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Predictors of Mortality in the Critically Ill Cirrhotic: Is MELD Enough?

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Abstract

Background: Cirrhotic patients in the ICU urgently require liver transplantation but are at high risk for perioperative mortality. The Model for End Stage Liver Disease (MELD) score, which was recently updated to incorporate serum sodium, estimates survival probability in patients with cirrhosis but needs further evaluation in the critically ill. The purpose of this study was to evaluate the predictive power of ICU admission MELD scores in the ICU population and identify clinical risk factors associated with increased mortality.

Study Design: This was a retrospective review of all cirrhotic patients admitted to the ICU between January 2011 and December 2014. Patients who were discharged or underwent a transplant (Survivors) were compared to those who died (Nonsurvivors). Demographics, admission MELD scores, and clinical risk factors were recorded. Multivariate regression was utilized to identify independent predictors of mortality, and measures of model performance were assessed to determine predictive accuracy.

Results: Of 276 patients who met inclusion criteria, 153 (55%) patients were considered survivors and 123 (45%) patients were nonsurvivors. Survivor and nonsurvivor cohorts were similar in age, gender, and etiology of cirrhosis. Nonsurvivors had increased median MELD, GI bleeding, infection, mechanical ventilation, encephalopathy, vasopressors, dialysis, renal replacement therapy, requirement of blood products (PRBCs, platelets, FFP), and ICU length of stay. MELD demonstrated low predictive power, with a c-statistic of 0.73. Multivariate analysis identified MELD score (AOR 1.05), mechanical ventilation (AOR 4.55), vasopressors (AOR 3.87),

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and CRRT (AOR 2.43) as independent predictors of mortality, with stronger predictive accuracy (c-statistic 0.87).

Conclusion: MELD demonstrated relatively poor predictive accuracy in critically ill patients with cirrhosis and may not be the best indicator for prognosis in the ICU population. Prognostic accuracy is significantly improved when variables indicating organ support (mechanical ventilation, vasopressors, and CRRT) are included in the model.

Keywords

Critical Care; Liver Transplantation

Introduction

Patients with decompensated liver cirrhosis frequently require critical care management, accounting for approximately 26,000 Intensive Care Unit (ICU) admissions each year in the United States (1). In the ICU, liver disease is often accompanied by sepsis and multiple organ dysfunction (2), resulting in mortality rates between 43% and 87% (3–7). Due to high resource utilization and high mortality (1, 8), accurate prognostic indicators for use in the ICU are important for guiding treatment decisions, talking with patients and families, and identifying patients who may benefit most from continued ICU care.

The Model for End-stage Liver Disease (MELD) is currently used to predict 90-day mortality in patients with cirrhosis and provides an objective, continuous scale of liver disease severity. While MELD was originally developed for patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure, it has been examined as a prognostic indicator across a range of liver diseases and populations (9–11) and is now the key factor in assigning priority for liver transplantation. The initial MELD score implemented in 2002 incorporated laboratory values of creatinine, bilirubin, and international normalized ratio (INR) for prothrombin time, but did not include any surrogate for portal hypertension. In 2016, the Organ Procurement and Transplantation Network (OPTN) updated the model to include serum sodium (MELD-Na), as several studies have found sodium to be an important predictor of survival among liver transplantation candidates (12, 13).

While MELD and the new MELD-Na have high prognostic value in the cirrhotic population as a whole (12, 14), these models were not designed to predict survival in critically ill patients (15). The use of MELD and MELD-Na as prognostic indicators in the ICU, where liver-specific complications are often compounded by extrahepatic organ dysfunction, needs further investigation. The purpose of this study was to determine whether adding clinical factors indicative of organ dysfunction to MELD and to MELD-Na improves the predictive accuracy for survival of these models in a subset of patients whose severity of illness is significantly higher than that of traditionally studied cirrhotic populations.

Methods

This is a single-center retrospective review of all adult patients (≥18 years of age) who were admitted to the intensive care unit (ICU) with a diagnosis of liver cirrhosis between January 1, 2011 and December 31, 2014. Demographics and clinical data including age, sex, number of pre-transplant ICU admissions during the hospital stay, first ICU admission MELD and MELD-Na scores, and incidence of gastrointestinal (GI) bleeding, infection, hepatic encephalopathy, ascites, mechanical ventilation requirement, vasopressor requirement, dialysis requirement, continuous renal replacement therapy (CRRT) requirement, and transfusion data [packed red blood cells (PRBCs), platelets, and fresh frozen plasma (FFP)] during pre-transplant ICU stays were collected via chart review.

MELD and MELD-Na scores were calculated according to current OPTN guidelines(16). MELD was calculated using the equation $0.957 \times \text{Log}_e(\text{Creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{Bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$, rounded to the nearest tenth decimal place and multiplied by 10. When calculating MELD, laboratory values less than 1.0 were set to 1.0 and creatinine values were adjusted for dialysis with a limit of 4.0 mg/dL. For patients with a MELD score greater than 11, MELD-Na was calculated using the equation MELD-Na = MELD + 1.32*(137-Sodium mmol/L) – [0.033*MELD*(137-Sodium mmol/L)]. Sodium values less than 125 mmol/L were set to 125 and sodium values greater than 137 mmol/L were set to 137, per OPTN policy. An upper limit of 40 was not applied for MELD and MELD-Na scores.

If MELD and MELD-Na scores were not available on the date of admission, the earliest available scores within 7 days of admission were used for analysis. When more than one laboratory result for the same test was recorded within a 24-hour period, the earliest test value was used in MELD and MELD-Na calculations. GI bleeding was demonstrated on esophagogastroduodenoscopy or noted on the medical record during the ICU stay. Infection was defined by any positive culture, including blood, sputum, urine and paracentesis fluid cultures. Hepatic encephalopathy and ascites were defined by a noted diagnosis on the medical record. Vasopressor requirement was defined by any vasopressor (norepinephrine, epinephrine, vasopressin, dobutamine, dopamine, ephedrine) or combination of vasopressors administered in the ICU. Outcomes included mortality, hospital length of stay (LOS), and total ICU LOS.

Patients were followed until transplant, discharge, or death and were categorized by disposition status; patients who were discharged or underwent a transplant were considered survivors while those who died or were discharged to hospice after withdrawal of care were considered nonsurvivors. Clinical data and outcomes were compared between survivors and nonsurvivors. Continuous variables were analyzed using the Student's *t* test for parametric data and the Mann Whitney U test for non-parametric data. Categorical variables were analyzed using chi-squared or Fisher's exact test.

Logistic regression analysis was used to calculate the adjusted odds ratio for mortality in univariate analyses of MELD and MELD-Na. A multivariate model was then constructed to adjust for relevant clinical risk factors in addition to MELD scores. The variables age, GI

bleeding, infection, hepatic encephalopathy, ascites, mechanical ventilation, vasopressors, hemodialysis, CRRT, units of PRBCs transfused, units of platelets transfused, units of FFP transfused, and MELD score were entered into a forward stepwise regression. This was then repeated using MELD-Na in the place of MELD. The accuracy of each logistic regression model for predicting mortality was assessed using the concordance statistic (c-statistic) as a measure of discrimination and the Hosmer-Lemeshow goodness-of-fit test to measure calibration. The c-statistic indicates how well the model can distinguish between outcomes —in this case, between patients who survive and those who do not. The c-statistic ranges from 0 to 1, where 0.5 indicates what would be predicted by chance alone and 1 indicates perfect discrimination. The Hosmer-Lemeshow test measures how well a model fits the data, with a p-value >0.05 indicating acceptable calibration. Statistical analysis was performed using Statistical Package for the Social Sciences (Version 22, SPSS Inc., Chicago, IL). P-values less than 0.05 were considered statistically significant. This study was approved by the institutional review board of Cedars-Sinai Medical Center.

Results

A total of 276 pre-transplant patients admitted to the ICU with a diagnosis of cirrhosis were included in the analysis. Mean age was 58 years and (59%) of patients were male. The predominant etiologies of cirrhosis were viral hepatitis (33%), alcoholic liver disease (28%), cryptogenic, and nonalcoholic steatohepatitis (13%). Median ICU admission MELD was 30+/−11.5 and median ICU admission MELD-Na was 31+/− 11.0. One hundred and fifty three (55%) patients were considered survivors and 123 (45%) patients were nonsurvivors (Table 1).

Survivor and nonsurvivor cohorts were similar in age, gender, etiology of cirrhosis, history of prior transplant, incidence of hyponatremia (serum sodium <135 mmol/L) on ICU admission, and hospital LOS (Table 1). Nonsurvivors had higher median MELD–Na at the time of ICU admission (36 v. 26, p<0.01) and longer ICU LOS (12 v. 4 days, p<0.01). When clinical risk factors were compared between cohorts, nonsurvivors had a significantly higher incidence of gastrointestinal bleeding (37% v. 16%, p<0.01), infection (72% v. 43%, p<0.01), hepatic encephalopathy (80% v. 59%, p<0.01), mechanical ventilation requirement (87% v. 37%, p<0.01), vasopressor requirement (81% v. 28%, p<0.01), dialysis requirement (44% v. 31%, p=0.03), PRBC requirement (85% v. 49%, p<0.01), platelet requirement (72% v. 33%, p<0.01), and FFP requirement (81% v. 33%, p<0.01). In addition, nonsurvivors required a higher median number of units of PRBCs (7 v. 2 units, p<0.01), platelets (4 v. 1 units, p<0.01), and FFP (10 v. 2 units, p<0.01) (Table 2).

Both MELD and MELD-Na at the time of ICU admission were found to be independently associated with mortality on univariate analysis (Table 3). Multivariate analysis identified MELD score (AOR 1.05), CRRT (AOR 2.43), vasopressors (AOR 3.87), and mechanical ventilation (AOR 4.55) as independent predictors of mortality. When the MELD-Na score was used in place of MELD in the regression model, the same four predictors of mortality were identified, with little difference in respective AORs (Table 3).

Each regression model demonstrated acceptable calibration, according to the Hosmer and Lemeshow test. The univariate model of MELD had a c-statistic of 0.74, while the multivariate model including mechanical ventilation, vasopressors, CRRT and MELD had a c-statistic of 0.87. Replacing MELD with MELD-Na did not affect the c-statistic in either the univariate or the multivariate model (Table 3).

Discussion

Although the MELD score remains the gold standard for determining priority for liver transplantation, the use of MELD and MELD-Na as prognostic indicators for cirrhotic patients in the ICU needs further evaluation. In our study, we found that both MELD and MELD-Na had a reasonable predictive power of in-hospital mortality in ICU patients. When adjusting for clinical variables associated with organ dysfunction in multivariate analysis, model accuracy improved significantly, increasing the c-statistic in each model.

In agreement with previous studies on critically ill patients (17, 18), adding serum sodium to MELD did not significantly improve predictive accuracy in the ICU population. Although hyponatremia has been found to be associated with ascites, hepatorenal syndrome and liver-related death (19–22), several studies have shown a decreasing effect of hyponatremia with increasing MELD score (12, 23). In a study examining predictors of early death in cirrhotic patients, Heuman and colleagues found that the predictive advantage of incorporating serum sodium, persistent ascites and MELD in logistic regression was most apparent in patients with MELD scores below 21(23). In patients with MELD scores above 21, the regression model that included serum sodium, ascites and MELD score performed similarly to MELD alone, and serum sodium was not found to be independently associated with 180-day mortality. Kim and colleagues investigated the effect of serum sodium at different MELD scores, and found the effect of hyponatremia to be small at MELD scores above 30(12). In agreement with these studies, we found that MELD and MELD-Na were comparable predictors of mortality in the ICU, where patients had a median MELD score of 30 (20–38).

Previous studies have found that scoring systems for predicting survival in the general ICU population, such as the Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiology Score (SAPS II), have better predictive accuracy than liver-specific scoring systems in critically ill cirrhotic patients (15, 17, 18, 24). These findings and ours suggest that using scoring systems that incorporate markers of organ dysfunction, rather than using those specific to liver disease severity, may improve prognostication in this population. When validating MELD as a predictor of 3-month mortality in cirrhotic patients, Kamath and colleagues found that adding individual complications of portal hypertension, such as variceal bleeding, ascites, and encephalopathy to MELD did not offer additional prognostic information. In patients hospitalized for hepatic decompensation, the addition of each variable added only 0.01 to the overall c-statistic(14). Of note, the patients included in Kamath's analysis had a relatively low median MELD of 9 compared to the ICU patients in our study who had a median MELD of 30. When we added surrogate variables for organ dysfunction (CRRT, vasopressors, and mechanical ventilation) to MELD in our population of patients with advanced liver disease, a significant increase in c-statistic was observed (+0.14).

The factors identified as independent predictors of mortality in this study—mechanical ventilation, requirement of vasopressors, and CRRT—are important indicators for prognosis in the critically ill cirrhotic patient(2). Previous studies have found that cirrhotic patients who require mechanical ventilation often progress to multiorgan failure and have high mortality rates(25–27). Additionally, mechanical ventilation has been shown to be independently associated with mortality in this population (17, 28). In agreement with these findings, we observed a 65% in-hospital mortality rate in patients who required mechanical ventilation and found that ventilated patients had an adjusted odds of mortality over four times that of patients who did not require lung support.

In addition to developing pulmonary dysfunction, patients with decompensated cirrhosis often develop changes in their cardiovascular profile, including hyperdynamic circulation with low systemic vascular resistance, low systemic arterial pressure, elevated cardiac output, and abnormal distribution of blood volume (2, 29). The requirement of vasopressors, a marker of hemodynamic instability and cardiovascular dysfunction, was observed in 51% of our total population and 81% of nonsurvivors. In agreement with previous literature (4, 17), the requirement of vasopressors was an important indicator of prognosis and was found to be independently associated with increased mortality (AOR 3.9).

Renal dysfunction is also common in critically ill patients with cirrhosis and is associated with increased morbidity and mortality (30, 31). CRRT is typically initiated when a patient in renal failure is unable to tolerate fluid shifts associated with hemodialysis, indicating high disease severity and poor prognosis. In our study, 98 patients required CRRT during their ICU stay and of these patients, 73 (74.5%) died. Additionally, the adjusted odds of mortality in patients who required CRRT were 2.4 times the odds of mortality in those who did not require replacement therapy, emphasizing the importance of renal support as a prognostic indicator in this population.

As a retrospective analysis, this study has several limitations. Many of the variables investigated in this study were categorically defined by the presence of a specific comorbidity or type of organ support. Defining our variables in this way did not allow us to account for varying degrees of severity. Additionally, as this study focused on the care of cirrhotic patients in the ICU and predictors of pre-transplant mortality, we did not examine post-transplant outcomes. Identifying which patients may be “too sick” for transplantation continues to be an important issue, and analyzing post-transplant outcomes in future studies is necessary to examine this issue. At our institution, we do not have specific pre-trasnplant criteria which each patient must exactly meet prior to considering them and OLT candidate, but rather use a combination of clinical factors on a patient to patient basis. However, this limitation is somewhat corrected for by the utilization of a multidisciplinary team in a well-established transplant center, located in a region where the median MELD at the time of transplantation is 35, well above the national median of 28 (32).

Conclusion

Both MELD and MELD-Na demonstrated reasonable accuracy in critically ill patients with end-stage liver disease and secondary organ dysfunction. Including organ support variables

such as CRRT, vasopressors, and mechanical ventilation in addition to MELD may help to improve prognostication in the ICU setting. Future studies examining how ICU patients with these risk factors fair after liver transplantation are warranted and may help to maximize overall patient and graft survival.

Abbreviations:

CRRT	continuous renal replacement therapy
ICU	intensive care unit
INR	international normalized ratio
LOS	length of stay
MELD	Model for End Stage Liver Disease
OPTN	Organ Procurement and Transplantation Network

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Table 1.

Patient Demographics

	All patients n=276	Survivors n=153 (55.4%)	Nonsurvivors n=123 (44.6%)	p-value
Age (years)				0.22
mean (SD)	57.9 (10.9)	57.2 (11.5)	58.7 (10.1)	
median [IQR]	59 [51–65]	58 [50–64]	59 [52–65]	
Male, n (%)	163 (59.1)	93 (60.8)	70 (56.9)	0.52
Etiology of Cirrhosis				0.36
viral infection, n (%)	91 (33.0)	46 (30.1)	45 (36.6)	
alcohol intake, n (%)	76 (27.5)	48 (31.4)	28 (22.8)	
nonalcoholic steatohepatitis, n (%)	35 (12.7)	15 (9.8)	20 (16.3)	
cholestatic, n (%)	17 (6.2)	10 (6.5)	7 (5.7)	
cryptogenic/other, n (%)	57 (20.7)	34 (22.2)	23 (18.7)	
Number of ICU Admissions				**0.03**
mean (SD)	1.2 (0.6)	1.1 (0.4)	1.3 (0.7)	
median [IQR]	1 [1–1]	1 [1–1]	1[1–1]	
Prior Liver Transplant, n (%)	12 (4.3)	6 (3.9)	6 (4.9)	0.70
ICU Admission Creatinine				<0.01
mean (SD)	2.5 (1.9)	2.3 (1.9)	2.9 (1.8)	
median [IQR]	2 [1–3.6]	1.6 [0.8–3.2]	2.6 [1.5–4]	
ICU Admission Bilirubin				<0.01
mean (SD)	12.6 (13.8)	9.6 (12.6)	16.2 (14.4)	
median [IQR]	6.2 [2.2–19.0]	3.7 [1.6–12.65]	10.75 [4.5–26]	
ICU Admission INR				<0.01
mean (SD)	2.4 (1.4)	2.0 (0.9)	3.0 (1.8)	
median [IQR]	2 [1.5–2.9]	1.7 [1.4–2.4]	2.6 [1.9–3.6]	
ICU Admission Na				0.53
mean (SD)	136.6 (6.5)	136.6 (6.1)	136.6 (7.1)	
median [IQR]	137 [133–140]	137 [134–140]	136 [132–141]	
Hyponatremia (Na <135mmol/L), % (n)	95/263 (36.1)	46/145 (31.7)	49/118 (41.5)	0.100
ICU Admission MELD				<0.01
mean (SD)	28.8 (11.5)	24.6 (10.5)	33.9 (10.7)	
median [IQR]	30 [20–38]	23 [15.5–34]	35 [27–41]	
ICU Admission MELD-Na				<0.01
mean (SD)	29.4 (11.0)	25.5 (10.3)	34.3 (10.0)	
median [IQR]	31 [22–38]	26 [17–34]	36 [28–41]	
Hospital LOS				0.97
Mean # of days (SD)	22.8 (22.0)	22.7 (22.8)	22.8 (21.2)	
median [IQR]	16 [8–30]	15 [8–31]	18 [8–29]	
Total ICU LOS				<0.01
Mean # of days (SD)	11.6 (13.7)	8.0 (10.5)	16.1 (15.7)	
median [IQR]	7 [3–15]	4 [3–9]	12 [5–21]	

SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; INR, international normalized ratio; MELD(i), initial model for end-stage liver disease before incorporation of serum sodium; MELD, model for end-stage liver disease; MELD-Na, MELD incorporating serum sodium; LOS, length of stay

Table 2.

Clinical Risk Factors in the ICU

	All patients n=276	Survivors n=153	Nonsurvivors n=123	p-value
Gastrointestinal Bleeding, n (%)	69 (25.0)	24 (15.7)	45 (36.6)	<0.01
Infection, n (%)	154 (55.8)	66 (43.1)	88 (71.5)	<0.01
Hepatic Encephalopathy, n (%)	188 (68.1)	90 (58.8)	98 (79.7)	<0.01
Ascites, n (%)	152 (55.1)	81 (52.9)	71 (57.7)	0.44
Mechanical Ventilation, n (%)	164 (59.4)	57 (37.3)	107 (87.0)	<0.01
Vasopressor Requirement, n (%)	142 (51.5)	42 (27.5)	100 (81.3)	<0.01
Dialysis Requirement, n (%)	102 (37.0)	48 (31.4)	54 (43.9)	0.03
CRRT Requirement, n (%)	98 (35.5)	25 (16.3)	73 (59.3)	<0.01
PRBC Requirement, n (%)	180 (65.2)	75 (49.0)	105 (85.4)	<0.01
units, mean (SD)	4.5 (7.7)	2.3 (5.1)	7.3 (9.4)	<0.01
units, median (IQR)	1.0 (0–5.4)	0 (0–2.2)	3.7 (1–9.6)	
Platelet Requirement, n (%)	139 (50.4)	50 (32.7)	89 (72.4)	<0.01
units, mean (SD)	2.5 (5.1)	1.1 (3.1)	4.2 (6.4)	<0.01
units, median (IQR)	0.7 (0–2.2)	0 (0–1.0)	1.3 (0–5.4)	
FFP Requirement, n (%)	151 (54.7)	51 (33.3)	100 (81.3)	<0.01
units, mean (SD)	5.5 (11.4)	2.0 (5.3)	9.9 (15.0)	<0.01
units, median (IQR)	0.8 (0–4.7)	0 (0–1.0)	3.1 (0.8–12.5)	

CRRT, continuous renal replacement therapy; PRBCs, packed red blood cells; FFP, fresh frozen plasma; SD, standard deviation; IQR, interquartile range; 1 unit PRBCs=350 cc; 1 unit platelets=250 cc; 1 unit FFP= 350 cc

Table 3.

Logistic Regression for Predicting Mortality

Regression Model	Predictors of Mortality	AOR (95%CI)	p-value	c-statistic
MELD[1]	MELD score	1.08 (1.06–1.11)	<0.01	0.73
MELD-Na[2]	MELD-Na score	1.09 (1.06–1.12)	<0.01	0.73
Multivariate Model with MELD[3]	MELD score	1.05 (1.02–1.08)	<0.01	0.87
	CRRT	2.43 (1.21–4.91)	0.01	
	Vasopressors	3.87 (1.91–7.82)	<0.01	
	Mechanical Ventilation	4.55 (2.15–9.61)	<0.01	
Multivariate Model with MELD-Na[4]	MELD-Na score	1.05 (1.02–1.09)	<0.01	0.87
	CRRT	2.44 (1.21–4.92)	0.01	
	Vasopressors	3.86 (1.91–7.82)	<0.01	
	Mechanical Ventilation	4.58 (2.17–9.68)	<0.01	

[1] Hosmer Lemeshow χ^2: 4.4, p=0.817

[2] Hosmer Lemeshow χ^2: 8.9 p=0.348

[3] Variables entered into a forward stepwise regression: Age, MELD score, GI Bleed, Infection, Hepatic Encephalopathy, Ascites, Mechanical Ventilation, Vasopressors, Dialysis, CRRT, units of PRBCs, units of Platelets, units of FFP. Hosmer Lemeshow χ^2: 10.1, p=0.258

[4] Variables entered into a forward stepwise regression: Age, MELD-Na score, GI Bleed, Infection, Hepatic Encephalopathy, Ascites, Mechanical Ventilation, Vasopressors, Dialysis, CRRT, units of PRBCs, units of Platelets, units of FFP. Hosmer Lemeshow χ^2: 10.9, p=0.207

MELD, model for end stage liver disease; MELD-Na, MELD incorporating serum sodium; CRRT, Continuous Renal Replacement Therapy