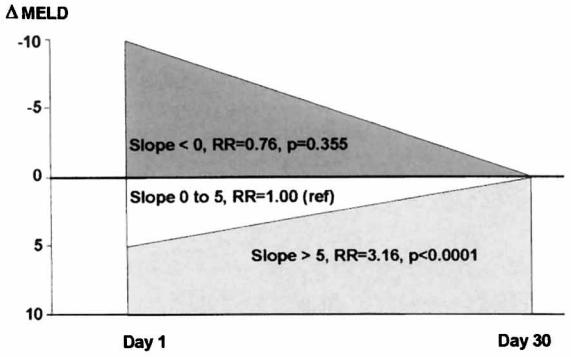

Figure 2. Independent effect of the slope of MELD scores during 30-day intervals (ΔMELD) on waitlist mortality. An increase of more than five MELD points during any 30-day interval (positive ΔMELD) was associated with a threefold increase in waitlist mortality risk independent of the MELD score at the end of the interval (RR, 3.16; $P < .0001$).

Change of MELD Score

To determine the effect of changes in MELD score over time for a given patient, the slope representing that change during the 30 previous days was studied (ΔMELD). The reference group for this analysis was composed of 30-day intervals in which modest changes from 0 to +5 MELD score points were recorded, reflecting gradual worsening of liver disease in the waitlist population. Decreasing MELD scores (negative ΔMELD) during the 30-day interval (slope < 0) were associated with a slightly protective effect (slope < 0; RR, 0.76; $P = .355$; Fig. 2). Positive ΔMELD of more than 5 points during 30 days (slope > 5) was accompanied by a threefold greater risk for death compared with the reference group (slope > 5; RR, 3.16; $P < .0001$). This effect was independent of and additive to the absolute MELD score at the end of each 30-day interval (current MELD; RR, 1.17; $P < .001$).

Discussion

Allocation of donor livers in the United States is guided primarily by assessment of the risk of recipient death in the absence of a transplant as part of the overall goal to maximize overall transplant benefit. Until February 2002, stratification of candidates used medical urgency statuses that divided patients into those with acute (status 1) and chronic (status 2a, 2b, and 3) liver disease.[3] Medical criteria associated with disease severity were used to assign patients to the three chronic-disease status designations, and donor livers were allocated in descending order of status on a point system based on blood group type compatibility and waiting time within defined geographic areas (local Organ Procurement Organization [OPO], OPTN region, entire nation).

Increasing recognition that, especially within statuses 2b and 3, wide variations exist in degree of medical urgency prompted the application of the MELD to liver allocation. In part, the MELD creates a more finely granular allocation system (40 levels) than the chronic-disease status system (3 levels). However, data concerning the ability of the MELD to accurately predict liver waitlist mortality during the prolonged periods that patients must wait for liver transplants has been lacking and will be some time forthcoming from the newly enacted national system.

Because the MELD was first developed as a tool to predict mortality after TIPS placement in cirrhotic patients, it is important to determine its predictive value for actual waitlisted patients who are awaiting liver transplantation. A recently published study showed that 3-month mortality could be predicted by the MELD in patients who had a range of chronic hepatic disorders.[6] That study suggested the MELD is a generalizable tool for prognostication in such patients, but did not directly test that hypothesis on a population of waitlisted patients.

We found that baseline MELD scores were significantly associated with liver waitlist mortality and MELD scores were more predictive than medical status level. This supports previous work[6] and is consistent with the direction in which national liver allocation policy has been evolving.

Unfortunately, a single MELD score determined at the time of placement on the waitlist is unlikely to accurately reflect mortality risk across a patient's entire residence on the list. Median waiting time for a liver transplant in the United States is greater than 1 year,[4] and the course of chronic liver disease is progressive and unpredictable. Thus, the new national system provides for periodic updates of MELD score for patients remaining on the waitlist. Availability of an existing longitudinal set of data in the current study provided three ways to validate and extend the utility of MELD score as a predictor of waitlist mortality and hopefully to preview some of the effects that may be expected under the new system.

First, the present study reports the first analysis of repeated MELD scores over time from patients on the liver transplant waitlist and provides strong evidence that updated MELD scores are a significantly better predictor of waitlist mortality than waitlist status levels or baseline (nonupdated) MELD scores. Patients in the cohort had a mean of 11 MELD determinations during

their residence on the waitlist, corresponding to 1.85 MELD scores per month. In the Cox model combining updated MELD scores and updated waitlist status levels as covariates, each point of the 40-point MELD score was associated with a 22% increased risk for waitlist death ($P < .001$), whereas status level was not a significant independent predictor. These results are substantively in support of the current OPTN policy to mandate periodic updating of MELD scores and provide additional evidence that such a practice may result in more equitable allocation of donor livers in the United States.

Second, the Cox model based on University of Michigan data produced statistically significant and robust regression coefficients for each of the three laboratory components of the MELD score. In addition, these regression coefficients were within the estimated confidence bands for the original published coefficients. Because our cohort is different from all others on which MELD scores have been tested in the past, findings of this study provide further validation of the utility of the MELD in predicting pretransplantation mortality. Data collection from all waitlisted liver transplant candidates in the United States is under way, and subsequent analyses will determine whether adjustments to the coefficients are necessary over time.

Third, our analyses clearly show that ΔMELD, a measure of the magnitude and direction of change in MELD score during the previous 30 days, is an important and independent predictor of liver waitlist mortality. Patients with a positive ΔMELD greater than five during a 30-day period had more than a threefold greater waitlist mortality risk than patients for whom MELD scores increased more gradually. Patients with a ΔMELD of zero or negative ΔMELD during the preceding 30 days had slightly lower mortality risk compared with the reference group. Under the initial MELD-based liver allocation system currently implemented by the OPTN, allocation decisions among two or more candidates with the same MELD score are to be adjudicated by comparing the amount of waiting time at or above that score. Such patients would be likely to have a negative 30-day ΔMELD. In this circumstance, the existing tiebreaker rule may incorrectly order patients with the same MELD score.

For example, suppose there are three patients with identical MELD scores (e.g., 20) who are eligible candidates to receive a donor liver today. Patient A had two additional MELD scores of 20 during the previous month. Patient B had a MELD score of 30 a month previously, and a score of 25 two weeks previously. Thirty days ago, patient C had a MELD score of 10, and it increased to 15 two weeks ago before reaching its current level of 20. In this set of patients, the existing allocation system would offer the liver first to patient B (based on most time $\geq$ 20) and then adjudicate between patients A and C solely on the basis of waiting time. However, the ΔMELD analysis suggests that patient C actually has the greatest predicted mortality risk on the basis of a positive ΔMELD of 10 points over 30 days. Patient A has a zero 30-day ΔMELD and therefore would be prioritized second under a ΔMELD mortality risk tiebreaker, and patient B would be third in line for the donor liver because of a negative ΔMELD. Further analyses using national data are critical to examine this issue and are under way. Incorporation of ΔMELD as a fourth component of a modified MELD score also should be considered.

There are some limitations to the present study. Most importantly, patterns of pretransplantation mortality and transplantation will change as the MELD-based system is used for organ allocation. All patients in the current study underwent transplantation under the existing medical status–based allocation system. Thus, censoring at transplantation would have affected a different set of patients had the available donor organs been allocated according to MELD score. For example, some patients with high MELD scores who died on the waitlist would likely have undergone transplantation, whereas patients with higher medical status with low MELD scores would have remained on the waitlist for a longer time. Despite this, the current study offers valuable insight into the effects of changing MELD scores over time in patients followed up longitudinally on the waitlist. It will take several years to accumulate similar longitudinal data at the national level.

We have considered a methodological issue that could arise because of nonrandom censoring because we try to perform transplantation in those at greatest risk for death and then censor them at transplantation in the analysis. If the sickest patients all received a transplant before death, then waitlist mortality rates clearly would be underestimated. However, under the allocation system before February 2002 for patients with chronic liver disease (statuses 2a, 2b, and 3), there are geographic distribution features that allocate donor organs within the local OPO area to lower risk patients, primarily on the basis of waiting time rather than severity. Regional and national patients at greater risk have lower priority than these local patients. In addition, a donor liver is not always available on a timely basis for the highest status persons on the waitlist. This results in substantial waitlist mortality for high-risk patients and, unfortunately, prevents them from receiving a trans-

plant. These realities of the previous allocation system mitigate the effects of nonrandom censoring.

Pediatric candidates for liver transplantation were not included in the study because of lack of sufficient data. Children do not have the same risk for death on the waitlist as adults, and separate analyses have been developed using a Pediatric End-Stage Liver Disease score.[12,13]

Finally, patients with fulminant liver failure (status 1) also were excluded. The MELD score was developed for individuals with chronic liver disease, so we focused on these patients. Because the liver allocation system recently made operational by the OPTN retains status 1 as a separate allocation class and only uses MELD-based allocation for those with chronic disease, the use of MELD scores to assess mortality risk among status 1 patients will be possible once enough data have been collected at the national level.

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