

Systematic review: the model for end-stage liver disease – should it replace Child-Pugh’s classification for assessing prognosis in cirrhosis?

E. CHOLONGITAS, G. V. PAPTAEODORIDIS, M. VANGELI, N. TERRENI, D. PATCH & A. K. BURROUGHS

Liver Transplantation and Hepatobiliary Medicine Unit, Royal Free Hospital, London, UK

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SUMMARY

Background: Prognosis in cirrhotic patients has had a resurgence of interest because of liver transplantation and new therapies for complications of end-stage cirrhosis. The model for end-stage liver disease score is now used for allocation in liver transplantation waiting lists, replacing Child-Turcotte-Pugh score. However, there is debate as whether it is better in other settings of cirrhosis.

Aim: To review studies comparing the accuracy of model for end-stage liver disease score vs. Child-Turcotte-Pugh score in non-transplant settings.

Results: Transjugular intrahepatic portosystemic shunt studies (with 1360 cirrhotics) only one of five, showed model for end-stage liver disease to be superior to Child-Turcotte-Pugh to predict 3-month mortality, but not for

12-month mortality. Prognosis of cirrhosis studies (with 2569 patients) none of four showed significant differences between the two scores for either short- or long-term prognosis whereas no differences for variceal bleeding studies (with 411 cirrhotics). Modified Child-Turcotte-Pugh score, by adding creatinine, performed similarly to model for end-stage liver disease score. Hepatic encephalopathy and hyponatraemia (as an index of ascites), both components of Child-Turcotte-Pugh score, add to the prognostic performance of model for end-stage liver disease score.

Conclusions: Based on current literature, model for end-stage liver disease score does not perform better than Child-Turcotte-Pugh score in non-transplant settings. Modified Child-Turcotte-Pugh and model for end-stage liver disease scores need further evaluation.

HISTORICAL BACKGROUND

In 1964, Child and Turcotte¹ published a classification to assess the operative risk in cirrhotic patients who recovered from variceal bleeding, undergoing portosystemic shunt surgery. They considered five variables selected by clinical experience: ascites, encephalopathy, nutritional status and serum levels of bilirubin and albumin, classifying patients in class A, B or C in

relation to best (A), moderate (B), or worse (C) prognosis.

In 1973, Pugh *et al.*² used a modified version of this classification for patients undergoing surgical transection for oesophageal varices. They replaced nutritional status with prothrombin time (PT) and assigned a score ranging from 1 to 3 to each variable. Subsequently, this classification was used to predict the outcome of surgery in cirrhotic patients in general, and more recently, to stratify patients on the waiting list for liver transplantation (LT). Similar to the original Child’s grading, neither the division of the grades nor the scoring system was validated statistically.

Correspondence to: Dr E. Cholongitas, Liver Transplantation and Hepatobiliary Medicine Unit, Royal Free Hospital, Pond Street, London NW3 2QG, UK.
E-mail: cholongitas@yahoo.gr

Over many years, the routine use of these classifications have revealed some problems. First, both the degree of ascites and encephalopathy are subjective assessments evaluated by physical examination alone. The widespread use of ultrasonography has led to more sensitive detection of ascites, but it is unclear how ascites diagnosed by ultrasonography alone is being categorized by various authors. Hepatic encephalopathy (HE) is often assessed by psychometric testing or slowing of frequency on an electroencephalography (EEG). It is not clear how these abnormalities are fitted into Child-Turcotte-Pugh (CTP) classification. Secondly, both ascites and HE can be influenced by therapy such as diuretics, albumin infusion and lactulose and it is not clear if ascites and HE are scored at their best, or worst, or independent of specific therapy.

As regards the continuous variables in the CTP classification, they are categorized with arbitrary cut-off points. Thus, patients with bilirubin of 55 μM who have a better prognosis than those with a bilirubin of 250 μM ; in the CTP classification both these patients have the same score of severity for bilirubin concentration ('the ceiling effect'). Changes in bilirubin concentration with specific therapy such as ursodeoxycholic acid (for which improvements is in doubt) are difficult to interpret using CTP classification.^{3, 4} A similar problem exists for serum albumin so that the CTP classification does not differentiate between patients with an albumin of 17 g/L vs. 25 g/L ('the floor effect'). The increased use of intravenous albumin if given close to an assessment may further complicate the interpretation.

Pugh's modification of Child-Turcotte criteria substituted PT for nutrition. However, the PT (expressed in s) as well as the prothrombin index (expressed as a percentage of the control value), varies depending on the sensitivity of the thromboplastin reagent used so that it can vary greatly from laboratory to laboratory. CTP scoring for PT does not take this into account. The International Normalized Ratio (INR) now overcomes this using a standardized thromboplastin reagent. The conversion from INR to PT and vice versa using a normogram is not used routinely and INR has not been incorporated into CTP score. Although it would seem sensible to use INR, it should be remembered that INR was designed to standardize the anticoagulation effect of warfarin and not to evaluate the severity of liver disease. As a result, INR may not be valid to assess liver impairment,^{5, 6} despite its use in model for end-stage liver disease (MELD) scoring (see below).

Partly due to the grading system, the CTP classification does not distinguish the 'mild' grade C from the severe grade C patient with sufficient clinical discrimination. Moreover, it does not include a measure of renal function, which is a well-established prognostic marker in cirrhosis, as well as in acute liver disease.⁷⁻⁹

During recent years, several new prognostic models have been developed and validated in order to overcome these limitations of the CTP score. The performance of the majority of these models was evaluated statistically by measurement of their discriminative ability, estimated by the concordance (c)-statistic [i.e. the area under the Receiver Operator Characteristic (ROC) curve].¹⁰ The latter describes the ability of the model to separate patients who die, from those with the same score who live. The c-statistic ranges from 0 to 1, with 0.5 corresponding to what is expected by chance alone and 1.0 to perfect discrimination. In general, a c-statistic >0.7 indicates a useful test, whereas a value >0.8 indicates very good prognostication, but can never be 1.0. For this reason, prognostic models cannot predict the outcome of individual patients but give estimates: e.g. for a model with an area under the ROC curve 0.8-0.9, by definition a significant proportion of the patients (10-20%) has an outcome which is not predicted accurately.

In 2000, Malinchoc *et al.*¹¹ published an article on 'a model to predict poor survival in 231 patients who had undergone transjugular intrahepatic portosystemic shunt (TIPS)'. They developed a statistical model to (i) predict survival and (ii) identify those patients whose liver-related mortality post-TIPS would be 3 months or less. Cox proportional hazard regression identified serum concentration of bilirubin and creatinine, the INR (for PT), and the aetiology of cirrhosis as predictors of survival. In particular, these variables were used to calculate a risk score for undergoing elective TIPS by combining their prognostic values with their regression coefficient: $R = 0.957 \times \log_e(\text{creatinine mg/dL}) + 0.378 \times \log_e(\text{bilirubin mg/dL}) + 1.120 \times \log_e(\text{INR}) + 0.643 \times (\text{cause of cirrhosis: } 0 \text{ for alcohol related and cholestatic liver disease; } 1 \text{ for viral hepatitis and other liver disease})$. This model was found to be superior to both CTP classification and score in predicting survival, especially in patients with CTP class B with impaired renal function.

In 2001 the same group,¹² used this MELD, to score severity of liver disease and consequent risk of mortality for patients awaiting LT. The MELD score is slightly modified from the original TIPS risk score, multiplying

the score by 10 and then rounding up to the nearest integer. The MELD score formula is: $R = 9.6 \times \log_e(\text{creatinine mg/dL}) + 3.8 \times \log_e(\text{bilirubin mg/dL}) + 11.20 \times \log_e(\text{INR}) + 0.64 \times (\text{cause of cirrhosis: 0 for alcohol related or cholestatic liver disease; 1 for viral hepatitis and other liver disease})$.

The model's validity was tested¹² with data obtained from different patient populations including (i) patients hospitalized for hepatic decompensation, (ii) ambulatory patients with non-cholestatic cirrhosis, (iii) patients with primary biliary cirrhosis (PBC) and unselected patients from the 1980s with cirrhosis ('historical' patients). In these groups the model's ability to accurately predict death within 3 months was evaluated using the c-statistic.

The MELD score compared with the CTP score was able to predict death within 3 months with a c-statistic of (i) 0.87 for hospitalized patients (compared with 0.84 for CTP score), (ii) 0.80 for non-cholestatic ambulatory patients, (iii) 0.87 for PBC patients and (iv) 0.78 for 'historical' cirrhotic patients. The authors¹² evaluated the addition of a history of important complications of portal hypertension such as ascites, encephalopathy, variceal bleeding and spontaneous bacterial peritonitis (SBP) to the MELD score for each patient. However, only a minimal improvement in the prediction of the 3-month mortality was obtained. Importantly, no calibration of the model was evaluated, i.e. an assessment of whether it performed uniformly well across the spectrum of severity of liver disease.

In the original prognostic model,¹¹ designed for patients selected for TIPS, cholestatic and alcoholic liver disease were given a lower risk score. In cholestatic disease, the bilirubin concentration has a different association with liver dysfunction [and reduction with ursodeoxycholic acid (UDCA) therapy] compared with other liver diseases. This was also true in the Child-Pugh (CP) modification in which the A, B, C categories have different bilirubin boundaries. The modified model that excluded the aetiology of liver disease found that in the four patient validation sets, which there was minimal change of the c-statistic, and so aetiology was dropped. However, there remains an issue of whether individuals with diseases in which bilirubin falls with therapy, e.g. ursodeoxycholic acid in primary sclerosing cholangitis (PSC) and PBC, do have an improved prognosis or not,⁴ whereas in alcoholic cirrhotics with abstinence, even if initially very jaundiced, prognosis improves.

The authors concluded that MELD score showed advantages compared with the CPT score and proposed the MELD score as criterion for organ allocation for LT. An editorial¹³ agreed with them '...MELD score, with its applicability to the pretransplantation prognosis, easy to use and verifiability, is a useful addition to the array of prognostic instruments and appears likely to dislodge the CP system from its perch'.

The study by Wiesner *et al.*,¹⁴ published in 2003, confirmed the predictive accuracy of MELD score for short-term (3 months) outcome in patients on the liver transplant waiting list and could be applied to the liver allocation system. Although one must bear in mind that in this context, allocation by MELD score represents a justice and not a utility system,¹⁵ the first results after MELD implementation are satisfactory: for the first time after 20 years, there was a reduction in the number of patients on the waiting list and a significant decrease in the presence of severe HE at the time of LT, which suggested that HE was exaggerated by transplant centres, when CTP score was used for liver allocation.¹⁶ Furthermore, there was a decrease in new registrations and in mortality of patients on the waiting list and an increase in the number of cadaveric transplants for almost all aetiologies.¹⁷⁻¹⁹

Despite its particular and specific development in the area of liver donor allocation, MELD has also been reported as the novel and better prognostic score to CTP for many complications or therapies in cirrhosis. Is this enthusiasm justified particularly as MELD was developed solely to evaluate 3-month mortality to patients already listed for LT? In this review, we examine the evidence for the prognostic utility of MELD compared with CTP score in non-transplant settings.

MELD IN CIRRHOTICS WITH TIPS PLACEMENT

Schepke *et al.*²⁰ compared the prognostic prediction by MELD score with CTP and Emory scores²¹ in 162 consecutive cirrhotics who had TIPS, evaluating survival after 3, 12, 24 and 36 months. In the multivariate Cox model only bilirubin, sodium (Na) and MELD score [hazard ratio (HR) 2.086, 95% CI: 1.530-2.846], but neither CTP nor Emory score were identified as independent predictors of survival. However, the c-statistics for the prediction of survival after 3, 12, 24 and 36 months were only marginally different between the MELD and CTP scores, whereas the MELD score was significantly better than the

Table 1. Prediction of 3-month mortality based on MELD and CTP score in cirrhotic patients underwent TIPS placement

Author	Patients (N)	MELD score†	CTP score†	P-value
Schepke <i>et al.</i> ²⁰	162	0.71	0.72	N.S.
Salerno <i>et al.</i> ^{*22}	140	0.84	0.70	0.038
Angermayr <i>et al.</i> ^{*26}	475	0.72	0.70	N.S.
Ferral <i>et al.</i> ²⁷	166	0.76	0.78	N.S.

MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh score; N.S., not significant; TIPS, transjugular intrahepatic portosystemic shunt; ROC, Receiver Operator Characteristic.

* The end point was either death or liver transplantation.

† The predictive accuracy is based on the area under the ROC curve.

Table 2. Predictive accuracy of MELD and CTP score for 12-month survival in cirrhotic patients underwent TIPS placement

Author	Patients (n)	MELD score†	CTP score†	P-value
Schepke <i>et al.</i> ²⁰	162	0.73	0.67	N.S.
Cejna <i>et al.</i> ²⁵	349	0.78	0.67	0.059
Salerno <i>et al.</i> ^{*22}	140	0.69	0.66	N.S.
Angermayr <i>et al.</i> ^{*26}	475	0.66	0.66	N.S.

MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh score; N.S., not significant; TIPS, transjugular intrahepatic portosystemic shunt; ROC, Receiver Operator Characteristic.

* The end point was either death or liver transplantation.

† The predictive accuracy is based on the area under the ROC curve.

Emory score, except for the 3-month survival estimate (Tables 1 and 2).

Salerno *et al.*²² studied 140 cirrhotics who had elective TIPS. During a median follow-up of 23.7 months, 55 patients died, 14 underwent LT and seven were lost to follow-up. The c-statistic of MELD score, as proposed by Malinchoc *et al.*,¹¹ for 3-month survival was 0.84 (95% CI: 0.74–0.94), significantly better than that of CTP score (0.70; 95% CI: 0.52–0.89; $P = 0.038$). However, the discriminative power of the MELD score for 6- and 12-month survival [0.81 (95% CI: 0.70–0.910) and 0.71 (95% CI: 0.58–0.84), respectively] was not significantly different from that of CTP score [6 months: 0.69 (95% CI: 0.56–0.83), $P = 0.07$; 12 months: 0.66 (95% CI: 0.54–0.78), $P = 0.41$].

Salerno *et al.*²² also divided patients in subgroups, according to the three classes of CTP or to quartiles of the MELD score.¹¹ Child A had a better survival than Child B or C patients ($P = 0.013$), but Child B and C patients did not differ in their survival probabilities ($P = 0.26$). Similarly, survival did not differ between

the first, second and third quartile of the MELD score (0–1.16; $P = 0.57$), while it was significantly worse in the fourth quartile (1.17–2.27; $P = 0.0001$). The overall population was then separated into two groups (low and high risk) with a cut-off at the 75th percentile of the MELD score 1.17. When the predicted and the observed survival rates of each subgroup were compared, MELD score overestimated the general risk to die, but it identified two subgroups of Child C patients with different overall survival ($P = 0.027$). This suggests that CP scoring does not sufficiently discriminate prognosis in patients with severe liver disease.

Alessandria *et al.*²³ confirmed that the MELD score overestimated the risk of death in 68 cirrhotics who underwent elective TIPS placement, particularly in the group of cirrhotics with refractory ascites (as indication for the TIPS placement) and creatinine levels >1.5 mg/dL. Interestingly, in the multivariate Cox regression analysis, only the age of the patients was independently associated with short- and long-term (24 months) survival after TIPS. Their results are in contrast to the randomized-control trial by Salerno *et al.*,²⁴ in which the MELD score and the type of treatment (TIPS placement vs. paracentesis plus albumin infusion) were the only independent predictors of mortality ($P = 0.009$ and 0.008, respectively).

Cejna *et al.*²⁵ analysed 349 cirrhotics who underwent TIPS; 261 for prevention of variceal rebleeding and 88 for refractory ascites. Both CPT and MELD separated groups of patients with significantly different survival. CPT and MELD correlated significantly (Spearman $r = 0.6$, $P < 0.0001$). Survival was not affected by the aetiology of cirrhosis. Both scores had similar predictive value with no significant difference. In viral-related cirrhosis and in cirrhotics with refractory ascites, both scores did not significantly correlate with survival whereas they did for alcoholic cirrhosis (CPT: $r = -0.31$, $P = 0.0006$; MELD: $r = -0.24$, $P = 0.0007$).

Angermayr *et al.*,²⁶ from the same centre, analysed retrospectively the largest series ($n = 475$) of cirrhotics who had elective TIPS placement. In multivariate analysis, MELD was the single independent predictor for both overall and 3-month survival. However, the predictive accuracy of MELD score for 1-month, 3-month and 1-year survival was not significantly different, compared with the CPT (c-statistics for 3-month survival: 0.72 vs. 0.70). Finally, Ferral *et al.*²⁷ made a retrospective evaluation in 166 cirrhotics who underwent elective TIPS. The c-statistic for

3-month survival of MELD score was 0.76 compared with 0.78 for CTP score.

In conclusion, all but one study²² did not confirm the superiority of the MELD score to the CPT score in cirrhotics who undergoing elective or emergency^{20, 25–27} TIPS placement (Tables 1 and 2). The discrepant results could be attributed to the exclusion of patients with bilirubin > 6 mg/dL and the lower mean value of baseline bilirubin (1.3 mg/dL) in the study by Salerno *et al.* (24), compared with the other studies (> 2.2 mg/dL). However, Salerno *et al.*²² also found that the MELD score had limitations, because it overestimated the risk of death, a finding confirmed recently by Alessandria *et al.* (23). These results are interesting, because the original cohort of cirrhotics, in which the MELD score based its development, where those who underwent TIPS placement.¹¹ This exemplifies that generalizability of prognostic models in other cohorts with similar characteristics to the original cohort may not be as good as expected.

MELD AND VARICEAL BLEEDING

Chalasani *et al.*²⁸ compared MELD and CTP scores in 239 consecutive cirrhotics following acute variceal bleeding. The mean CTP and MELD scores were 8.8 ± 2.2 and 11 ± 8 , respectively. The in-hospital and 1-year mortality rates were 14.2% and 27%, respectively. MELD was predictive of in-hospital mortality (c-index: 0.82; 95% CI: 0.72–0.92). However, its prognostication was not different than CTP (c-index: 0.85; 95% CI: 0.76–0.94). For 1-year mortality rates, MELD had a c-statistic of 0.75 (95% CI: 0.67–0.82) but it was not different than CTP score (c-statistic: 0.78; 95% CI: 0.70–0.86). The discriminative ability of the

MELD score was also assessed after excluding aetiology of liver disease: the c-statistic for in-hospital and 1-year mortality was 0.83 (0.74–0.92) for MELD and 0.78 (0.69–0.87) for CTP without statistical difference.

Amitrano *et al.*²⁹ evaluated 172 cirrhotics [54 with hepatocellular carcinoma (HCC)] admitted for the first episode of variceal bleeding. Survivors at 6 weeks and 3 months had significantly higher MELD scores on admission, compared with non-survivors. Similar to the previous study, the area under the ROC curve of MELD and CTP scores were not significantly different for prediction of 6-week (0.80 vs. 0.76, $P = 0.25$) or 3-month (0.79 vs. 0.76, $P = 0.34$) mortality. The cut-off value of 15 points for MELD score had the best sensitivity and specificity to distinguish survivors from non-survivors, particularly, if MELD > 15 with advanced HCC, the latter having independent prognostic significance for 3-month survival.

MELD IN CHRONIC LIVER DISEASE

MELD vs. CTP scores

Botta *et al.*³⁰ evaluated the short- and medium-term prognosis in a European series of 129 cirrhotics followed for at least 1 year, comparing the MELD and CTP scores (Table 3). All patients had monoethylglycinexylidide (MEGX) test. They recorded 12 deaths within 6 months and 31 within 1 year of follow-up. The CPT and MELD score, as well as MEGX serum levels were significantly different between survivors and non-survivors. Serum creatinine, INR and MEGX60 were independently associated with 6-month mortality. The same variables and ascites were associated with 1-year mortality. MELD score showed significant correlation with both

Table 3. Predictive value of MELD and CTP score for mortality in patients with chronic liver disease

Author	Patients (N)	Multivariate analysis	Predictive accuracy*	P-value
Said <i>et al.</i> ³⁴	1611	1 year: MELD, CTP, encephalopathy 7 years: MELD, encephalopathy	3 years: MELD = 0.79, CPT = 0.83 5 years: MELD = 0.69, CPT = 0.74	N.S.
Sheth <i>et al.</i> ³¹	34	–	1 month: MELD = 0.82, DF = 0.86	N.S.
Dunn <i>et al.</i> ³²	73	MELD	1 month: MELD = 0.83, DF = 0.74 3 months: MELD = 0.86, DF = 0.83	N.S.
Botta <i>et al.</i> ³⁰	129	Cr, INR, MEGX60 (for 1 year: plus ascites)	6 months: CTP = 0.69, MELD = 0.67, MEGX60 = 0.68	N.S.

MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh score; DF, discrimination function; Cr, creatinine; MEGX, monoethylglycinexylidide test; N.S., not significant; ROC, Receiver Operator Characteristic; INR, International Normalized Ratio.

* The predictive accuracy is based on the area under the ROC curve.

MEGX ($r = -0.542$, $P < 0.0001$) and CPT ($r = 0.817$, $P < 0.0001$). The c-statistics for CTP, MELD and MEGX60 were similar for 6-month (0.82, 0.79 and 0.82, respectively) and 12-month survival (0.69, 0.67 and 0.68, respectively).

Sheth *et al.*³¹ used the MELD score and discrimination function (DF) [$4.6 \times (\text{patient's PT} - \text{control PT}) + \text{total bilirubin (mg/mL)}$] in assessing prognosis and 30-day mortality in 34 patients with alcoholic hepatitis (AH). A DF score >32 identified patients who had $>50\%$ mortality at 1 month. The mean MELD score at admission for survivors at 30 days was 4.3, while for non-survivors it was 18.7. Although the MELD and DF scores had similar area under the ROC curves for prediction of 30-day mortality (0.82 and 0.86, respectively), and the same sensitivity (86%) for the optimal cut-off points (MELD: >11 points and DF: >32 points), the MELD score had significantly better specificity, compared with DF (82% vs. 48%) for the same cut-off points. Thus, a MELD score of >11 identified more accurately those patients with AH at high risk of short-term mortality. An elevated bilirubin >8 mg/dL and the presence of ascites were highly predictive of mortality, with a sensitivity of 71% and a specificity of 96%.

The accuracy of MELD score to predict mortality in AH was confirmed in the study of Dunn *et al.*³² The authors evaluated retrospectively 73 patients with AH and found that the c-statistics for MELD score for 1- and 3-month mortality were 0.83 and 0.86, respectively without significant difference compared with the DF (c-statistic 0.74 and 0.83, respectively). For the optimal cut-off points (MELD: 22 and DF: 41), both scores had the same sensitivity (0.75), but DF again had lower specificity, compared with MELD score (0.69 vs. 0.75). In multivariate analysis, MELD score was the only predictive factor for 3-month mortality.

Giannini *et al.*³³ evaluated the 1-year prognostic utility of the aspartate to alanine aminotransferase ratio (AST/ALT), MELD and CPT in 99 hepatitis C virus (HCV)- or hepatitis B virus (HBV)-positive cirrhotic patients prospectively followed up for at least 1 year. AST/ALT ratio was correlated to both MELD and CPT scores ($P \leq 0.0001$). In addition, baseline AST/ALT ratio, MELD and CPT were higher in patients who died. The ROC curves identified an AST/ALT ratio cut-off of 1.2 with 87% sensitivity and 52% specificity, and MELD cut-off of 8.8 with 57% sensitivity and 74% specificity in discriminating between survivors and those who died. Kaplan–Maier survival curves showed that both AST/

ALT ratio ($\chi^2 = 116.2$, $P < 0.0001$) and MELD ($\chi^2 = 76.1$, $P < 0.0001$) discriminated similarly between those who survived and those who died. These findings seem to suggest a prognostic role for the AST/ALT ratio and a complementary use to both MELD and CPT.

Said *et al.*³⁴ evaluated the predictive ability of the MELD score in 1611 patients with chronic liver disease and found that it had good predictive value, particularly in the first year but was poorer thereafter. This suggests as expected that MELD is not sufficiently calibrated to give good estimates of survival in early stage cirrhosis. In clinical practice, MELD should not be used to predict survival for more than a year ahead. In a multivariate Cox proportional hazards model, MELD score was an independent predictor of both 1- and 7-year survival ($P < 0.0001$ and $P = 0.0009$, respectively), but CPT score had also a good predictive ability for 1-year survival ($P = 0.006$) and approached significance for 7-year survival. Interestingly, HE was also an independent predictor factor for 1- and 7-year survival ($P < 0.0001$ and $P = 0.002$, respectively). The area under the ROC curves demonstrated that MELD and CTP score were not significantly different in predicting 1-year mortality in non-alcoholic liver disease (0.79 and 0.82, respectively), nor compensated cirrhosis (0.75 and 0.66, respectively), and neither for 3- (0.85 for both) and 6-month mortality in AH (0.83 and 0.81, respectively). When HE was added to the MELD score, the area under the ROC curve at 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.

MELD vs. CTP and modified CTP scores

The development of renal failure in cirrhotics is the most important predictor factor of survival,^{35, 36} and it is possible that the perceived superiority of MELD to CTP in chronic liver disease is related to using serum creatinine as a variable (Table 4).

Gunsar *et al.*³⁷ analysed a cohort of 222 cirrhotics with prospectively collected parameters of dry weight, anthropometric indices, as well as previously validated subjective global assessment (SGA) of nutrition, with concomitant scoring of CP's parameters, age, aetiology of cirrhosis and renal function with respect to survival. Multivariate models showed that MELD was not superior to CTP score. SGA was also significantly associated multivariately ($P = 0.0006$) with mortality, SGA improved the CTP model. The most useful model had

Table 4. Predictive value of MELD, CTP score and modified CTP scores for 3-month survival in patients with chronic liver disease

Author	Patients (N)	MELD score†	CTP score†	Modified CTP score†
Angermayr <i>et al.</i> ³⁸	475	0.72 ^{N.S.}	0.70 ^{N.S.}	CTPC: 0.72 ^{N.S.}
Giannini <i>et al.</i> ³⁹	145	0.95*	0.75*	M-CTP: 0.82*
Papatheodoridis <i>et al.</i> ⁴⁰	102	0.79 ^{N.S.}	0.73 ^{N.S.}	CTP-I: 0.76 ^{N.S.} , CTP-II: 0.78 ^{N.S.}

MELD: model for end-stage liver disease; CTP: Child-Turcotte-Pugh score; N.S.: not significant; CTPC: 0 point for serum creatinine <1.3 mg/dL and 4 points for serum creatinine >1.3 mg/dL; M-CTP: 1 point for creatinine ≤ 1.1 mg/dL, 2 points for creatinine between 1.2 and 1.8 mg/dL and 3 points for creatinine >1.8 mg/dL; CTP-I: as CTPC; CTP-II: 0 point for creatinine ≤ 1.3 mg/dL, 2 points for creatinine 1.4–1.8 mg/dL and 4 points for creatinine >1.8 mg/dL; ROC, Receiver Operator Characteristic.

* MELD vs. CTP: $P = 0.01$, MELD vs. modified CTP: $P = 0.047$.

† The predictive accuracy is based on the area under the ROC curve.

the relative hazards of creatinine 4.86 ($P = 0.004$), SGA 2.8 ($P = 0.0006$), age 1.61 ($P = 0.0001$), CTP score 1.27 ($P = 0.01$) and PT 1.08 ($P = 0.004$). Thus, nutritional indices as well as renal function add significantly to CTP score. This study suggests that important prognostic information is contained in the nutritional state and renal function in cirrhotics over and above the standard CTP and MELD scores.

Angermayr *et al.*,³⁸ used the cohort of cirrhotics who underwent elective TIPS placement²⁶ to evaluate the MELD score in comparison with the classic CTP and modified CTP scores. The modified CTP score (CTPC) was derived from CTP by adding creatinine as a simplified parameter (0 point for serum creatinine <1.3 mg/dL and 4 points for serum creatinine >1.3 mg/dL). The c-statistics for 3-month survival for MELD, CTP and CTPC were 0.72, 0.70 and 0.72, respectively, which were not statistically different. They concluded that even though MELD score was more objective, adding serum creatinine to the other five variables of CTP improved the predictive power of CTP, which retained its simplicity as a bedside test.

Furthermore, Giannini *et al.*³⁹ evaluated the predictive values of MELD and CTP scores for 3-month mortality in 145 European cirrhotic patients. Similar to Angermayr *et al.*,³⁸ the authors developed a creatinine-modified CTP score (1 point for creatinine ≤ 1.1 mg/dL, 2 points for creatinine between 1.2–1.8 mg/dL and 3 points for creatinine >1.8 mg/dL). Comparison of the c-statistics for MELD-, CTP- and creatinine-modified CTP scores, showed that the MELD score was significantly better

than the CTP score (0.947 vs. 0.757, $P = 0.01$) and marginally better compared with the modified CTP score (0.827, $P = 0.047$).

Recently, Papatheodoridis *et al.*⁴⁰ studied 102 patients with decompensated cirrhosis and the impact of two different modified CTP scores (CTP-I and CTP-II) in predicting short- and medium-term survival. The CTP-I was the same as Angermayr *et al.*³⁸ and the CTP-II as follows: 0 point for creatinine ≤ 1.3 mg/dL, 2 points for creatinine 1.4–1.8 mg/dL and 4 points for creatinine >1.8 mg/dL. The MELD, CTP, CTP-I and CTP-II scores had similar predictive accuracy, in terms of ROC curves, for 3, 6, 12 and 24 months survival. MELD and CTP-II scores had almost identical discriminative ability for 3- (0.79 vs. 0.78) and 6-month (0.77 vs. 0.76) survival, but MELD score was slightly, but not significantly better in predicting 12- and 24-month survival, compared with CTP-II score. The differences between these three studies, may be related to the cut-offs given to creatinine, but may also due to different biochemical assessments of creatinine, which give rise to different values and thus affect scores.^{41, 42}

In conclusion, the MELD and CTP scores had usually similar discrimination in predicting short- and medium-term survival in patients with chronic liver disease. Modified CTP scores (particularly adding serum creatinine as a trichotomous variable⁴⁰) deserve further evaluation, as they are superior to the classical CTP score and identical or marginally less accurate, compared with the MELD score, keeping their simplicity as a bedside test.

MELD AND COMPLICATIONS OF CIRRHOSIS (HEPATIC ENCEPHALOPATHY AND ASCITES)

The MELD score does not include HE. However, HE can be disabling for patients and affect their quality of life. Yoo *et al.*⁴³ determined the correlation between MELD score and the presence of HE as determined by clinical assessment, EEG and neuropsychometric testing. There were 66 patients, 22 with clinical HE. As perhaps could be expected, linear comparison between EEG or clinical assessment and or neuropsychiatric assessment score, showed MELD score to be far less sensitive in reflecting the presence or severity of HE. MELD scores did not show any correlation with clinical or subclinical HE: 14 of 22 patients with clinical HE, 12 of 21 patients with abnormal EEG and 28 of 42 patients with abnormal neuropsychometric tests had MELD score <20 points. As the MELD score does not reflect the presence of

encephalopathy, these patients need to be allocated separately for LT if MELD is used to prioritize organ allocation. In addition, Said *et al.*³⁴ found that HE, MELD and CTP scores were the only factors associated independently with short- and long-term mortality in cirrhotic patients. Furthermore, Huo *et al.*⁴⁴ found that Δ MELD score at 3 months was independently associated only with the development of HE and ascites. These studies suggest that HE, if its assessment could be standardized, would add to the prognostic estimation of survival in cirrhosis.

Ascites and/or low serum Na, as manifestations of advanced haemodynamic derangement of cirrhosis, were found to associate significantly with mortality on the transplantation list. Heuman *et al.*⁴⁵ analysed 507 patients (296 patients as a training group and 211 patients as validation group) referred of consideration for LT. In multivariate analysis MELD score, persistent ascites and low Na (<130 mm) were the only factors independently associated with 6-month mortality. Although MELD score was the only predictor of 6-month mortality in the subgroup of patients with advanced liver disease (MELD score: ≥ 21), only ascites and hyponatraemia (as a continuous or categorical variable using a cut-off of the lower limit of normal of 135 mm) were independent factors associated with 6-month mortality in patients with less severe liver disease (MELD score: <21).

Biggins *et al.*⁴⁶ evaluated retrospectively 513 patients listed for LT. Cox proportional HR revealed that serum Na <126 mm at listing and at any time whilst on the list was associated with increased risk of death (HR: 7.8 and 6.3, respectively), independently of the MELD score. Exclusion of HCC patients further increased the association of low serum Na (<126 mm) and the risk of death (HR: 11.6 and 24.7, respectively). MELD score combined with Na <126 mm had better discriminative ability compared with MELD score alone for 3-month (c-statistic: 0.917 vs. 0.883, respectively) and 6-month mortality (c-statistic: 0.92 vs. 0.87, respectively).

Finally, Ruf *et al.*⁴⁷ analysed retrospectively 194 patients on LT list, who either died or survived without LT during the 3-month follow-up. All patients with hyponatraemia (serum Na: ≤ 130 mm) had ascites. The c-statistic of MELD with serum Na either above or below 130 mm or MELD and serum Na as a continuous variable, were better than MELD alone for prediction of 3-month (0.905, 0.908 and 0.894, respectively) and 6-month mortality (0.850, 0.855 and 0.841, respec-

tively). The authors concluded that although hyponatraemia is also related to renal dysfunction, it was an earlier and more sensitive marker of worse prognosis, compared with serum creatinine.

CONCLUSION

To date the history of MELD has been similar to that of CTP score. It was developed to assess prognosis following a treatment for portal hypertension. Then, it was used as a justice system to allocate donors for LT, and then translated into other areas. However, the predictive accuracy of the MELD score in patients who have TIPS (the original population), variceal bleeding or chronic liver disease is not significantly superior to the CTP score (Tables 1–4). The value of the MELD score is that it incorporates renal function in the prognostic evaluation of cirrhotics which has been recognized for many years to be an independent marker of prognosis.^{35, 36} Its other advantage that it is a continuous or progressive score, which increases with worsening of its parameters. It does not have categories, which give 'floor and ceiling effect', but its 'upper cap' has been set to 40 points (so, the range is 36 points and not 15 as is the case of CTP score).

The advantage of MELD score is that it is based on objectively measured and widely available laboratory tests, compared with the CTP score. However, whilst it is possible to calculate CTP score easily at the bedside of the patients by mental arithmetic, on the contrary for the MELD score it is necessary to use a calculator or an Internet connection with the UNOS web site <http://www.unos.org>. In addition, recent studies have shown that the predictive ability of MELD score increases by adding other clinical (HE, ascites) and laboratory (Na) parameters.^{34, 45–47} Interestingly, HE, ascites and hyponatraemia (as an indicator of ascites) are components of the CTP score, but are not included in the MELD score.

In Wiesner *et al.*'s opinion,⁴⁸ the MELD score compared with the CTP score provides the mean values to measure liver disease severity more objectively, more accurately and to better predict which patients are at risk of dying on a LT waiting list. However, MELD score is not without drawbacks. The MELD score underestimates the risk of death in patients with ELD and intractable HE⁴⁹ or acute on chronic liver disease who developed HE.⁵⁰ Its three components may be affected by non-hepatic factors, and although they were derived

from multivariate analysis (and not by empirical selection, like CTP score), they have been selected as *a priori* important factors of mortality. As a result, other more important variables might not be taken into account.⁵¹ In addition, the relationship between INR and PT is not linear and for that reason INR may not accurately reflect the severity of liver disease.^{6, 51} Furthermore, significant variations to INR have been found due to different laboratory methodologies.⁵² Recently, the same variations were reported with different assays of creatinine measurements, particularly in patients with high bilirubin and MELD scores, i.e. the candidates with the highest priority for LT.⁴¹

Moreover, it is known that larger muscle mass means a higher serum creatinine which does not signify worse renal function^{53, 54} leading to a positive bias for Afro-Caribbean, compared with south Asian patients. Similarly, creatinine measurements should be corrected for gender difference, i.e. higher muscle mass and higher creatinine in men compared with women.^{15, 53} For this reason, the normal range for women is lower than for men.¹⁵ It is perceived that MELD score applies equally to all patients independent of age, gender or race, but the absence of 'correction factors', it in fact leads to an inherent discrimination against various groups of patients – it does not fulfil the premise of equity. Indeed, a recent study⁵⁵ revealed that women on the transplant waiting list are less likely to receive LT than men using the MELD-based allocation system. We believe that the unimodal assessment of serum creatinine may be the reason for this inequality.

On the contrary, most prognostic models evaluate short- and long-term mortality as an outcome index, but other end points may also be important. For example, Saab *et al.* found that quality of life does not correlate well with severity of liver disease as measured by MELD score, as HE and ascites, which had strong relationship with quality of life, are not included in MELD score.⁵⁶

In conclusion, it is still not clear, whether MELD is better than CTP score for predicting survival in patients with chronic liver disease outside of liver transplant waiting lists (Tables 1–4), or whether its superiority is mainly related to the use of creatinine in the MELD score. This is surprising as CTP score is an 'empirical score' and has never been validated statistically. Heuman *et al.*⁵⁷ recently re-examined statistically the traditional cut-off points of CTP classification (A, B and C). They found that these divisions are suboptimal for short-term prognosis in

599 cirrhotics referred for LT and they proposed new CTP subclasses: A (5–6), B1 (7–8), B2/C1 (9–11), C2 (12–13) and C4 (14–15). In the same study⁵⁷ traditional CTP and MELD scores had similar discriminative ability for short- and long-term survival. Another proposal is to evaluate CTP score with the addition of creatinine and perhaps nutritional status, a factor in the original Child score, both of which have well-known parameters which influence prognosis in cirrhotic patients. An indicator of portal hypertension (presence or size of varices, previous bleeding, hepatic venous pressure gradient), might also be added in an effort to ameliorate prognostic capacity of CTP score without losing its advantages. Another factor to take into account in the future, when comparing MELD or its modifications with CP, is the 'artificial loading' of a higher MELD score to cirrhotics with HCC. This is needed for prioritization for LT but is not related to the prognosis of the liver disease. In our review, only one study separately evaluated HCC patients.²⁹

Based on the available data, we propose to keep using the CTP score for individual assessment of liver disease in daily clinical practice. On the contrary, the MELD score may be best suited as a verifiable system in prioritizing candidates for LT, but factors affecting measurement of creatinine, such as different assays,⁴¹ gender and race as well as different INR measurements⁵² must be accounted for in what a justice system rather than utility system.¹⁵ Further improvements in MELD such as 'sodium – MELD'^{45–47} may result in a distinct advantage for new forms of MELD over CP, but these need to be compared formally, and all model comparisons should also look at model calibration, as well as discriminative ability. However, it is only short-term survival that is potentially being assessed more accurately with MELD modifications and not medium- or long-term survival, and thus the value of 'sodium – MELD' or other types as general prognostic tools in cirrhosis may not be as great as anticipated.

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