pISSN 2287-2728
eISSN 2287-285X

CMH

http://dx.doi.org/10.3350/cmh.2013.19.2.105
Clinical and Molecular Hepatology 2013;19:105-115

Review

Important predictor of mortality in patients with end-stage liver disease

Hyung Joon Kim and Hyun Woong Lee

Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, Korea

Prognosis is an essential part of the baseline assessment of any disease. For predicting prognosis of end-stage liver disease, many prognostic models were proposed. Child-Pugh score has been the reference for assessing the prognosis of cirrhosis for about three decades in end-stage liver disease. Despite of several limitations, recent large systematic review showed that Child-Pugh score was still robust predictors and it's components (bilirubin, albumin and prothrombin time) were followed by Child-Pugh score. Recently, Model for end-stage liver disease (MELD) score emerged as a "modern" alternative to Child-Pugh score. The MELD score has been an important role to accurately predict the severity of liver disease and effectively assess the risk of mortality. Due to several weakness of MELD score, new modified MELD scores (MELD-Na, Delta MELD) have been developed and validated. This review summarizes the current knowledge about the prognostic factors in end-stage liver disease, focusing on the role of Child-Pugh and MELD score. **(Clin Mol Hepatol 2013;19:105-115)**

Keywords: Cirrhosis; MELD score; Child score

INTRODUCTION

The high mortality of end-stage liver disease is a global public health problem. The course of cirrhosis is extremely variable from patient to patient due to several factors, including hepatic synthetic function (or "hepatic reserve"), the cause of cirrhosis, and the occurrence of liver malignancy. Therefore, establishing a prognosis in a given patient with cirrhosis remains a challenging issue.

With the rapid progress of medical science, liver transplantation significantly improves the survival and quality of life of patients with end-stage liver disease. Therefore, predicting the prognosis has been the important issue for allocating the liver transplantation, the only definite treatment for these patients. Many prognostic models and scores have been proposed in the last two decades to predict prognosis in patients with end-stage liver disease and to determine the most appropriate therapeutic option.

Child score[1] and modified Child-Pugh score[2] thereafter, has been the reference for assessing the prognosis of cirrhosis for about three decades in end-stage liver disease. The longevity of the Child-Pugh score can be explained by its empirical simplicity, its intuitiveness, and, overall, its good accuracy across a broad spectrum of causes and specific situations.

Among additional prognostic scores proposed,[3-6] the model for end-stage liver disease (MELD) is more reproducible than the Child-Pugh score because it does not include subjective variables such as ascites and encephalopathy. Therefore, the MELD has replaced the Child-Pugh score for prioritizing liver donor allocation.[7] In recent large systematic review, the Child-Pugh score and MELD score were found to be predictive of death.[8] Therefore, whether Child-Pugh score should be definitely abandoned for MELD score

Abbreviations:

CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; HE,hepatic encephalopathy; HRS, hepatorenal syndrome; ICU, intensive care unit; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SOFA, sequential organ failure assessment; TIPS, transjugular intrahepatic portosystemic shunt

Corresponding author : Hyung Joon Kim
Department of Internal Medicine, College of Medicine, Chugna-Ang University, 224-1, Heukseok-dong, Dongjak-gu, Seoul 156-755, Korea
Tel. +82-2-6299-1376, Fax. +82-2-825-7571
E-mail; mdjoon@cau.ac.kr

Received : May 16, 2013 / **Accepted :** May 23, 2013

remains uncertain.

This review article will highlight current status about the prognostic scores in end-stage liver disease focusing on the Child-Pugh score and MELD score.

CLASSIFICATION OF END-STAGE LIVER DISEASE AND PROGNOSIS

Cirrhosis is classified into two stages compensated and decompensated. This classification is simple and reproducible and identifies patients at a similar rate of disease progression and survival. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy and/or jaundice.[4,9] Transition from a compensated to a decompensated stage occurs at a rate of 5-7% per year.[10] In fact, it is well known that life expectancies in compensated and decompensated cirrhosis are strikingly different and it is, therefore, conceivable that prognostic indicators may be different or may have a different weight according to the disease stage.[11] And, Child-Pugh score and MELD score may be unsatisfactory when applied separately to compensated and decompensated patients.[11] Recent systemic review found the Child-Pugh score was still most significant among the predictors of death despite the absence of ascites, encephalopathy and jaundice in the patients with compensated cirrhosis, because its laboratory components, bilirubin, albumin and prothrombin time continued to be among the most frequent predictors, indicating that even subtle abnormalities in these laboratory parameters are predictive of death.[8] In addition to these markers of liver insufficiency, in the compensated stage, significant predictors that come to light are those related to portal hypertension, such as the presence of varices, splenomegaly and platelet count as well as gamma-globulin levels (as hyper gamma-globulinemia is an indirect marker of portosystemic shunting). This probably indicates that, in a compensated stage, measurements of portal pressure will be of important prognostic value. This is strengthened by a recent study in which the most important predictor of the development of varices was a hepatic venous pressure gradient (HVPG) of >10 mmHg in patients with stage 1 liver cirrhosis (no varices and no ascites). Conversely, the set of significant prognostic variables in the group of patients with decompensated cirrhosis reflect a more advanced stage, as bleeding and hepatocellular carcinoma (HCC) become predictive of death. It is in this group that the Child-Pugh score (and its components) has the most important prognostic value. In addition to the Child-Pugh score, parameters that reflect a further deterioration of the circulatory status of the cirrhotic patient, such as parameters of renal dysfunction (creatinine and blood urea nitrogen) arise as powerful prognostic indicators in this setting and, therefore, it is not surprising that the MELD score (which incorporates creatinine in addition to markers of liver dysfunction) has become a valuable method to allocate organs. On the contrary, it is predictable that the MELD score would not be useful to predict survival in patients with compensated cirrhosis.

From the clinical point of view, it will be important to assess prognostic variables separately for the different stages of cirrhosis, at a minimum, separating those with compensated and those with decompensated cirrhosis. In patients with decompensated cirrhosis, any study of predictors of death should include important variables identified by the majority of studies, such as the Child-Pugh score (or its components) and age. In patients with compensated cirrhosis (or status 1 and 2), particularly in those who remain at a compensated stage, the risk of dying is low and in this group of patients it would be more useful to look at predictors of decompensation rather than at predictors of mortality.

CHILD-PUGH SCORE, ITS APPLICATION AND LIMITATION

Child-Pugh score has been the reference for more than 30 years for assessing the prognosis of cirrhosis. At the bedside, Child-Pugh score is widely used as a simple descriptive or prognostic indicator and is frequently associated to other indicators. Initially, the Child score included two laboratory variables (bilirubin and albumin) and there quantitative variables (ascites, encephalopathy and nutritional status). The five variables were arranged so as to define their groups of severity (A, B and C).[1] It was originally designed for predicting the outcome after surgery for portal hypertension (portocaval shunting) in patients with cirrhosis. Child-Pugh score, a modified version, proposed 10 years later.[2] The only change in this modified version was that nutritional status was replaced by prothrombin time. In previously reported studies, the variation in survival explained by Child-Pugh score remains somewhat low (less than 50%), as it is the case with most survival models[12] emphasizing the fact that other factors play an important role in prognosis. In recent large systematic review, the most consistent and 'robust' predictor of death in cirrhosis is the Child-Pugh score. And, this was followed by its all components (albumin, bilirubin, ascites, encephalopathy and prothrombin time).[8]

However there are several limitations of Child-Pugh score. The

http://dx.doi.org/10.3350/cmh.2013.19.2.105

first is that score consisted of variables that were subjective (ascites and encephalopathy) making it difficult to categorize patients according to their own disease severity. And, both ascites and hepatic encephalopathy (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. The second is that all variables have been selected empirically, and cut-off values for continuous variables such as bilirubin, albumin and prothrombin time are arbitrary. Thus, patients with bilirubin of 55 μm who have a better prognosis than those with a bilirubin of 250 μmol/L; in the Child-Turcotte-Pugh (CTP) classification both these patients have the same score of severity for bilirubin concentration ('the ceiling effect'). 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'). And, laboratory variables are influenced by interlaboratory variability (prothrombin time, albumin) and lacked statistical validity (equal weights to all elements). The third is that Child-Pugh score does not take into account the cause of cirrhosis, the possible coexistence of several causal factors, and the persistence of a damaging process such as persistent alcohol abuse, ongoing hepatitis B virus (HBV) or hepatitis C virus (HVC) replication, or inflammatory activity of autoimmune hepatitis.[13,14] Finally, it does not include a measure of renal function, which is a well-established prognostic marker in cirrhosis.[15-18]

MELD SCORE, ITS APPLICATION, DERIVATIVES AND LIMITATION

While Child score was originally designed for assessing the prognosis of cirrhotic patients undergoing surgical treatment of portal hypertension, MELD was initially created to predict survival following elective placement of TIPS.[18]

Before February 2002 in the US, transplant candidates were prioritized to receive organs for liver transplantation based on the United Network of Organ Sharing (UNOS) status that primarily reflected their CTP scores. In a prospective study of candidates on the waiting list, MELD was an excellent predictor of waiting-list mortality.[19] In this study, the MELD scoring system was shown to predict 3-month mortality more accurately than the traditional CTP system for patients with UNOS statuses of 2A (CTP score >10 plus cirrhosis-related complications such as active variceal haemorrhage, hepatorenal syndrome, refractory ascites/hepatic hydrothorax or stage 3 or 4 HE) and 2B (CTP score >10, or score >7 plus complications) patients.[19]

The "c" statistic represents a global estimate of the ability of a score to predict an event. This statistic, which is derived from the area under the receiver operating characteristic curve, ranges from 0 to 1. A "c" statistic of 0.5 means that the score is of no value for predicting a given event. A "c" statistic of 1 means that the score is perfect. A c-statistic of 0.7 is thought to have reasonable clinical utility, while a c-statistic of >0.8 in a prediction model lends strong support to its accuracy. The concordance (c-statistic), with 3-month mortality as the end point, for the MELD score was 0.83 indicating that when a pair of patients is randomly drawn out of the study population, 83% of the time the model correctly predicts the first patient to die.[20] Most studies that evaluated MELD to rank patients according to their risk of mortality have yielded "c"-statistics upwards of 0.8, and usually superior to the CTP class.

In February 2002 the MELD score was adopted as the basis for allocation of allografts for liver transplantation (LT) in the United States. According to the MELD-based policy, patients with the highest score have a priority for organ allocation.[21] More recently, MELD score has also been adopted in several European countries as well as in South America.

COMPONENTS OF THE MELD SCORE

MELD incorporates 3 widely available laboratory variables including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The original mathematical formula for MELD is: MELD 0.957×log (creatinine)+0.378×log (total bilirubin)+1.120 log (INR)+0.6431. The score can be calculated on handheld computing devices, and is available at *www.mayoclinic.org/gi-rst/mayomodel5.html*. To lessen the influence of extreme values, the natural logarithm of bilirubin INR and creatinine were entered into the model.

Creatinine

It is common to see a substantial degree of variability in renal function in patients with end-stage liver disease. More importantly, diminished renal function is an important predictor of survival in those patients.[22-25]

Serum creatinine has a sigmoid pattern in that the increase in mortality is linear within a range of creatinine, in partial support of the current lower and upper bounds of 1 and 4, respectively.

 http://dx.doi.org/10.3350/cmh.2013.19.2.105

however, substantial changes in serum creatinine may occur, especially in those undergoing large-volume paracentesis and/or receiving diuretics. Laboratory methods may also interfere with the value of serum creatinine. To measure serum creatinine level, O'Leary modified Jaffe, compensated kinetic Jaffe, enzymatic and standard kinetic Jaffe methods have been used and compared in the calculation of the MELD score. There is a poor agreement among different creatinine assays, especially as serum bilirubin rises.[26] Accordingly, the new standard is an enzymatic method for measuring serum creatinine.

And, accuracy of noninvasive measurement of renal function, including serum creatinine, has been shown to be suboptimal among cirrhotic patients.[27-29] Measured glomerular filtration rate (GFR) is better at assessing prognosis than creatinine and mathematical equations containing creatinine.[27,28] A multivariable model that incorporates calculated GFR and/or serum sodium is superior to the MELD score.[29]

Billirubin

Serum bilirubin concentration is a well established marker of the hepatic synthetic function, although it represents excretory function. Of the 3 MELD variables, serum total bilirubin is the most important. It has a linear relationship with 90-day mortality in patients waiting for LT.[30]

INR

Prothrombin time and the INR reflect coagulopathy associated with synthetic dysfunction in patients with end-stage liver disease. After adjusting for bilirubin and creatinine, INR is associated with a steep increase in mortality risk. However, once it reaches approximately 3, the risk does not seem to increase any further. However, there are some limitations. First, it has been shown that interlaboratory variation in INR is ~25%. Among the three variables of MELD score, INR has the highest multiplicative value. Therefore variations in INR may translate to up to 20% differences in MELD score.[31] Second, when applied to individuals with liver disease, this method of calculation for INR proves to be suboptimal.[31,32] Because, 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.[33,34] In studies in which plasma samples of patients with liver disease were tested using different prothrombin reagents, there was a substantial degree of variation in INR values.[35,36] In contrast, if calibration is done using standards derived for patients with liver disease, interassay and interlaboratory variability could be reduced significantly.

Despite of several limitations of INR, INR remains a practically useful and statistically significant correlate of mortality risk in patients with end-stage liver disease.[37] It is also widely available and is likely continue to be used as an indicator of survival in patients with end-stage liver disease and as a component of the MELD score.[20]

MELD APPLICATION

In comparison with the CTP system, recent studies suggested that the MELD may more accurately predict the survival for patients with cirrhosis.[38,39] However, other studies reported different results, showing that the MELD was not necessarily better than the CTP system. A recent systemic review showed that of the 11 studies, only four studies (4,512 patients) demonstrated a statistical superiority of the MELD in comparison with the CTP system, whereas seven studies (8,020 patients) showed no statistical difference. There have been no satisfactory explanations for these discordant results. A possible reason could be that lower range MELD scores may have a less accurate predictive ability.

The MELD score, as an objective scale of disease severity, has been used in the management of patients with chronic liver disease in the non-transplant setting as below.

Further, the MELD score has been used in the management of patients with a wide spectrum of liver disease including alcoholic cirrhosis and alcoholic hepatitis.[13]

MELD AND COMPLICATION OF CIRRHOSIS

MELD score also proved to be a reliable marker of 1-year and 5-year survival across a broad spectrum of liver diseases including alcoholic cirrhosis and alcoholic hepatitis.[13] In addition, MELD score has been shown to be a good prognostic marker in cases of variceal bleeding,[40] spontaneous bacterial peritonitis, and hepatorenal syndrome (HRS). In patients with variceal bleeding, 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. In the study of HRS, all patients with type 1 HRS had a high MELD score (>20) and showed an extremely poor outcome (median survival: 1 mo). By contrast, the survival of patients with type 2

http://dx.doi.org/10.3350/cmh.2013.19.2.105

HRS was longer and dependent on MELD score (>20, median survival 3 mo; <20, median survival 11 mo; P<0.002).[41] However, the MELD score does not include HE and MELD score is far less sensitive in reflecting the presence or severity of HE. MELD scores did not show any correlation with clinical or subclinical HE.[42] Other study showed that HE, MELD and CTP scores were the only factors associated independently with short- and long-term mortality in cirrhotic patients.[13] The MELD score underestimates the risk of death in patients with end-stage liver disease and intractable HE[43] or acute on chronic liver disease who developed HE.[44] 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. In multivariate analysis MELD score, persistent ascites and low Na (<130 mmol) 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 hyponatremia (as a continuous or categorical variable using a cut-off of the lower limit of normal of 135 mmol) were independent factors associated with 6-month mortality in patients with less severe liver disease (MELD score: <21).

In several studies, it was confirmed that the etiology of cirrhosis was a less important variable in determining survival in other patient cohorts with end-stage liver disease. Therefore, etiology of liver disease was removed as a variable from the model. The advantage of dropping etiology of cirrhosis as a variable was that the subjective element in determining etiology was removed, and the model could be based purely on objective laboratory variables.

MELD AND ALCOHOLIC HEPATITIS

In severe alcoholic hepatitis has been defined by a "discriminant function" above 32.[45] In addition to this discriminant function, generally termed as "Maddrey score" (or Maddrey discriminant function), several specific scores have been created to predict early mortality in patients with severe alcoholic hepatitis.[46,47] The more general MELD score has also been assessed in this setting. MELD score proved to be as efficacious as or even superior to the original Maddrey discriminant function. This finding is not surprising since MELD score includes the two variables (bilirubin and prothrombin time) included in the Maddrey discriminant function.

MELD AND PRIMARY BILIARY CIRRHOSIS (PBC)

PBC is one of the causes of cirrhosis for which specific prognostic scores were first proposed.[48,49] The aim of scoring was to determine the optimal timing for transplantation. Even though specific scores exist for PBC, there is no evidence that patients with PBC are misclassified with MELD score. Nor there is evidence that specific scores are superior to MELD. However, no discriminant value of MELD score has been established to specifically identify PBC patients who may benefit from transplantation.

MELD AND PRIMARY SCLEROSING CHOLANGITIS (PSC)

The course of PSC is much more variable than that of PBC. Therefore, it is more difficult to create reliable prognostic scores, especially for assessing long-term outcome. MELD score has not been specifically assessed for PSC. However, most patients with advanced PSC have high bilirubin level. In these patients, it is unlikely that disease severity is underestimated by MELD score compared with other chronic liver diseases.

MELD AND ICU SETTING

In the particular setting of ICU, it can be reasonably assumed that Child-Pugh and MELD score have significant limitations for predicting very short-term survival. Previous study showed that cirrhotics admitted to ICU with three or more failing organ systems have 90% mortality and that SOFA (Sequential Organ Failure Assessment) and MELD were better predictors than APACHE II or Child-Pugh scores.[50]

MELD AND HEPATOCELLULAR CARCINOMA

The MELD has been suggested to be incorporated into the staging system for hepatocellular carcinoma (HCC) to replace the CTP system. Mayo group showed that neither minor hepatic resections (≤3 segment resection) nor major resection (≤4 segment) were associated with any mortality 30 days postoperatively if MELD score was ≤8. Moreover, patients with HCC smaller than 5 cm in diameter and MELD score ≤8, had a 5-year survival of 80%.[51] Studies showed that the modified staging systems had an in-

 http://dx.doi.org/10.3350/cmh.2013.19.2.105

creased predictive accuracy in comparison with the original staging systems for HCC.[52,53] These findings implicate that although the MELD was originally created to study the 3-month survival in cirrhotic patients, it can also be used to predict the long-term outcome of HCC.

MELD AND NONTRANSPLANT SURGERY

Child-Pugh score has been used for predicting the setting of nontransplant surgery. The MELD score has also been shown to be a useful model in predicting the outcomes in cirrhotic patients undergoing major surgical procedures.[54-56] In general, there is approximately a 1% increase in mortality risk per MELD point below a score of 20. There is a 2% increase in mortality risk per MELD point over 20.[57] Mortality is higher for intra-abdominal surgery (up to 25%) compared with other types of surgery. The c statistic of the MELD score for predicting 30-day mortality was found to be 0.72 in the whole population of patients undergoing surgery and 0.8 in the subgroup with intra-abdominal surgery. However, there are no simple limits with MELD score such as Child-Pugh grades A, B, and C for estimating patients' risk. This algorithms based on MELD score for different types of surgery would be helpful to replace Child-Pugh score.

MODIFYING MELD

The outcome of cirrhosis is quite variable from patient to patient according to different causes, different stages, and different therapeutic options. And, with the expansion of MELD score, several "MELD exceptions" emerged. Therefore, several models have been proposed to refine and improve the MELD score. As many as 11 different scores are available for addressing general or more specific issues regarding the prognosis of cirrhosis (Tables 1, 2).

MELD NA

Cirrhotic patients often have dilutional hyponatraemia because of altered vascular haemodynamics. Systemic arterial vasodilation leads to the release of antidiuretic hormone which, in turn, induces dilution hyponatremia. The activation of these mechanisms correlates with the degree of portal hypertension.[58] In this view, hyponatremia can be considered an indirect marker of portal hypertension during cirrhosis. Notably, profound hyponatraemia is frequently associated with severe complications in liver cirrhosis, including ascites, hepatorenal syndrome and liver related mortality[15,59-62] and is associated with neurologic dysfunction, refractory ascites, hepatorenal syndrome, and death from liver disease.[63,64] Therefore, hyponatremia, with lower sodium values predicting worse outcomes, has been shown to be an independent predictor

Table 1. Modifying MELD scores

Score	Components
MELD score	0.957 × log (creatinine) + 0.378 × log (total bilirubin) + 1.120 log (INR) + 0.6431
MELD-Na	MELD + 1.59 × (135-Na [mEq/L])
Delta MELD	Difference between current MELD and the lowest MELD measure within 30 days prior to current MELD

MELD, model for end-stage liver disease; INR, international normalized ratio.

Table 2. Prognostic models of cirrhosis

Cause	Model	Components
Alcoholic cirrhosis/alcoholic hepatitis	Maddrey discriminant fuction	4.6 × (prothrombin time patient-prothrombin time control) + (serum bilirubin [μmol/L]/17.1)
Decompensated HBV-cirrhosis	–	0.5 × bilirubin (mg/dL) + 1.7 × creatinine (mg/dL) + 1.8 × HBV-DNA
PBC	Mayo risk score for PBC	0.039 × age [yr] + 0.871 × loge bilirubin [mg/dL] - 2.53 × $\log_e$ albumin [g/dL] + 2.9 × $\log_e$ prothrombin time [sec] + 0.859 × edema
PSC	Mayo risk score for PSC	0.0295 × (age [yr]) + 0.5373 × $\log_e$ (bilirubin [mg/dL])-0.8389 × (albumin [g/dL]) + 0.5380 × $\log_e$ (AST [IU/L]) + 1.2426 × (points for variceal bleeding)

INR, international normalized ratio; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AST, aspartate aminotransferase.

http://dx.doi.org/10.3350/cmh.2013.19.2.105

of survival at 3 and 12 months.[65,66] Hyponatraemia may independently predict the survival in cirrhotic patients, even in the individual category of the ascites, HE, variceal bleeding, spontaneous bacterial peritonitis or renal failure, with a hazard ratio of 5.9-16.5.[66] Several studies have shown that hyponatremia is a strong predictor of early mortality, independent of MELD score.[66-68] After controlling for MELD, serum sodium was associated with a higher risk of mortality: each 1 mmol/L decrease in the serum sodium concentration for values between 125 and 140 mmol/L was associated with 5% increase in mortality (P<0.001).[65] Changes in survival are especially pronounced for sodium concentrations ranging from 120 to 135 mEq/L. Within this range, a decrease in serum sodium of 1 mEq/L corresponds to a 12% decrease in 3-month probability of survival.[66] A modified score including serum sodium, termed MELD-Na, has been proposed as an alternative to MELD score (Table 1).[66-68] The addition of Na to the MELD improves its predictive accuracy, especially for patients with lower range MELD scores. As reported in most studies, when the MELD score increases, serum Na contributes much less to increasing mortality prediction.[69,70] However, the addition of serum Na did not significantly improve the accuracy of the MELD score in the prediction of survival at 3 and 12 months.

A limitation to the addition of serum sodium into MELD is that during cirrhosis, marked changes in serum sodium concentration can result from several factors, including the administration of diuretics and intravenous hypotonic fluids.[71] In contrast, the use of V2-receptor antagonists for treating refractory ascites induce a significant increase in serum sodium. Again, serum sodium is not as objective as it was thought to be. In summary, the contribution of hyponatraemia to outcome prediction is possible only under a specific clinical setting (such as a low MELD score) rather than a direct linear relationship.

DELTA MELD

Another concern of the MELD is whether a single point determination of the score can adequately differentiate the degree of urgency for transplantation. The usefulness of a change in MELD (delta MELD) in predicting waiting-list mortality has been studied with different results.[39,72-74] In recent systematic review, delta MELD was reported to predict more accurately the survival in cirrhotic patients awaiting liver transplantation.[75] However, the prognostic value of delta MELD has not been confirmed in another study and may require further investigations.[72] The increase in MELD is confounded by (1) patients with a sharp increase in MELD tending to have a high MELD score currently, and (2) in retrospective analysis, patients who are acutely worsening have frequent laboratory testing, which may represent the clinician's clinical judgment of the worsening patient's condition.

MELD AND PROGNOSIS ACCORDING TO COMPLICATION OF PORTAL HYPERTENSION

Studies showed that individual complications of portal hypertension, such as spontaneous bacterial peritonitis, encephalopathy, variceal bleeding, or ascites, did not provide further prognostic information when added to MELD.[76]

LIMITATION OF MELD

First, on the basis of variables, they initially, were also selected empirically because they were felt to have a potential prognostic influence. Therefore, it cannot be excluded that some important variables have not been taken into account for analysis.[76]

Second, another limitation comes from the absence of clear-cut discriminant values with MELD score. Such discriminant limits with MELD score have not yet been determined in a broad scope of situations.

Third is come from that some important prognostic predictors, such as intractable hepatic encephalopathy, oesophageal variceal bleeding and spontaneous bacterial peritonitis, which are common adverse complications in cirrhosis, are not included in the MELD. Fourth, one must remember that MELD was created and validated in a cohort of patients who were absent of acute, reversible complications, such as bacterial infection or azotemia. Therefore, in patients on the waiting list for liver transplantation, the MELD score should be calculated only after acute reversible processes are adequately treated.

Finally, depending on the population to which MELD is applied, mortality seen in patients with a given MELD score may not necessarily be the same. Similarly, hospitalized patients with cirrhosis who were not candidates for liver transplantation may have a higher mortality than candidates for liver transplantation who are younger and devoid of comorbidity. Thus, it is not possible to provide a universally applicable survival prediction by MELD.

 http://dx.doi.org/10.3350/cmh.2013.19.2.105

CONCLUSION

In recent years, MELD score emerged as a "modern" alternative to Child-Pugh score.

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. However, MELD score has several strengths compared with Child-Pugh score. The variables incorporated into the MELD score are simple and more objective. The weight of each variable has been determined by statistical analysis. MELD is a continuous score, which makes it more convenient for scoring individuals within large populations. In addition to organ allocation, the MELD score has been an important contribution to hepatology given its ability to accurately gauge the severity of liver disease and effectively assess the risk of mortality. By design, it is continually evolving; it lends itself to continued refinement and improvement in a data-driven fashion. All these reasons make the MELD score likely to be the core tool for assessing the prognosis of cirrhosis in the future.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1-85.
2. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-649.
3. Christensen E, Schlichting P, Andersen PK, Fauerholdt L, Schou G, Pedersen BV, et al. Updating prognosis and therapeutic effect evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. Scand J Gastroenterol 1986;21:163-174.
4. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987;7:122-128.
5. Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). Hepatology 1996;23:1041-1046.
6. Poynard T, Naveau S, Doffoel M, Boudjema K, Vanlemmens C, Mantion G, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis using matched and simulated controls: 5-year survival. Multi-centre group. J Hepatol 1999;30:1130-1137.
7. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
8. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-231.
9. Saunders JB, Walters JR, Davies AP, Paton A. A 20-year prospective study of cirrhosis. Br Med J (Clin Res Ed) 1981;282:263-266.
10. D'Amico G. Natural history of compensated cirrhosis and varices. In: Boyer TD, Groszmann RJ, eds. Complications of cirrhosis: pathogenesis, consequences and therapy. VA: American Association for the Study of Liver Diseases 2001:118–123.
11. D'Amico G, Garcia-Tsao G, Abraldes JG, Christensen E, Gine`s P, Kim WR, et al. Prognostic indicators in cirrhosis. In: de Franchis R, ed. Portal Hypertension IV. Proceedings of the Fourth: Proceedings of the Fourth Baveno International Consensus Workshop. MA: Wiley-Blackwell, 2005:53-103.
12. Christensen E. Prognostic models including the Child-Pugh, MELD and Mayo risk scores-where are we and where should we go? J Hepatol 2004;41:344-350.
13. Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. J Hepatol 2004;40:897-903.
14. Pessione F, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, et al. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int 2003;23:45-53.
15. Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, Uriz J, Quinto L, Ventura PJ, et al. A prognostic model for predicting survival in cirrhosis with ascites. J Hepatol 2001;34:46-52.
16. Angermayr B, Cejna M, Karnel F, Gschwantler M, Koenig F, Pidlich J, et al. Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003;52:879-885.
17. Longheval G, Vereerstraeten P, Thiry P, Delhaye M, Le Moine O, Deviere J, et al. Predictive models of short- and long-term survival in patients with nonbiliary cirrhosis. Liver Transpl 2003;9:260-267.
18. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-871.
19. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-96.
20. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007;45:797-805.
21. Freeman RB, Wiesner RH, Edwards E, Harper A, Merion R, Wolfe R. Results of the first year of the new liver allocation plan. Liver Transpl 2004;10:7-15.

http://dx.doi.org/10.3350/cmh.2013.19.2.105

22. Charlton MR, Wall WJ, Ojo AO, Gines P, Textor S, Shihab FS, et al. Report of the first international liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. Liver Transpl 2009;15:S1-S34.
23. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). Am J Transplant 2008;8:2243-2251.
24. Sharma P, Welch K, Eikstadt R, Marrero JA, Fontana RJ, Lok AS. Renal outcomes after liver transplantation in the model for end-stage liver disease era. Liver Transpl 2009;15:1142-1148.
25. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179-1185.
26. Cholongitas E, Marelli L, Kerry A, Senzolo M, Goodier DW, Nair D, et al. Different methods of creatinine measurement significantly affect MELD scores. Liver Transpl 2007;13:523-529.
27. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. J Hepatol 2010;52:605-613.
28. Francoz C, Prie D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl 2010;16:1169-1177.
29. Lim YS, Larson TS, Benson JT, Kamath PS, Kremers WK, Therneau TM, et al. Serum sodium, renal function, and survival of patients with end-stage liver disease. J Hepatol 2010;52:523-528.
30. Gish RG. Do we need to MEND the MELD? Liver Transpl 2007;13:486-487.
31. Trotter JF, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. Am J Transplant 2007;7:1624-1628.
32. Arjal R, Trotter JF. International normalized ratio of prothrombin time in the model for end-stage liver disease score: an unreliable measure. Clin Liver Dis 2009;13:67-71.
33. Robert A, Chazouilleres O. Prothrombin time in liver failure: time, ratio, activity percentage, or international normalized ratio? Hepatology 1996;24:1392-1394.
34. Kovacs MJ, Wong A, MacKinnon K, Weir K, Keeney M, Boyle E, et al. Assessment of the validity of the INR system for patients with liver impairment. Thromb Haemost 1994;71:727-730.
35. Bellest L, Eschwege V, Poupon R, Chazouilleres O, Robert A. A modified international normalized ratio as an effective way of prothrombin time standardization in hepatology. Hepatology 2007;46:528-534.
36. Tripodi A, Chantarangkul V, Primignani M, Fabris F, Dell'Era A, Sei C, et al. The international normalized ratio calibrated for cirrhosis (INR(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. Hepatology 2007;46:520-527.
37. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology 2011;140:1952-1960.
38. Salerno F, Merli M, Cazzaniga M, Valeriano V, Rossi P, Lovaria A, et al. MELD score is better than Child-Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. J Hepatol 2002;36:494-500.
39. Huo TI, Wu JC, Lin HC, Lee FY, Hou MC, Lee PC, et al. Evaluation of the increase in model for end-stage liver disease (DeltaMELD) score over time as a prognostic predictor in patients with advanced cirrhosis: risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. J Hepatol 2005;42:826-832.
40. Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, et al. Model for end-stage liver disease (MELD) for predicting mortality in patients with acute variceal bleeding. Hepatology 2002;35:1282-1284.
41. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jimenez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. Hepatology 2005;41:1282-1289.
42. Yoo HY, Edwin D, Thuluvath PJ. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. Am J Gastroenterol 2003;98:1395-1399.
43. Hassanein T, Tofteng F, Brown RS, McGuire BM, Lynch P, Mehta R, et al. MELD and SOFA Scores As a Predictor of Transplant Free Survival Time in Patients With End Stage Liver Disease Complicated By Intractable Hepatic Encephalopathy Grades 3 and 4. Gastroenterology 2005;128:A705.
44. Sheehan EM, Zeifer B, Futterer S, Sufit R, Blei A. MELD Scores, Encephalopathy and Survival in Acute-On-Chronic Liver Failure. Gastroenterology 2005;128:A705.
45. Carithers RL Jr, Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Ann Intern Med 1989;110:685-690.
46. Forrest EH, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 2005;54:1174-1179.
47. Mathurin P, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 2003;38:1363-1369.
48. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A.

Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989;10:1-7.
49. Grambsch PM, Dickson ER, Kaplan M, LeSage G, Fleming TR, Langworthy AL. Extramural cross-validation of the Mayo primary biliary cirrhosis survival model establishes its generalizability. Hepatology 1989;10:846-850.
50. Cholongitas E, Senzolo M, Patch D, Kwong K, Nikolopoulou V, Leandro G, et al. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. Aliment Pharmacol Ther 2006;23:883-893.
51. Testa R, Testa E, Giannini E, Botta F, Malfatti F, Chiarbonello B, et al. Trans-catheter arterial chemoembolisation for hepatocellular carcinoma in patients with viral cirrhosis: role of combined staging systems, Cancer Liver Italian Program (CLIP) and Model for End-stage Liver Disease (MELD), in predicting outcome after treatment. Aliment Pharmacol Ther 2003;17:1563-1569.
52. Huo TI, Lin HC, Hsia CY, Wu JC, Lee PC, Chi CW, et al. The model for end-stage liver disease based cancer staging systems are better prognostic models for hepatocellular carcinoma: a prospective sequential survey. Am J Gastroenterol 2007;102:1920-1930.
53. Huo TI, Lin HC, Huang YH, Wu JC, Chiang JH, Lee PC, et al. The model for end-stage liver disease-based Japan Integrated Scoring system may have a better predictive ability for patients with hepatocellular carcinoma undergoing locoregional therapy. Cancer 2006;107:141-148.
54. Farnsworth N, Fagan SP, Berger DH, Awad SS. Child-Turcotte-Pugh versus MELD score as a predictor of outcome after elective and emergent surgery in cirrhotic patients. Am J Surg 2004;188:580-583.
55. Befeler AS, Palmer DE, Hoffman M, Longo W, Solomon H, Di Bisceglie AM. The safety of intra-abdominal surgery in patients with cirrhosis: model for end-stage liver disease score is superior to Child-Turcotte-Pugh classification in predicting outcome. Arch Surg 2005;140:650-655.
56. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for End-Stage Liver Disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. Ann Surg 2005;242:244-251.
57. Ziser A, Plevak DJ, Wiesner RH, Rakela J, Offord KP, Brown DL. Morbidity and mortality in cirrhotic patients undergoing anesthesia and surgery. Anesthesiology 1999;90:42-53.
58. Albillos A, Colombato LA, Groszmann RJ. Vasodilatation and sodium retention in prehepatic portal hypertension. Gastroenterology 1992;102:931-935.
59. Porcel A, Diaz F, Rendon P, Macias M, Martin-Herrera L, Giron-Gonzalez JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002;162:323-328.
60. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: pathophysiological basis of therapy and current management. J Hepatol 2003;38(Suppl 1):S69-S89.
61. Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229-236.
62. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis 2000;32:605-610.
63. Gines P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. Hepatology 2008;48:1002-1010.
64. Gines P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361:1279-1290.
65. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018-1026.
66. Londono MC, Cardenas A, Guevara M, Quinto L, de Las Heras D, Navasa M, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut 2007;56:1283-1290.
67. Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32-39.
68. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006;130:1652-1660.
69. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 2004;40:802-810.
70. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005;11:336-343.
71. Gines P, Arroyo V, Quintero E, Planas R, Bory F, Cabrera J, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology 1987;93:234-241.
72. Bambha K, Kim WR, Kremers WK, Therneau TM, Kamath PS, Wiesner R, et al. Predicting survival among patients listed for liver transplantation: an assessment of serial MELD measurements. Am J Transplant 2004;4:1798-1804.
73. Kamath PS, Kim WR. Is the change in MELD score a better indicator of mortality than baseline MELD score? Liver Transpl 2003;9:19-21.
74. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl 2003;9:12-18.

http://dx.doi.org/10.3350/cmh.2013.19.2.105

75. Cholongitas E, Marelli L, Shusang V, Senzolo M, Rolles K, Patch D, et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl 2006;12:1049-1061.
76. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol 2005;42(Suppl 1):S100-S107.