Pandey and Saluja, J Clin Trials 2014, 4:5
DOI: 10.4172/2167-0870.1000186

Journal of Clinical Trials
ISSN: 2167-0870

Review Article Open Access

Prognostic Models in Cirrhosis: An Anesthetist Perspective

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Abstract

There has been an increase in the number of patients suffering from liver disease who present for surgery/ noninvasive procedures in diverse clinical scenarios and non transplant settings. Risk estimation and prognostication, therefore, becomes very important for the anaesthetist who will encounter such patients in different clinical settings. The knowledge of merits and demerits of various prognostic models is necessary. Apart from estimation of the life expectancy, these models also tell us about the ability of these patients to withstand a particular procedure or whether the therapeutic option offers an acceptable chance of survival. Improved care in the critical care setting has also enabled many patients with decompensated liver disease to undergo liver transplantation successfully.

Presently prognostication mainly involves the CTP (Child Turcotte Pugh) and MELD (Modification of End Stage Liver Disease) scores. Various attempts have been made to modify them to overcome the shortcomings of the original scores. Knowledge of merits and demerits of each score is essential for appropriate prognostication. However in the critical care setting the ICU scores have been found to be better indicators of mortality. The SOFA (Sequential organ failure assessment) score has been recently modified for critically ill patients with liver disease.

In this review article, we have attempted to summarise the various prognostic scoring systems for risk stratification of patients with liver disease.

Keywords: Prognosis; Liver disease; Surgery; ICU; CTP; MELD; SOFA

Introduction

The understanding of the pathophysiology of liver diseases has grown over the years and so has the therapeutic options available for their management. Progress has been made from shunt surgeries to Transjugular intrahepatic portosystemic shunts (TIPSS) and liver transplant. Improved survival in these patients has resulted in an increase in the number of patients suffering from liver disease who present for surgery/noninvasive procedures in diverse clinical scenarios [1] Improved care in the critical care setting has also enabled many patients with decompensated liver disease to undergo liver transplantation successfully. Risk estimation and prognostication, therefore, becomes very important for the anaesthetist who will encounter such patients in different clinical settings.

End stage liver disease is associated with significant periprocedural morbidity and mortality. Risks in such patients include further deterioration of liver function, worsening of hepatic encephalopathy, renal dysfunction, bleeding due to presence of coagulopathy, unmasking of cirrhotic cardiomyopathy and deterioration of hepatopulmonary syndrome. In order to simplify the process of risk assessment in these patients, a preoperative liver assessment (POLA) check list has been proposed by Im et al. [2].

CTP (Child Turcotte Pugh) and MELD (Model for End stage Liver Disease) scores are being commonly used for peri procedural prognostication of these patients by anesthesiologists. Many of the risks described above i.e. worsening of encephalopathy, coagulopathy, worsening liver function, and kidney dysfunction are accounted for by CTP and MELD scores. Various modifications of these scores have been proposed to predict prognosis in different clinical settings. Apart from estimation of the life expectancy, these models also tell us about the ability of these patients to withstand a particular procedure or whether the therapeutic option offers an acceptable chance of survival. The aim of this review is to help the anaesthesiologist in using the appropriate scoring system in commonly encountered clinical settings. Accordingly the background, merits and demerits of these scoring systems have been discussed.

Child Turcotte Score

Score derivation

The Child-Turcotte classification has been used to assess liver dysfunction and predict surgical morbidity and mortality. Developed in 1964 by Child and Turcotte, it was an empirically derived formula [3,4].

It was used for predicting the outcome after surgery (portocaval shunting and trans-section of the esophagus) in patients with cirrhosis and portal hypertension.

Score variables and range

The Child-Turcotte score included two continuous variables (bilirubin and albumin) and three discrete variables (ascites, encephalopathy, and nutritional status) [5].

Merits

The Child Turcotte score was an easy bedside assessment, not needing difficult algorithmic equation for calculation and prognostication.

Demerits

Assessment of ascites, encephalopathy and nutritional status is a highly subjective, which may lead to variability in the calculated score.

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Received June 19, 2014; **Accepted** September 26, 2014; **Published** September 28, 2014

Citation: Pandey CK, Saluja V (2014) Prognostic Models in Cirrhosis: An Anesthetist Perspective. J Clin Trials 4: 186. doi:10.4172/2167-0870.1000186

The use of this score has been abandoned after its modification to the Child Turcotte Pugh Score.

Child Turcotte Pugh Score (CTP Score)

Score derivation

The Child score was modified in 1972 by Pugh et al. and was termed the Child Turcotte Pugh score (Table 1**).** The most subjective component of the Child-Turcotte score i.e. nutritional status was replaced by prothrombin time [5].

Score variables and range

Thus the score includes variables of bilirubin, prothrombin time, albumin, ascites and hepatic encephalopathy. The score ranges from 5-15, indicating severity as score increases. It has been used to define three classes of liver disease i.e. A, B, and C (Table 1).

In cirrhotics undergoing nontransplant surgery, CTP classes of A, B and C have been historically associated with mortality of 10%, 30%, and 76-82% respectively [6]. Other post operative complications like liver failure, worsening encephalopathy, bleeding, infection, renal failure, hypoxia and intractable ascites have also been correlated with CTP class [1]. Even in patients with CTP class A, the risk of perioperative morbidity is increased when there is associated portal hypertension. It can be reduced by preoperative placement of a transjugular intrahepatic portosystemic shunt (TIPS) in such patients [7,8]. Emergency surgery is associated with a higher mortality rate than non-emergent surgery: 22% versus 10% for patients in Child class A; 38% versus 30% for those in Child class B; and 100% versus 82% for those in Child class C [9].

Risk and morbidity varies with type of surgery and state of decompensation of liver (Table 2**).** For patients with CTP class C cirrhosis, attempts should be made to improve the patients liver function to near class B before surgery. Measures to improve the hepatic function include hepatic function protection, control of ascites, nutritional support, correction of coagulopathy, and reduction of portal vein pressure.

Merits

The major advantage of the CTP score is that it is easily calculated at bedside and does not require complicated mathematical algorithm.

Demerits

1. Variables like ascites and hepatic encephalopathy are influenced by subjective interpretation.
2. The five variables of the CTP score are given the same weight.
3. The conventional CTP system has a ceiling effect at the highest score of 15 points. For instance, patient whose serum bilirubin level is 4 mg/dL has the same CTP score as those whose bilirubin level is 20 mg/dL or higher.
4. The variables included in CTP score are not specific markers of the synthesis (albumin and prothrombin) and elimination (bilirubin) functions of the liver. Changes in serum albumin may be also related to increased vascular permeability, especially in cases of sepsis, and large-volume ascites [10,11]. Similarly, bilirubin can be increased as a consequence of impaired renal function, hemolysis, or sepsis [12]. Prolonged prothrombin time can be a consequence of an intravascular activation of coagulation during sepsis [13].

Model for End Stage Liver Disease Score (MELD)

Score derivation

The MELD score was derived from a population of 231 patients with cirrhosis who underwent elective TIPS (Transjugular intrahepatic portosystemic shunt) placement. The model was subsequently validated in an independent cohort of patients from the Netherlands undergoing TIPS placement [14]. It was found to be a good predictor of three month mortality after TIPS.

Score variables and range

The original MELD contained four variables which included etiology of liver disease. It included INR, serum creatinine, serum bilirubin level and a disease etiology factor for alcoholic liver disease and cholestatic liver disease. The etiology factor was removed as it was not observed to affect mortality prognosis. This modified MELD score was found to be a good predictor of early mortality (3 month) after placement on waiting list for liver transplant [15]. Excluding the cause of cirrhosis had minimal impact on the model accuracy. According to this modified score, patients with bilirubin and creatinine values below 1 mg/dL (17 and 90 mmol/L, respectively) are rounded off to 1 mg/dL to avoid negative logarithmic values. Similarly, patients with INR below 1 are rounded off to 1. Whatever the individual values, the score is empirically capped at 40. Consequently, MELD score represents a

	1 point	2 points	3 points
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	Absent	Slight	Moderate
Albumin	>3.5	2.8-3.4	<2.8
Biliruin	<2	2-3	>3
Bilirubin(PBC/PSC)*	<4	4-10	>10
Prothrombin time(seconds prolonged)	<4	4-6	>6
Inr	<1.7	1.7-2.3	>2.3

Total CTP scores ranges 5 to 15: CTP 5–6 = Child's class A; CTP 7–10 = Child's class B; CTP 11–15 = Child's class C
*PBC-primary biliary cirrhosis
*PSC-primary sclerosing cholangitis

Table 1: CTP Scoring System.

Type of surgery	Score	Conclusion	References
Biliary tract surgery cholecystectomy	CTP A AND CTP B without portal hypertension	Laproscopic cholecysyectomy can be done	[63-66]
	CTP B with portal hypertension and CTP C	Cholecystostomy or open cholecystectomy	
	MELD ≥ 8	Good predictor of morbidity post procedure	
Cardiac surgery	CTP A	CTP scores <8 can safely undergo cardiac surgery with cardiopulmonary bypass, CTP score up to 7, is not a risk factor for death after cardiac surgery.	[67-69]
	CTP ≥ 8	High risk of mortality 50% and 100% with CTP B and C respectively.	
Liver resection	MELD ≥ 9 CTP>6 ASA>2	In patients with MELD ≥9, other treatment modalities to be considered. CTP and ASA scores also independently predict short term (30 day) mortality.	[70-72]

Table 2: Operative risk depending on liver dysfunction in different surgeries.

continuous variable ranging from 6 to 40 (Table 3). Serum creatinine values above 4 mg/dL are rounded to 4. Patients on hemodialysis are given a creatinine value of 4 mg/dL.

MELD has been demonstrated as an excellent predictor of survival in patients who have end stage liver disease [15,16]. Currently MELD score is in popular use for predicting postoperative mortality for cirrhotics undergoing non transplant surgery. The other major use is presently to prioritize organ allocation for liver transplant because it is a good predictor of short term mortality on waiting list [4].

Preoperative MELD scores have been found to be related to development of acute renal failure post liver transplant [17], but poor predictors of post-transplant mortality [18].

Post operative MELD scores within first week after orthotopic liver transplant have been found to predict very early death [19].

Apart from organ allocation and assessment of severity of liver disease, MELD has been positively correlated with other organ dysfunction associated with liver disease. It has been found that higher MELD scores are associated with a higher incidence of features of cirrhotic cardiomyopathy. Some parameters which have shown a positive correlation with a higher MELD score are enlarged left atrial diameter, increased intervenricular septum thickness, increased QTc interval and cardiac output. It was also found that QTc prolongation is more common in patients with alcoholic cirrhosis (50%) as compared to the viral etiology (39%). A higher frequency of diastolic dysfunction is found in patients with MELD ≥ 20. Diastolic dysfunction has also been proposed a predictor of slow clearance of ascites [20].

In a retrospective study, it was found that if the MELD score is less than 11, the post operative mortality is low and risk of surgery is acceptable. The mortality at 30, 90 days and 1 year was 10%, 17% and 28%, respectively [21]. However, it is advisable to conduct surgery in this patient group at an institution with a centre for liver transplantation. With a MELD score of 16-20, the risk of 30 day, 90 day and 1 year mortality is 44%, 55% and 70% respectively. This increases with a rise in MELD score. Therefore, elective procedure should be postponed with score>20. For scores between 12-19, transplant evaluation should be completed before surgery so that they can proceed with urgent transplant, if required. The final score at which elective surgery should be postponed until after liver transplant may also vary with the surgical expertise and organ availability. Any surgery in a decompensated cirrhotic should be done in a tertiary care institute with intensive care support and if possible, liver transplant facilities.

Merits

The MELD score has several distinct advantages over the Child classification [4].

1. The variables which constitute MELD are selected by statistical analysis rather than clinical judgement.
2. The variables are objective and calculated from easily available laboratory parameters.
3. It does not rely on arbitrary cut off values.
4. Appropriate weight is given to each variable according to its influence on prognosis.
5. The MELD score is a continuous variable from 6 to 40. This helps in a better assessment of a larger population.

Demerits

1. Calculation of MELD score is difficult, not user friendly and needs a difficult algorithmic computation.
2. Absence of clearly defined cut-off values for categorizing cirrhotic patients
3. Absence of validation in certain clinical scenarios [4].
4. Complications of cirrhosis which could have a significant impact on the prognosis like portopulmonary hypertension, hepatopulmonary syndrome, hepatocellular carcinoma, hyponatremia, female gender and complications of portal hypertension like ascites, variceal bleed are not considered.
5. Patients with refractory ascites, normal creatinine, and preserved hepatic function could be under-scored with MELD.
6. Even objective parameters like creatinine are subject to changes at different laboratories.

Modifications of CTP Score

Addition of serum creatinine

Giannini et al., [22] prospectively derived the CTP creatinine score from 145 patients and compared it with the the CTP and MELD scores to evaluate 3 month survival in patients with cirrhosis. Patients with serum creatinine<1.1 were assigned a score of 1, serum creatinine between 1.2-1.8 was assigned a score of 2 and those with serum

Score	Formula
MELD£	9.6 loge (creatinine mg/dL)+3.8 loge (bilirubin mg/dL)+11.2 loge (INR)+6.4
UPDATED MELD	1.266 $\log_e$ (1+creatinine) +0.939 $\log_e$ (1+bilirubin) +1.658 $\log_e$ (1+INR).
REFIT MELD	4.082×Log_e (bilirubin c)* +8.485×Log_e (Creatinine c) ** +10.671×Log_e (INR c) *** +7.432.
MELD NA	MELD£ + 1.59 (135-Na [mEq/L])
Integrated MELD	MELD + (age (years) x 0.3) – (0.7xNa (mmol/L)) + 100
REFIT MELD NA	4.258×Loge (bilirubinC)*+6.792 ×Loge (creatinineC)**+ 8.290 × Loge (INRC)*** + 0.652 + (140-NaCα)- 0.194 × (140-NaC) × BiliCCαα+6.327.
Donor MELD	Preoperative MELD × Donor age (years)
MESO Index	(MELD/Na) × 10

*Bilirubin c = bilirubin bounded below by 1 mg/dL.
**Creatinine c = creatinine capped by 0.8 mg/dL below and 3 mg/dL above.
*** INR c = INR bounded by 1 below and 3 above.
£Values of creatinine, bilirubin, and INR below 1 are rounded to 1. Serum creatinine values above 4 mg/dL are rounded to 4. Patients on hemodialysis are given a creatinine value of 4 mg/dL.
αNaC = Na bounded by 125 mEq/L below and 140 mEq/L above.
ααbiliCC = bilirubin bounded below by 1 mg/dL and above by 20 mg/dL.

Table 3: MELD and its various modifications.

creatinine>1.8 were assigned a score of 3. It was observed that though the creatinine modified score had better prognostic accuracy than the CTP score, it was not better than the MELD score.

CTP D score

To overcome the drawback of the ceiling effect, attempts have been made to modify the CTP score by adding another dimension i.e. CTP D class. An additional 1 point was given for patient whose serum bilirubin level and PT prolongation were more than 8 mg/ dL and 11 seconds, respectively and there was a decrease in serum albumin level below 2.3 g/dL. A modified CTP score of 16-18 indicates severely decompensated cirrhosis, was proposed as CTP class D [23]. It was prospectively compared with the original CTP score and MELD score in 436 cirrhotic patients to asses 3 and 6 month mortality.

The predictive ability of the modified CTP was significantly better than original CTP system and was similar to the MELD system. It was able to differentiate disease severity and improve its performance by partially offsetting the ceiling effect. Majority of the patients had chronic Hepatitis B infection in which this modified CTP score was evaluated therefore may not be readily applicable where alcoholism and Hepatitis C are common etiologies. In India, the major etiology of end stage liver disease is Hepatitis C [24]. Therefore, further validation this new class is necessary across different clinical scenarios.

It can be considered a good tool for assessment of severity in centres with non availability of computerised systems for calculation of MELD scores.

Apart From differentiating disease severity i.e. CTP C and CTP D, there is very little role of this classification for the anesthetist.

Modifications of MELD Score

Updated MELD score

Score derivation: Liver transplant candidates with mild hepatic synthetic dysfunction and marked renal insufficiency may have a higher MELD score than candidates with severe liver disease and normal renal function [25]. Since the adoption of MELD, the number of kidney and liver transplants has increased from 2.6% in 2001 to 5.2% in 2005 [26]. This demonstrates that creatinine is heavily weighed in the existing MELD.

It is assumed that mortality is constant for a creatinine less than 1 mg/dl in the original MELD. For a hypothetical increase in serum creatinine from 0.3 mg/dl to 0.6 mg/dl, it reflects a 50% reduction in glomerular filtration rate (GFR). In view of the poor nutritional status, a relatively large numbers of patients are likely to have a serum creatinine of <1 mg/dl at the time of listing.

To overcome this, the updated MELD was derived from 38,899 retrospective patient's waitlisted for liver transplant. To preserve the non negative property of each component, and yet to retain the lower limits, the updated MELD was scored by adding 1 to the value of the individual parameters. Hence, the actual value of the individual parameters can be used instead of the values assigned as lower or upper limit in the original MELD score (Table 3).

Score variables and range: It has been found that candidates with higher serum creatinine (and, by definition, lower bilirubin and/or INR to result in the same MELD score) had significantly lower mortality than candidates with lower serum creatinine (and therefore higher bilirubin and/or INR). In contrast, patients at the same MELD score with higher bilirubin had significantly higher mortality. Hence the Updated MELD assigns lower weight to creatinine and international normalized ratio and higher weight to bilirubin. Since the score is using the actual values of parameters for calculation, no range or capping of the score is done.

Refit MELD Score

Score derivation

The MELD score was originally developed based on data from patients who underwent TIPSS. The refit MELD proposed has been prepared from data of patients who are on waiting list of liver transplant [27].

Wait-list data from adult primary liver transplantation candidates from the Organ Procurement and Transplantation Network were divided into a model derivation set (number of patients=14,214) and validation set (number of patients=13,945).

Optimized MELD score implemented new upper and lower bounds for creatinine (0.8 and 3.0 mg/dL, respectively) and international normalized ratio (1 and 3, respectively). Patients receiving renal replacement therapy were automatically assigned the upper bound for creatinine (3 mg/dL) (Table 3).

Score variables and range

The importance of INR has been reduced in the new formula because it was found that the risk of death was less beyond an INR of three [3]. The serum creatinine demonstrated a triphasic pattern with risk of death, which was linear between 0.8 mg/dL and 3.0 mg/dL. It has been argued that the original upper and lower limits set for the three variables in the United Network for Organ Sharing (UNOS) MELD were based entirely on the clinical intuition of the policy-making body. The new upper limit boundary for INR addresses recent concerns that that the INR might not be an ideal marker to gauge coagulopathy associated with liver dysfunction [28].

It is well known that serum creatinine is influenced by muscle mass, which is frequently decreased in patients with end stage liver disease [29]. The new lower limit of 0.8 mg/dL makes intuitive sense because in patients with end-stage liver disease, normal creatinine does not necessarily mean normal renal function [30]. Lowering the upper limit from 4.0 to 3.0 mg/dL because there is too much emphasis on renal function in the MELD score and that patients with a component of intrinsic renal function are disproportionately advantaged under the current scheme. Score range for refit MELD have not been prescribed yet.

MELD Derivatives

MELD sodium (Na) score

MELD underscores the patients with normal creatinine, preserved hepatic function cand refractory ascites. Patients with persistent ascites with a low serum sodium and a MELD score below 21 are at high risk of early death [31]. The role of hyponatremia as a predictor of mortality has been established for patients on LT waiting list leading to several attempts to incorporate serum sodium (S Na) into the MELD score [32,33]. A modified score including serum sodium, termed MELD-Na, has been proposed as an alternative to MELD score [34] (Table 3).

The accuracy of MELD-Na was shown to be slightly superior to that of MELD in candidates for transplantation [33-35]. A MELD Na level more than 10 was found to be an independent risk factor for

postoperative 90 days mortality in cirrhotics undergoing surgery under general anaesthesia [36].

Demerits

Scores incorporating serum sodium should be interpreted with caution. Many of these patients are on diuretics for ascites, renal dysfunction requiring dialysis, on hypotonic fluids like dextrose. All these conditions can cause alterations of serum sodium. In such patients, alternate scores should be considered.

Integrated (i) MELD Score

The i MELD score incorporates age and serum sodium to increase the prognostic capability. It has been found to be more accurate than the original MELD, in predicting the mortality at 3, 6 and 12-months in an independent cohort of patients with cirrhosis listed for liver transplantation [37] (Table 3).

In a retrospective study of 190 patients with cirrhosis undergoing elective surgery, MELD and 4 MELD based indices were compared with CTP. i MELD was found to have the highest prognostic capacity for predicting mortality after elective surgery. For an i MELD score of less than 35, 35 to 45, and more than 45, the probability of death was 4, 16 and 50.1% respectively [38].

MESO Index

MESO index was retrospectively developed from 213 cirrhotic patients. A value of more than 1.6 independently predicted a higher mortality rate [39] (Table 3).

Refit MELD Sodium

Authors who have proposed the MELD score have also proposed the Refit MELD Na score in the same study [25]. They found that the 90-days wait-list mortality increased as the Na decreased between 140 mEq/L and 125 mEq/L. There was a significant interaction between sodium and bilirubin. The impact of Na on mortality became smaller as the serum bilirubin increased. This interaction was most pronounced when serum bilirubin was between 1 and 20 mg/dL (Table 3).

MELD Gender

The serum creatinine is poorly reflective of renal dysfunction in cirrhotic patients [31]. This issue may be magnified in females because for a given level of creatinine, on an average, women have a lower GFR than men due to their reduced muscle mass [40]. In fact, this sex-related difference in creatinine concentrations may partially account for gender disparities in outcomes on the waiting list in the MELD era. In an analysis of United Network of Organ Sharing (UNOS) data, women were more likely than men to die or become too sick for transplantation and less likely to receive a transplant [41]. Therefore, it has been proposed that a correction factor for gender should be introduced or a more accurate serum marker of renal function could be used, such as cystatin-C to be substituted in prognostic scores [42].

D MELD (Donor MELD)

MELD has been found to be a good predictor of wait list mortality since its introduction in 2002. However, it is a poor predictor of post transplant mortality. The reason for this may be that numerous donor and recipient risk factors interact to influence the probability of survival after liver transplantation. The mortality risk of different donor/recipient combinations is less well defined [43].

Avoidance of D-MELD scores above 1600 has resulted in improved results for subgroups of high-risk patients with donor age ≥ 60 and those with preoperative MELD ≥ 30. D-MELD ≥ 1600 accurately predicted worse outcome in recipients with and without hepatitis C.

Demerits

D MELD score has limited utility in regions where deceased organ availability is limited and majority of the transplants are from live related donors.

Comparative Evaluation of Prognostic Scoring Systems

The refit MELD and updated MELD have been compared with MELD, Meso index, MELD Na and Refit MELD Na by Magdee et al. in 27473 patients [44]. This study was based on the number of lives that would have been saved had additional donor livers been available. Therefore they compared the models with respect to lives saved on transplant list. With respect to number of lives saved there was no significant difference among the models. But the MELD score performed the poorest and the refit MELD performed the best. The degree to which each score predicted death in a month from best to worst were MELD Na, refit MELD Na, MESO, refit MELD and updated MELD.

A Korean study compared the refit MELD, refit MELD Na with MELD, MELD Na and CTP score to predict three month mortality in 882 patients with cirrhosis [45]. The most common etiology of cirrhosis in this study was alcohol. The refit MELD Na was found to be a poor predictor as compared to MELD, MELD NA, and refit MELD. The MELD Na was the best performing score.

The same authors have compared the refit MELD and refit MELD Na with CTP score in patients with cirrhosis and ascites to asses three month mortality [46]. Refit MELD and refit MELD Na showed good predictability for 3 month mortality. But refit MELD Na was not found to be better than refit MELD, inspite of the known relationship between hyponatremia and mortality in cirrhotic patients with ascites.

The above studies suggest that the refit MELD appears to be the most promising modified MELD score. But it has not been evaluated in perioperative/periprocedural settings. Comparison with MELD, MELD Na and CTP scores in such settings is needed.

In a recent retrospective study on 490 cirrhotics who underwent surgery under general anaesthesia, CTP, MELD and MELD Na were compared with respect to the postoperative mortality at 90 days. It was found that the CTP and MELD Na were superior to MELD score in predicting mortality at 90 days [36]. In non-transplant setting also, Cholongitas et al. reviewed literature and stated that MELD does not perform better than CTP score [47].

Cirrhotic patients with Oesophageal variceal Bleed, a MELD of 18 or more, platelet count less than 100,000 and requiring transfusion of 2 or more units of PRBC were at an increased risk of in hospital mortality [48]. In fact, Kumar et al. have suggested that adding the variceal status to CTP score improves its performance in predicting early mortality in cirrhosis [49].

In trauma patients with liver dysfunction addition of specific scores like MELD or CTP to Injury severity score (ISS) also enhances the ability of the latter to predict mortality [50].

However, in a very recent prospective, observational study of 216 cases of hospitalised patients with decompensated cirrhosis, CTP and MELD scores were calculated and followed till discharge or death. The authors concluded that MELD is superior to CTP score in predicting

survival at the time of discharge in decompensated cirrhotics. Addition of renal failure carries a poor prognosis and has a good prognostic value, even better than CTP/MELD [51].

In patients with cirrhosis undergoing major surgical procedures, the risk of mortality within 7 days of surgery is best assessed by American Society of Anaesthesiologists classification of physical status of the patient, whereas mortality after 7 days is best determined by MELD score [21]. Teh et al. have added the ASA classification to the original version of MELD scale as developed by investigators at Mayo Clinic. This modified prognostic scoring system can be used to calculate 7-day, 30-day, 90-day, 1-year, and 5-year surgical mortality risk based on a patient's age, ASA class, INR, and serum bilirubin and creatinine levels (the last 3 items constitute the MELD score) [21].

Other Prognostic Indicators

Sarcopenia

Muscle depletion (sarcopenia) has found to be an independent predictor of wait list mortality in patient with liver disease [52]. This is diagnosed by the measurement of L3 cross-sectional area on CT scan. Sarcopenia is present if the value is less than 52.4 and 38.5 cm^2/m^2 in males and females, respectively. It was found that the outcomes of patients with low MELD scores and sarcopenia were similar to the outcomes of patients with high MELD scores with or without sarcopenia. A diagnosis of sarcopenia can identify those patients who may benefit from more intensive nutritional supplementation and exercise therapy, both of which have been shown to improve outcomes for patients with cirrhosis. Subjective nutritional assesment tools like body mass index and subjective global assessment have proven to be inadequate in predicting mortality in this group of patients.

Demerits

Sarcopenia is objective but is time consuming due to the need of cross sectional muscle imaging.

Von Willebrand Factor Levels

Von Willebrand factor antigen (vWF-Ag) is elevated in patients with liver cirrhosis. This may be due to endothelial activation because of portal hypertension or induction of the synthesis of vWF-Ag in the cirrhotic liver. Reduced activity of ADAMTS13 (vWF-Ag cleaving protease) also increases the levels of vWF. Recently, Ferlitsch et al. have established the clinical significance of vWF levels. They found that a level>315% identified cirrhotic patients with a higher mortality and added prognostic value to the MELD score. In compensated patients with a vWF-Ag value<315%, median time to decompensation or death was 59 months, compared to 32 months in patients with vWF-Ag levels>315% [53].

Demerits

The limitation of using vWF levels for prognostication is that it can be fallaciously high or low in certain clinical scenarios. Infections, malignancies, interferon therapy and physical therapy can elevate vWF levels, whereas active bleeding and hereditary deficiency could reduce them and lead to false prognostication [53].

Prognosis in Setting of Critical Care

Cirrhotic patients admitted to an Intensive Care Unit (ICU) have a poor prognosis. Aim of prognostic models in intensive care settings is to identify patients who will benefit from aggressive treatment. A focussed approach in this situation can either help in the recovery of hepatic function or act as a bridge to "rescue" transplantation.

Prognositic scores in critically ill cirrhotic patients can be classified in three main categories

1. Liver specific (CTP and MELD scores)

2. General ICU scores (SAPS II and APACHE)

3. Organ failure scores (OSF AND SOFA)

Patients with liver disease admitted to ICU usually present with multiorgan dysfunction. Therefore scoring systems like CTP score and MELD which determine severity of liver disease have not found to be good predictors of ICU mortality. CTP score does not include any marker of other organ function and MELD score lacks any indicator of portal hypertension, the complications of which are a frequent cause of admission to ICU.

APACHE score

The original APACHE score was developed in 1981 to classify groups of patients according to severity of illness and was divided into two sections: a physiology score to assess the degree of acute illness; and a preadmission evaluation to determine the chronic health status of the patient [54]. APACHE II, now the world's most widely used severity of illness score. In APACHE II, there are just 12 physiological variables. The worst value recorded during the first 24 hours of a patient's admission to the ICU is used for each physiological variable. The principal diagnosis leading to ICU admission is added as a category weight so that the predicted mortality is computed based on the patient's APACHE II score and their principal diagnosis at admission. Subsequently APACHE III and APACHE IV have also been developed.

Simplified acute physiology score (SAPS)

SAPS was developed and validated in France in 1984. It used 13 weighted physiological variables and age to predict risk of death in ICU patients. SAPS is calculated from the worst values obtained during the first 24 hours of ICU admission [54]. In 1993, Le Gall et al. developed SAPS II, which includes 17 variables: 12 physiological variables, age, type of admission, and 3 variables related to underlying disease. SAPS III has also been developed in 2005.

SOFA score

The SOFA score defines organ failure by a score of three or four for each of the six respective organ systems (respiratory, cardiovascular, hepatic, renal, coagulation and neurologic) [54].

The development of three or more organ failures carries an extreme risk of death, which is higher in cirrhotic patients (an average of 79%) when compared with general ICU patients (55%). The mortality rate of cirrhotic patients with septic shock is higher than in noncirrhotic patients [55,56].

Organ failure scores like Sequential organ failure assessment (SOFA) have been found to perform better [55]: SOFA>SAPS II>MELD>Child-Pugh [57]. Mortality is best correlated with a SOFA score above nine.

The APACHE II and SAPS II score are the most commonly studied scores along with SOFA score to predict mortality in critically ill patients with liver disease [55]. In all these studies SOFA score has emerged the clear winner in the ability to predict mortality.

Organ/system	0	1	2	3	4
Liver (bilirubin, mg/dL)	<1.2	≥1.2 to ≤ 2.0	≥2.0 to <6.0	≥6.0 to <12.0	≥12.0
Kidney (creatinine, mg/dL)	1.2	≥1.2 to≤ 2.0	≥2.0 to <3.5	≥3.5 to <5.0	≥5.0 or use of renal replacement therapy
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (international normalized ratio)	<1.1	≥1.1 to ≤1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or platelet count ≤ 20×10^9/L
Circulation (mean arterial pressure, mm Hg)	≤ ≥70	<70	Dopamine ≤ 5 or dobutamine or terlipressin	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E >0.1 or NE >0.1
Lungs PaO/FiO_2 or	> 400	>300 to ≤400	200 to ≤ 300	>100 to ≤200	≤ 100
SpO_2/FiO_2	>512	357 to ≤ 512	>214 to ≤ 357	>89 to ≤ 214	≤ 89

Table 4: CLIF SOFA score.

Accuracy of organ failure scores increase when they are reassed 2 days after admission To ICU. Reassesment at 48 hours therefore may be a useful guide to the degree of intensification of efforts.

The European Association for the Study of the Liver-chronic liver failure (EASL-CLIF) Consortium recently defined the CLIF SOFA score with cut off values specifically identified in cirrhotic patients [58] (Table 4).

Like the original score, the CLIF-SOFA score assessed six organ systems (liver, kidneys, brain, coagulation, circulation, and lungs), but it also took into account some specificities of cirrhosis. The CLIF SOFA score was developed based on clinical experience of the authors. Based on the score the they identifed four groups of patients with varying number of organ failures. They found that patients with two organ failures had a 28 day mortality rate of 32%, while those with three or more organ failures had a 28 day mortality of 76%.

Sixty percent of the patients they studied had alcoholic liver disease and twenty percent had hepatitis C related liver disease. Therefore the authors have suggested evaluation of this score where other etiologies of liver disease may be predominat e.g Hepatitis B. Further validation of this score is therefore recommended.

The cause of ICU admission is also associated with the prognosis of patients. Patients admitted in ICU for acute variceal bleeding or hepatic encephalopathies have a markedly improved ICU survival of 76.5% vs. 36.2% for patients admitted for infection [59].

Karvellas et al. retrospectively assessed the outcome of 198 critically ill cirrhotic patients who received a liver transplant (LT) while in ICU in five transplant centres in Canada [60]. Eighty eight percent were on vasopressors, 56% received renal replacement therapy and 87% were mechanically ventilated prior to LT. The SOFA score was 12.5 ± 4 on ICU admission, 13 ± 5 at 48 hours and 14 ± 4 on the day of LT. Mortality after LT was 16% at 90 days, 26% at 1 year and 38% at 3 years. A SOFA score ≥ 10 in cirrhotic patients usually predicts mortality in >90% in a median time of 8 days without a liver transplant. The authors found that SOFA on admission, 48 hours after ICU admission and on the day of LT was not associated with increased risk of 90-day mortality. The only independent risk factor of death identified was the age. They concluded that SOFA at 48 hours is currently the best score to predict mortality in cirrhotic patients admitted to ICU. It is associated with a higher risk of death waiting for LT and is not associated with a worse outcome after LT while in ICU. These results appear to be promising for further prospective evaluation in regions with successful deceased donor transplant programs.

The persistence of three or more organ failures and the need for three or more organ supports (i.e. inotropic support, mechanical ventilation and continuous renal replacement therapy) may lead to consider a limitation in life sustaining treatments, as a fatal outcome is almost constant [55]. A multidisciplinary approach between hepatologists, intensivists and transplant surgeons is mandatory.

Conclusion

Inspite of the availability of various prognostic models for risk stratification and prediction of morbidity and mortality in patients with cirrhosis, the score most popularly used is the CTP score. It allows rapid bedside prognostication and is fairly reliable. It is still a good tool for anaesthesiologists for prognostication of patients with liver disease who undergo non transplant surgery. But the MELD score has recently challenged the flagship bearer status of the CTP score [2].

Prognostic scoring systems, especially the MELD score is constantly undergoing changes. In view of worldwide differences of liver transplantation with respect to indication and method (deceased donor v/s live donor), prognostication should be suited to the particular region. Few countries like Canada and United Kingdom have developed their own models of CAN wait and UKELD which are working well for them [61,62]. It is time, we developed our own Asian or Indian model for prognostication. ICU scores like the SOFA scores are more reliable in the critically ill cirrhotic patient. Modified scores like CLIF SOFA scores need further validation. Newer indicators like assessment of sarcopenia seem to be promising, but search for simpler cheaper and safer techniques of assessment is needed.

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