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Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease

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***Background/Aims*: The utility of the model for end stage liver disease (MELD) score in non-transplant patients, particularly in those with less severe chronic liver disease remains uncertain. We studied and compared the predictive abilities of the MELD score and the Child–Turcotte–Pugh (CTP) score for intermediate (1-year) and long-term (5-year) mortality.**

***Methods*: One thousand six hundred and eleven patients with chronic liver disease were studied. Observed and predicted survival curves were plotted to evaluate the predictive ability of the MELD score for survival. Receiver operating characteristic (ROC) curves was used to compare the MELD and CTP score. A multivariable model was constructed to examine predictors of mortality.**

***Results*: The MELD score was a good predictor of 1-year mortality in chronic liver disease (c-statistics for all subgroups $\geq$0.75) and of 3- and 6-month mortality in alcoholic hepatitis (c-statistic $\geq$0.83). The CTP score had similar predictive abilities as the MELD. Hepatic encephalopathy was a strong independent predictor of death (Hazard ratio—2.8, $P < 0.0001$).**

***Conclusions*: The MELD score is a valid prognostic score for intermediate term mortality in a heterogeneous population with chronic liver disease although the CTP score is equivalent in predicting survival. Inclusion of hepatic encephalopathy adds additional prognostic value to the MELD score.**

***Keywords*: Cirrhosis; Outcomes; Hepatic encephalopathy; Child–Turcotte–Pugh score; Receiver operating characteristic curves**

1. Introduction

The model for end stage liver disease (MELD) prognostic scoring system has been validated for short term and intermediate term mortality in a heterogeneous group of patients with cirrhosis and end stage liver disease (ESLD) [1,2] as well as alcoholic hepatitis and acute variceal bleeding [3,4]. Since February 2002, the MELD scoring system has replaced the Child–Turcotte–Pugh (CTP) score in prioritizing patients on the waiting list for liver transplantation in the United States [5].

Limited information exists on the role of the MELD score in assessing prognosis in patients with early stage cirrhosis. We examined the utility of MELD in predicting 1-year and 5-year survival in a cohort of patients with chronic liver disease referred to a tertiary care liver center including less advanced liver disease. We also examined the utility of the MELD score in alcoholic hepatitis.

In the group with severe end stage liver disease (ESLD)

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Abbreviations: MELD, model for end stage liver disease; CTP, Child–Turcotte–Pugh; ROC, receiver operating characteristic; ESLD, end stage liver disease; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; INR, international normalized ratio; ALD, alcoholic liver disease; WBC, white blood cell count; CLD, chronic liver disease; HR, hazard ratio; DNA, deoxyribonucleic acid.

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studied by Kamath et al. [1], the separate complications of ESLD did not add any prognostic ability to the MELD score. We evaluated if the complications of ESLD (hepatic encephalopathy, variceal bleeding, ascites) have any prognostic ability to predict 1-year and long-term prognosis independent of the MELD score.

2. Methods

We performed a retrospective cohort study using 2859 patients from the hepatology clinics and the hepatology inpatient service of a university hospital between January 1994 and December 2001. Patient records were identified by discharge diagnosis codes from a prospective patient database. Patients with transient liver test abnormalities, acute liver diseases, hepatocellular carcinoma (35), cholangiocarcinoma (6), and HIV (10) and those who died of cardiac disease ($n = 10$) were excluded. The 1611 consecutive patients with chronic liver disease were analyzed in the final cohort. To examine the predictive abilities of MELD in alcoholic hepatitis, we separately considered 98 patients with alcoholic hepatitis.

The determination of etiology of chronic liver disease was made using standard diagnostic criteria [6]. Hepatitis C virus (HCV) or hepatitis B virus (HBV) was diagnosed by serological detection of hepatitis C antibody (confirmed by RNA PCR) and hepatitis B surface antigen, respectively. Alcoholic liver disease (ALD) was diagnosed in those with consumption of at least 40 g of alcohol daily for 5 years or more [7]. Stage of liver disease at presentation was categorized as: ESLD, compensated cirrhosis, hepatitis, liver function test abnormalities or jaundice only.

Complications of ESLD were recorded at the initial visit. The diagnosis of hepatic encephalopathy was made according to the criteria of Gitlin [8] after exclusion of space occupying intracranial lesions as well as concurrent metabolic, endocrine, traumatic or epileptiform disorders and alcoholic or drug intoxication. The recording of hepatic encephalopathy was prior to transjugular intrahepatic portosystemic shunt (TIPS) placement. The MELD score was calculated at the initial visit using the formula: 3.8 lnBilirubin + 11.2 lnINR + 9.6 lnCreatinine + 6.4 [1]. Child–Turcotte–Pugh scores were calculated as described [6]. Patients with alcoholic liver disease were considered abstinent if they reported at the initial visit that they had quit alcohol or quit drinking by the first follow up visit and remained abstinent during subsequent follow up. At least six months without any alcohol intake and with no relapses was classified as abstinence for this study. Random alcohol screens were performed as clinically necessary. Active tobacco use was considered if patients were smoking actively or had quit only within 6 months of initial presentation.

Survival was calculated from the date of first clinical contact. Mortality data were abstracted from hospital records and the national social security death index. Survival was censored at transplantation. Kaplan–Meier estimates of survival were obtained for MELD categories with log-rank tests used to compare survival by MELD category. Predicted survival curves for the MELD categories were obtained using the method of Ederer et al. [9]. The one sample log-rank test was used to test the difference between observed and predicted survival curves [10]. Cox proportional hazards regression models were used to evaluate the impact of the MELD score as a continuous value. Final estimates and standard errors for the time varying effects of the MELD score were obtained using time-dependent covariates in a Cox model [11].

A multivariable Cox proportional hazards regression model was constructed to identify independent predictors of mortality and to evaluate if the complications of ESLD have independent prognostic value in addition to the MELD score. Adjustment was done for patients' age, gender, race, and etiology of liver disease, CTP score and its components, active alcohol and tobacco abuse. Hazard ratios with 95% confidence limits were reported. The Breslow test was used to handle time ties.

Kaplan–Meier estimates were also used to compare survival between patients with and without hepatic encephalopathy. Survival on the y-axis was plotted on a logarithmic scale with the slope of the curve at any given time representing the hazard rate at that time [12]. One year mortality within pre-defined MELD categories (Meld score ≤ 9, 10–19, 20–29, 30–39) was compared between patients with ESLD and those with compensated cirrhosis.

Receiver operating characteristics (ROC) curves were plotted to measure the performance of the MELD score and the CTP score for predicting 1-year mortality for the entire cohort as well as a broad spectrum of groups with chronic liver disease (see below). The c-statistic (equivalent to the area under a ROC curve) was used to evaluate the performance of the MELD and CTP scores with a score of more than 0.7–0.8 indicating a useful test and a score 0.8 or more a good test [13–15]. To test the performance of the MELD and the CTP score in predicting 1-year mortality in a cohort of patients with less advanced chronic liver disease, we plotted the ROC curve for the cohort of patients with non-alcoholic liver disease. This cohort had a 1-year survival of 92% and a 5-year survival of 78%. ROC curves were also plotted for MELD and CTP score in patients with compensated cirrhosis (a group with a 1-year survival of 95% and a 5-year survival of 58%). The utility of the MELD and CTP scores were similarly tested for 3-month and 6-month mortality in patients with alcoholic hepatitis (defined as elevated WBC, GGT and AST/ALT ratio > 1.2 with active or recent alcohol use) with biopsy evidence of hepatitis where available. Area under the ROC curves was calculated using the maximal likelihood estimation [16]. Comparison of the areas under the ROC curves was done utilizing standard errors estimated using the method of Hanley and McNeil [14].

Categorical variables were tested with the χ^2 test and continuous variables with the Mann–Whitney test. A two-sided P value of less than 0.05 was considered statistically significant.

The Institutional Review Board of the University of Wisconsin–Madison Medical School approved this study.

3. Results

Between 1994 and 2001, 1611 patients with chronic liver disease were seen at the University Hospital, 1196 (74%) in the outpatient clinic and 415 (26%) initially as inpatients. Alcoholic liver disease alone was the single most common diagnosis, accounting for 30% of all patients seen. The combination of alcohol and hepatitis C infection was reported in 14.5% and hepatitis C alone in 22%. Other etiologies made up a third of all patients with chronic liver disease (Table 1). Patients with hepatitis C virus and those with the combination of alcohol and hepatitis C were significantly younger than patients with alcoholic liver disease alone (median age 47 and 45 years versus 53 years, respectively), $P < 0.0001$. The alcohol-related diagnoses had a predominance of males (69–73%) unlike other diagnoses of chronic liver disease (34–56%). A majority of the patients with ALD (70%) presented initially with

Table 1
Baseline characteristics of chronic liver disease cohort

Age (range)	50 ± 12.5[a] (18–86)
Gender (% male)	55
Race (% Caucasian)	88
Etiology of chronic liver disease (%)	
ALD	482 (29.9)
ALD + HCV	234 (14.5)
HCV	351 (21.8)
Others	544 (33.8)
ESLD (%)	647 (40)
MELD Score	9.7 ± 9.2[a]
CTP Score	6 (5–14)[b]

ESLD, end-stage liver disease; MELD, model for end-stage liver disease, CPT, Child–Pugh–Turcotte; ALD, alcoholic liver disease, HCV, hepatitis C virus.

[a] Age (in years) and MELD are expressed as mean ± standard deviation.

[b] CTP score is expressed as median and range.

clinical manifestations of ESLD whereas for other etiologies including those with the combination of ALD and HCV, ESLD was seen in a minority at initial presentation (11–41%).

Outcomes for the cohort are shown in Table 2. Two hundred and ninety two (18%) of the patients underwent liver transplantation, patients with HCV (8%) significantly less so than with other etiologies during the period of observation (18–20%). Thirty-five hepatocellular carcinomas were diagnosed during the study period. Thirteen (3%) of the patients with ALD, 6 (2.9%) patients with ALD + HCV, 9 (2.9%) with HCV alone and 7 (1.6%) with other causes of liver disease developed hepatocellular carcinoma.

Kaplan–Meier estimates of survival for MELD categories are displayed in Fig. 1A. Higher MELD scores were associated with decreased survival; in pairwise comparisons, all categories are significantly different from each other (Fig. 1). Cox regression modeling showed that the impact of the MELD score on survival is initially very strong (HR 3.25, 95% CI 2.76–3.81 for each 10-step change in the MELD score), and decreases somewhat over the first year of follow up. Beyond 11 months of follow up, the impact of the MELD score on survival remains constant (HR 1.46, 95% CI 1.24–1.71 for each 10-step change in the MELD score). Predicted survival curves for the cohorts based on MELD categories are provided in Fig. 1B. The one sample log rank test demonstrated that except for MELD category 2 (MELD scores of 10–19), the observed and predicted survival curves are statistically not different for the different MELD categories. Using MELD as a continuous score, the difference in the observed and predicted survival curves was also non-significant (log rank $P = 0.18$).

In univariate analyses, patients with ALD had significantly higher mortality (1-year rate 16.4%) than patients with combined ALD + HCV (12%), HCV alone (3.4%) or other forms of liver disease (9%) (log rank test $P < 0.0001$). Five-year mortality was also higher in ALD (40%) and combined ALD + HCV (40%) than in those with HCV alone (19%, log rank test $P < 0.0001$). Patients with ALD however were also older than those with HCV or ALD + HCV and presented with more advanced liver disease.

Table 2
Outcomes of patients with chronic liver disease ($n = 1611$)

Follow up (months)	24 (1–72)
Died	
Total	321 (19.9%)
Within 3 months	102
Within first year	172
Transplanted	292 (18%)
Hepatocellular carcinomas	35 (2.2%)

Follow up—expressed as median (range). All other variables are number of patients with outcome of interest (percentages in parentheses).

Patients with hepatic encephalopathy had higher 1-year mortality than those without encephalopathy (log rank test $P < 0.0001$) (Fig. 2).

Predictors of survival were analyzed in multivariable Cox proportional hazards models for both the first year and the entire period of follow up (Table 3). Etiology of liver disease was not a significant predictor of survival after adjusting for the other explanatory variables in the model (Hazard ratio = 1.15, $P = 0.11$ Table 3). Mortality risk increased significantly with age as expected ($P < 0.00001$) and with male gender ($P < 0.0001$). The MELD score also predicted increased mortality, with each unit increase in the MELD score predicting a 4–9% increase in mortality ($P < 0.0001$). Hepatic encephalopathy was a strong, independent predictor of mortality (HR = 2.16, $P =< 0.0001$ for 1-year mortality and HR = 1.96, $P = 0.002$ for the entire period of follow up) (Table 3). The CTP score was also an independent predictor of 1-year mortality (HR = 1.30, $P = 0.006$) and approached significance for mortality over the entire follow up period as well (HR = 1.12, $P = 0.11$). Variceal bleeding ($P = 0.19$) and ascites ($P = 0.61$) did not contribute additionally to the predictive ability of MELD. Active tobacco use was also significant as an independent predictor of mortality over the entire follow up ($P = 0.03$). A higher mortality risk was seen in patients with ALD who continued to drink as compared to abstinent patients with ALD for both the entire period of follow up and 1-year mortality ($P =< 0.0001$).

When patients with end stage liver disease were examined separately, increasing age (HR = 1.04, $P = 0.0001$), hepatic encephalopathy (HR = 1.94, $P = 0.0012$), MELD score (HR = 1.07, $P < 0.0001$) and continued alcohol abuse in ALD patients (HR = 3.02, $P = 0.0002$) remained independent predictors of 1-year mortality.

Within each MELD category, higher 1-year mortality was seen in the patients with end stage liver disease as compared to the patients with compensated cirrhosis (Fig. 3).

Overall there were 321 deaths, 102 within 3 months and 172 within 1 year of presentation. The ROC curve c-statistic for the MELD as a predictor of 1-year mortality was 0.80 for all patients. In the non-alcoholic cohort ($n = 894$), the c-statistic was 0.79 for MELD and 0.82 for the CTP score ($P = 0.82$) (Fig. 4). For other subgroups the c-statistics are shown in Table 4. For the entire cohort of liver patients, considering 3-year mortality the c-statistic for the MELD score was 0.79 and for CTP scores 0.83 ($P = 0.10$). For 5-year mortality, the c-statistic for MELD was 0.69 and for CTP it was 0.74 ($P = 0.12$).

When the estimated risk for hepatic encephalopathy was added to that for the MELD score, the c-statistic for prediction of 1-year mortality for all patients improved from 0.80 to 0.85 and for patients with non-alcoholic liver disease from 0.79 to 0.89.

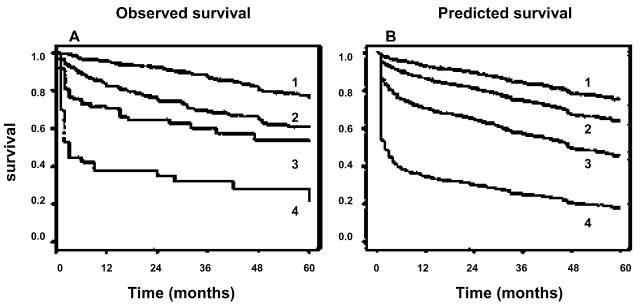


Fig. 1. Survival of cohort with chronic liver disease. Observed survival curves (Kaplan–Meier estimates) and predicted (Cox regression) survival curves predict increasing mortality with higher MELD categories. Categories: 1 = MELD ≤ 9, 2 = MELD 10 to 19, 3 = MELD 20 to 29, 4 = MELD ≥ 30. Pairwise comparisons: 1 vs 2, p < 0.0001; 1 vs 3, p < 0.0001; 1 vs 4, p < 0.0001; 2 vs 3, p = 0.004; 2 vs 4, p < 0.0001; 3 vs 4, p < 0.0001. Comparison of observed (A) and predicted (B) curves: Category 1 (≤9), p = 0.95; Category 2 (10–19), p = 0.05; Category 3 (20–29), p = 0.34; Category 4 (≥30), p = 0.51; Overall (non-categorized MELD), p = 0.18.

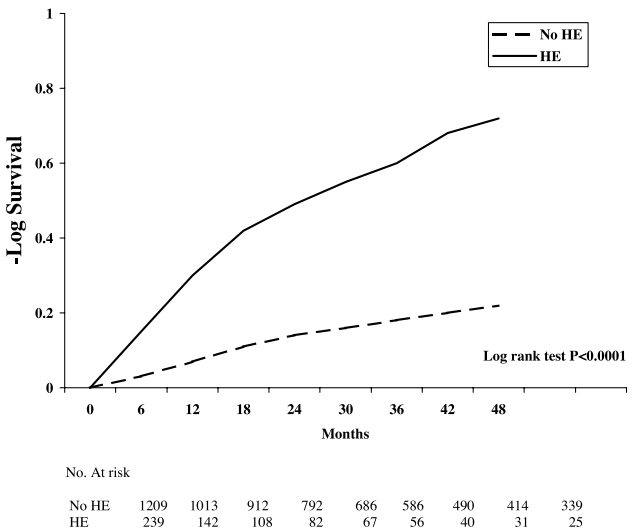


Fig. 2. Mortality differs by encephalopathy in chronic liver disease. In Kaplan–Meier analysis, patients with cirrhosis and hepatic encephalopathy had a significantly higher mortality rate than those with cirrhosis but no encephalopathy (log rank $P < 0.0001$) for 1-year mortality as well as for total duration of follow up. (HE—hepatic encephalopathy).

4. Discussion

Our study, utilizing a large cohort of patients with a broad spectrum of chronic liver disease, demonstrates that the MELD score predicts intermediate term (12-month) mortality with good sensitivity and specificity characteristics.

Previous validation studies of MELD have looked at patients with more advanced liver disease among whom the 3-month mortality ranged between 2 and 21% and 3-year mortality was 24% in the group with predominantly viral cirrhosis [1]. Demonstration of the validity of MELD for predicting 1-year survival in our relatively well-compensated chronic liver disease group, both in the outpatient and inpatient setting expands and broadens the utility of MELD in the objective assessment of prognosis of chronic liver disease.

Similarly the MELD score demonstrated useful predictive properties in predicting short-term mortality (both 3-month and 6-month) in patients with alcoholic hepatitis, a group with high short-term mortality [17,18]. Although these patients had high bilirubin levels, the c-statistic of the MELD and CTP score were similar suggesting that the 'ceiling effect' of bilirubin used in the CTP score is not of

Table 3
Predictors of mortality from chronic liver disease (all patients) Cox-proportional hazards regression

	Entire follow up period				1-Year mortality			
	Regression coefficient	Std error	Hazard ratio	*P* value	Regression coefficient	Std error	Hazard ratio	*P* value
Gender (male)	0.63	0.15	1.88	<0.0001	0.12	0.16	1.12	0.48
Age (years)	0.05	0.006	1.05	<0.0001	0.04	0.006	1.04	<0.0001
Race	−0.13	0.09	0.88	0.19	−0.11	0.05	0.95	0.66
MELD score[a]	0.04	0.01	1.04	0.0009	0.08	0.008	1.09	<0.0001
CTP score[b]	0.12	0.07	1.12	0.11	0.27	0.10	1.30	0.006
Variceal bleed	0.23	0.17	1.26	0.19	−0.04	0.19	0.96	0.84
Hepatic encephalopathy	0.67	0.22	1.96	0.002	0.77	0.19	2.16	<0.0001
Ascites	0.12	0.13	1.13	0.61	0.03	0.19	1.03	0.88
Etiology of liver disease[c]	0.14	0.08	1.15	0.11	0.03	0.09	1.04	0.70
Active alcoholism in ALD	1.11	0.22	3.01	<0.0001	1.03	0.26	2.81	<0.0001
Active tobacco use[d]	0.32	0.15	1.38	0.03	0.26	0.22	1.29	0.25

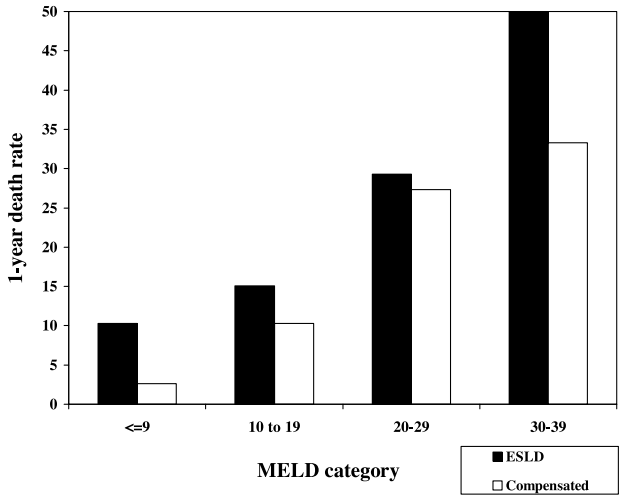
95% CI, 95% confidence interval; Std error, standard error.

[a] MELD score—applied as a continuous score. The hazard ratio is the increased risk of mortality associated with each unit increase in the MELD score.

[b] CTP Score—Child–Turcotte–Pugh Score (range 5–15). The hazard ratio is the increased risk of mortality associated with each unit increase in the CTP score: Gender—Risk of death in males compared to females; Race—White compared to other races; Encephalopathy, variceal bleed and ascites-mortality risk associated with the presence of these complications compared to their absence.

[c] Etiology of liver disease—Risk of mortality with alcoholic liver disease (ALD) compared to other etiologies.

[d] Active tobacco use—Risk of mortality compared to those who never used tobacco or quit >6 months prior to referral.



Average MELD In category				
ESLD (N)	5.7 (204)	13.7 (279)	23.7 (83)	33.6 (51)
Compensated Cirrhosis (N)	4.8 (116)	12.2 (69)	23.1 (15)	32.5 (4)

Fig. 3. One-year death rates for patients with and without end stage liver disease, categorized by MELD scores. Patients with any of the complications of ESLD (variceal bleeding, encephalopathy, ascites) had significantly higher 1-year mortality rates than patients with compensated cirrhosis within each MELD category. (ESLD—end stage liver disease).

major prognostic significance. The predictive and discriminant ability of the MELD score is highest in the first year of follow up after determination of a score. For longer-term mortality (3–5 years) the MELD score had significantly weaker predictive ability. This suggest that in clinical practice a single MELD measurement should not be used to predict survival beyond 1 year of follow up and long term follow up would be most accurate by repeated re-testing of MELD at regular intervals (1-year).

The CTP score performed relatively well compared with the MELD score in all categories and was an independent predictor of 1-year mortality even after adjusting for the MELD score. Other authors have recently reported that both

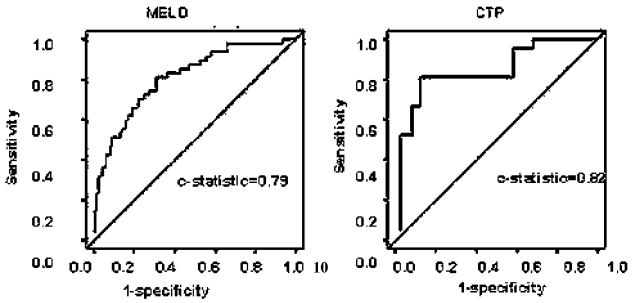


Fig. 4. Receiver operating characteristic (ROC) curves for the MELD score in predicting 1-year mortality. For non-alcoholic liver disease, the ROC curves demonstrate that both the MELD score (c-statistic = 0.79) and The CTP score (c-statistic = 0.82) have similar predictive abilities for 1-year mortality. (CTP—Child–Turcotte–Pugh score, MELD—model for end stage liver disease).

the MELD and CTP scores are fairly equivalent for predicting intermediate and short-term mortality in patients with cirrhosis [19] and in patients with advanced liver disease undergoing TIPS [20,21] although one study did show a superior discrimination power of MELD compared to CTP scores for predicting early mortality after TIPS [22]. The independent predictive ability of the CTP score may be because unlike the MELD score it accounts for hepatic encephalopathy. The advantages of MELD lie in the objective parameters that it uses which are statistically weighted according to significance [1], and that it is a continuous scale with no floor or ceiling effects.

When we examined the MELD score in the categories described by Kamath et al. [1], the discriminant ability of the MELD score was evident for 1-year mortality among both patients with ESLD and those with compensated cirrhosis (Fig. 4). However 1-year mortality was higher in the group that had experienced any of the complications of ESLD than in patients with compensated cirrhosis within the same MELD category. In our multivariate model hepatic encephalopathy was a strong and independent predictor of mortality in addition to the MELD score. This observation is consistent with previous studies of prognosis that have shown that hepatic encephalopathy is a strong, independent

Table 4
MELD and Child–Pugh scores predict mortality in a broad spectrum of chronic liver disease

	c-statistics—ROC curves MELD score	Child–Pugh–Turcotte score	*P* value
1-Year mortality			
Non-alcoholic liver disease	0.79 (0.72–0.86)	0.82 (0.74–0.89)	0.82
Compensated cirrhosis	0.75 (0.59–0.90)	0.66 (0.50–0.82)	0.12
3-Month mortality			
Alcoholic hepatitis	0.85 (0.76–0.95)	0.85 (0.75–0.95)	0.50
6-Month mortality			
Alcoholic hepatitis	0.83 (0.74–0.93)	0.81 (0.70–0.92)	0.33

Receiver operating characteristic curves—c statistics for predicting 1-year mortality in subgroups of patients with chronic liver disease reported (c-statistics are equivalent to the area under the ROC curve. More than 0.8 is a good predictive model and >0.7 a useful model). 95% confidence intervals and the *p* value for difference in the c-statistics are reported.

predictor of mortality in patients with cirrhosis [23,24]. A recent publication has also demonstrated that the MELD score does not correlate well with severity of hepatic encephalopathy [25]. Taken together, our data and those of Kamath indicate that other factors, not accounted for by MELD, particularly hepatic encephalopathy, differentially contribute to prognosis among hospitalized compared to outpatients with chronic liver disease.

Continued alcohol use in patients with alcoholic liver disease had a high adjusted relative risk for mortality when compared to all other etiologies of liver disease, including abstinent alcoholics with cirrhosis, thereby reiterating long-standing observations about the influence of alcohol use on the course of alcoholic cirrhosis [26]. Tobacco abuse also contributed independently to mortality in our cohort. Tobacco has been shown to independently increase fibrosis and histological activity scores in patients with viral hepatitis, even in the absence of alcohol intake [27,28].

Limitations to our study include those inherent in any retrospective cohort study. The diagnosis of hepatic encephalopathy was made clinically and may be prone to inaccuracies in assessment particularly in those with subclinical encephalopathy. However patients with the earliest clinical stages of encephalopathy as manifested by insomnia, sleep cycle reversal and mood and personality changes were included as were those with more severe manifestations and care was taken to include only those cases where alternative diagnoses had been excluded. Despite careful follow up and consultation with an alcohol abuse counselor, under-reporting of continued alcohol abuse is also possible in a retrospective design and would tend to exaggerate the mortality impact of alcoholic liver disease in reportedly abstinent patients. However no difference in survival was seen by etiology of liver disease in our cohort indicating that the impact of under-reporting of alcohol abuse may have been minimized.

Our data validate the MELD score as a useful prognostic score for intermediate term mortality in a broad spectrum of patients with compensated cirrhosis as well as ESLD and alcoholic hepatitis. Nevertheless for all cohorts examined thus far the MELD and the CTP score provide equally good prognostic information. Although the higher discriminant ability (because of the continuous scale) of the MELD score give it an advantage over the CTP score in triaging patients with ESLD for liver transplantation, this discriminant ability is not as useful in non-transplant patients with cirrhosis.

For the same category of MELD scores, the clinical parameters of ESLD, particularly hepatic encephalopathy, provide additional useful prognostic information than the use of the MELD score alone. The individual complications of ESLD though relatively subjective are more clinically informative measures to use than inpatient versus ambulatory status. It remains to be seen whether MELD replaces CTP in everyday clinical practice in the non-transplant setting [29].

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