Model for End-stage Liver Disease (MELD) in spontaneous bacterial peritonitis –a clinical study at a tertiary health center in Nepal

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ABSTRACT

Background and Aims: The aim of this study was to assess the predictive value of different variables including the Model of End-stage Liver Disease (MELD) scores in hospitalized patients with spontaneous bacterial peritonitis (SBP) and its correlation with adverse outcomes.

Methods: A cross-sectional study of 73 patients diagnosed with cirrhosis, ascites, and spontaneous bacterial peritonitis admitted to a gastroenterology department from February 2010 to November 2012. MELD scores were calculated using laboratory parameters and the United Network of Organ Sharing (UNOS) internet MELD tool.

Results: Categorical variables and mortality status were analyzed for association by chi-square test. MELD scores and all-cause mortality were found to be positively correlated. Mortality was higher among the groups with MELD scores greater than 15. Upon stratification of the groups by mortality status, only age and urea level were novel and consistent predictors of mortality.

Conclusions: In this Nepalese sample of cirrhotic patients, MELD scores along with age and urea level were confirmed as significant predictors of mortality.

INTRODUCTION

Patients with liver cirrhosis and ascites are particularly prone to spontaneous bacterial peritonitis due to suppression of the immune system, altered gastrointestinal tract permeability, and small intestinal bacterial overgrowth.[1,2] Studies from the western literature in the 1970s reported the prevalence of SBP to be between 5% to 10% in cirrhotic patients with ascites.[3,4] However, with improved awareness, better techniques, and greater availability of laboratory facilities, more recent estimates place SBP prevalence at 30%.[5]

Cirrhosis is a common diagnosis in the inpatient and outpatient populations seeking care at the Gastroenterology Department of the Institute of Medicine. The high rate of alcohol abuse, compounded by the prevalence of viral hepatitis in the Nepali community, results in the high incidence of SBP at our facility.[6,7] Because of low socioeconomic level and limited resource availability, repetition of laboratory tests for biochemical parameters is not feasible at every clinic visit.[8] A mechanism for predicting patient outcomes with minimal intervention would greatly facilitate patient care and is imperative in this low-resource setting.

MELD is a tool which has been used to predict outcomes in many end-stage liver conditions including adverse outcomes in viral or alcoholic hepatitis.[9,10] It was derived in 2001 by the Mayo Clinic and adopted by the UNOS (United Network of Organ Sharing) for allocation and quality control of liver transplantation.[11,12] Using three biochemical parameters (bilirubin, creatinine, INR), the MELD calculator has been demonstrated to successfully predict all-cause mortality.[9-12]

Because of the significant number of cirrhosis patients who develop SBP, we assessed the applicability and reliability of using the MELD tool to predict mortality in our patient population.

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METHODS:

Study design and population

The Institute of Medicine is a tertiary care facility located in the heart of Kathmandu. This patient base consists primarily of an indigent or lower-income population who has minimal resources for medical care or preventive services. Using laboratory and clinical parameters obtained at admission, a cross-sectional study was designed to 1) assess the applicability of the MELD tool in this low-income, low-resource setting and 2) determine if there were other clinical variables associated with increased mortality.

Patients with cirrhosis and new-onset SBP and who were admitted between February 2010 and November 2012 to the Gastroenterology Department of the Institute of Medicine were eligible for inclusion in the study. Patients diagnosed with SBP by diagnostic paracentesis during admission were eligible for the study irrespective of the etiology of cirrhosis. Patients with ascites fluid neutrophil cell counts greater than 250 cell/mm^3 were considered to have SBP according to the recommended guidelines of European Association for the Study of the Liver.[13] Mortality was defined as death occurring during the hospital admission.

Patients were excluded if they presented with: (i) antibiotics within 2 weeks of admission; (ii) gastrointestinal bleed within 2 weeks of admission; (iii) history of congestive heart failure or malignancy. A total of 73 unique patients were consecutively admitted during the enrollment period and included in this study.

Data collection

Data collected included demographic variables, clinical signs and symptoms, and laboratory values. Clinical findings assessed included: fever, altered sensorium, oliguria, jaundice, icterus, asterixis (flapping tremor), abdominal pain, distension and tenderness, hepatomegaly, splenomegaly and history of alcohol consumption, or gastrointestinal bleeding. Laboratory data included complete blood count, total serum hemoglobin, liver and renal function and coagulation studies. The MELD score was based on the laboratory parameters of bilirubin, creatinine and the international normalized ratio (INR) collected at admission and was determined by using the MELD calculator located on the UNOS Internet site.[14]

Statistical Analysis

Categorical variables were analyzed by chi-square test to determine if there were significant differences between the survivor and deceased cohorts. Mean and standard deviation (SD) were calculated for continuous variables and were assessed for significance using ANOVA and Fisher's Exact tests. A general linear model was used to assess the association of these continuous and categorical variables with the MELD score as stratified for mortality. Multivariate linear regression was used to assess the association between independent variables and MELD score. Default p values were set *a priori* at the 0.05 level and 95% confidence intervals (CI) were also calculated. The Statistical Package for Social Sciences (SPSS, version 15.0, Chicago, Il, USA) was used for all statistical analyses.

RESULTS:

This study included 73 patients (49 men, 24 women) diagnosed with liver cirrhosis, ascites and confirmed SBP. Of the 73 patients, 33 patients had alcohol as an etiology for their cirrhosis, eight were associated with hepatitis B and two were attributed to hepatitis C. Cirrhosis was associated with nonalcoholic steatohepatitis in six patients, whereas no cause of cirrhosis was ascertained in the remaining 24 patients.

The mean (± SD) age of patients in this study was 54.3 (± 10.3) years. Table 1 compares demographic, clinical findings and MELD scores for the deceased and survivor cohorts. The majority of patients in both groups were found to have abdominal distension, jaundice, fever, icterus and history of alcohol.

TABLE 1: Comparison of demographics, MELD scores, and clinical findings between survivor and deceased patient cohorts.*

	Survivor Cohort	Deceased Cohort	Total	P value
Demographics	*(n=40)*	*(n=33)*	*(n=73)*	
Age *(average ± SD)*	53.1 (± 10.5)	55.8 (± 9.9)	54.3 (± 10.3)	NS
Males	24 (60.0%)	25 (75.8%)	49 (67.1%)	NS
MELD Scores				
15 or less	5 (12.5%)	4 (12.1%)	9 (12.3%)	
16 to 24	33 (82.5%)	11 (33.3%)	44 (60.3%)	< 0.05
25 or greater	2 (5.0%)	18 (54.5%)	20 (27.4%)	
Average *(± SD)*	19.6 (± 3.64)	24.2 (± 6.5)	21.7 (± 5.6)	< 0.05
Clinical Findings				
Abdominal Distension	40 (100%)	33 (100%)	73 (100%)	NS
History of Alcohol	36 (90.0%)	29 (87.9%)	65 (89.0%)	NS
Jaundice	27 (67.5%)	26 (78.8%)	53 (72.6%)	NS
Fever	27 (67.5%)	23 (69.7%)	50 (68.5%)	NS
Icterus	28 (70.0%)	19 (57.6%)	47 (64.4%)	NS
Abdominal Pain	27 (67.5%)	13 (39.4%)	40 (54.8%)	< 0.05
Abdominal Tenderness	27 (67.5%)	13 (39.4%)	40 (54.8%)	< 0.05
History of GI Bleed	17 (42.5%)	14 (42.4%)	31 (42.5%)	NS
Altered Sensorium	14 (35.0%)	15 (45.5%)	29 (39.7%)	NS
Asterixis	14 (35.0%)	15 (45.5%)	29 (39.7%)	NS
Oliguria	14 (35.0%)	12 (36.4%)	26 (35.6%)	NS
Splenomegaly	9 (22.5%)	8 (24.2%)	17 (23.3%)	NS
Hepatomegaly	2 (5.0%)	0 (0.0%)	2 (2.7%)	NS

**Data presented as counts (% of cohort) unless otherwise specified; MELD = Model of End-stage Liver Disease; GI = gastrointestinal.*

The two cohorts were similar with a few notable exceptions: average MELD scores were significantly higher in the deceased cohort whereas the survivors demonstrated significantly greater prevalence of abdominal pain and tenderness on admission. Laboratory values for the survivor and deceased cohort are presented in Table 2.

TABLE 2: Comparison of laboratory values between survivor and deceased patient cohorts.*

	Survivor Cohort	Deceased Cohort
Laboratory Values	*(n=40)*	*(n=40)*
Bilirubin (mg/dL)	4.5 (± 2.8)	9.9 (± 10.1)§
AST (U/L)	116 (± 90)	132 (± 62)
ALT (U/L)	81 (± 65)	90 (± 49)
Albumin (gm/L)	25.0 (± 5.5)	25.2 (± 5.1)
Urea (mmol/L)	19.8 (±17.2)	26.2 (± 21.5)
Creatinine (mg/dL)	1.4 (± 0.6)	1.8 (± 0.9)§
Prothrombin Time (seconds)	21.9 (± 4.1)	22.9 (± 6.1)
INR	1.7 (± 0.3)	1.8 (± 0.5)
Hemoglobin (gm/dL)	9.5 (± 3.5)	9.3 (± 2.6)
Leukocytes (1000 cell/mm^3)	7.8 (± 3.6)	9.0 (± 4.8)
Platelets (1000 cell/mm^3)	91.6 (± 34.6)	107.9 (± 42.2)
Ascites Leukocytes (cell/mm^3)	1365 (± 458)	2301 (± 1618)§

** Data presented as average (± SD).*

§ Represents significance of $p < 0.05$ as compared to Survivor Cohort.

The deceased cohort demonstrated significantly elevated bilirubin, creatinine, and ascites leukocytes. There were no observed differences in INR between the two groups. Platelet count was greater in the deceased cohort but failed to reach significance (p = 0.074).

Mean (± SD) MELD score of patients was 21.7 (± 5.6). The majority of patients (60.3%) had MELD scores between 16 and 24; 12.3% patients had MELD scores 15 or less, and 27.3% of patients had MELD scores 25 or greater. MELD scores were significantly different between survivor and deceased cohorts and were significantly correlated with mortality (p<0.001). Mortality was high (25%) among the group with MELD scores between 16 and 24 and reached 90% in those with a MELD score of 25 or greater.

Univariate and multivariate linear regression modeling was used to assess the effect of the independent variables on MELD score. Categorical clinical variables are presented in Table 3. Both jaundice and a history of gastrointestinal hemorrhage were found to be significant contributors to the MELD score. MELD score decreased by 7.4 points in patients not having jaundice (95% CI: -9.7, -5.0) and increased by 3 points in those without a history of previous hemorrhage (95% CI: 0.4, 5.5).

Table 3: Univariate and multivariate linear predictors of MELD score and number (percentage) of categorical clinical variables

Categorical Characteristics		Mortality			Mean ± SD (MELD Score)	
		Yes	No		21.7 ± 5.6	
Variables	**Categories**	**n (%)**	**n (%)**	**P Value**	**Beta (95% CI)**	**P Value**
Abdominal Pain	Present	13 (39.4)	27 (54.8)		Ref	0.112
	Absent	20 (60.6)	13 (45.2)	0.016	2.1 (-0.5, 4.7)	
Abdominal Tenderness	Present	13 (39.4)	27 (54.8)		Ref	0.112
	Absent	20 (60.6)	13 (45.2)	0.016	2.1 (-0.5, 4.7)	
Jaundice	Present	26 (78.8)	27 (67.5)		Ref	<0.001
	Absent	7 (21.2)	13 (32.5)	0.282	-7.4 (-9.7, -5.0)	
History of Gastrointestinal Hemorrhage	Present	14 (42.4)	17 (42.5)		Ref	0.025
	Absent	19 (57.6)	23 (57.5)	0.995	3.0 (0.4, 5.5)	

Abdominal pain and tenderness, despite initial differences between cohorts, failed to demonstrate any significant impact on MELD scores.

Continuous laboratory variables are presented in Table 4. Age, AST, and urea were significant laboratory predictors of MELD scores besides that of bilirubin, creatinine and INR used for the MELD score computation. For every increase in age by 10 years the MELD score increased by 1.3 (95% CI: 0.01, 0.09).

Table 4: Univariate and multivariate linear regression predictors of MELD score, comparison with mortality status and mean (SD) of continuous variables.

Continuous Variables	Mean ± SD (Meld Score) Total samples			No mortality			Mortality		
	Mean (± SD)	Beta (β_o)	P Value	Mean (SD)	Beta (β_o)	P Value	Mean (SD)	Beta (β_o)	P Value
Age *(years)*	54.3 (± 10.3)	0.13	0.045	53.1 (± 10.5)	0.009	NS	55.8 (± 9.9)	0.08	0.049
AST *(U/L)*	123.7 (± 78.4)	0.01	0.011	116.8 (± 90.1)	0.005	NS	132.2 (± 61.5)	0.004	NS
Urea *(mmol/L)*	22.7 (± 19.4)	0.05	0.001	19.8 (± 17.2)	0.02	NS	26.2 (± 21.5)	0.04	0.031
Bilirubin *(mg/dL)*	7.0 (± 7.5)	0.3	<0.001	4.5 (± 2.8)	0.8	<0.001	9.9 (± 10.1)	0.28	<0.001
Creatinine *(mg/dL)*	1.6 (± 0.8)	4.2	<0.001	1.4 (± 0.6)	4.8	<0.001	1.8 (± 0.9)	4.7	<0.001
INR	1.7 (± 0.4)	6.1	<0.001	1.7 (± 0.3)	5.7	<0.001	1.7 (± 0.5)	6.4	<0.001

Increases in AST by 100 U/L increased the MELD score by 1 (95% CI: 0.002, 0.02). For every 100 mmol/L increase in urea the MELD score increased by 5 (95% CI: 0.02, 0.07). Upon stratifying the groups by mortality status only age (β_o=0.08, 95 % CI: 0.00, 0.15) and urea level (β_o=0.04, 95 % CI: 0.004, 0.08) were predictors of MELD score in deceased patients.

DISCUSSION:

Our study showed that MELD can prove to be an essential tool in providing the means to reliably predict mortality in our low-income patient population. Similar to previous studies, we found that increasing MELD scores portended a poor prognosis.[9-12,15-16] The MELD tool also allowed risk stratification of patients with minimal biochemical markers, which facilitates the provision of care in our low-resource setting.

MELD may be a better predictor in comparison to the Child-Turcotte-Pugh Score.[17] The inclusion of creatinine in the MELD model improves reliability of prognostication since creatinine has a profound impact on the progression of liver failure.[18,19] Hepatorenal syndrome contributes significantly to the increased mortality seen in patients with cirrhosis and SBP.[20] However, our study suggests that other variables should be included in the predictive model. Specifically, age and urea were shown to be significantly and positively correlated with adverse outcomes, albeit orders of magnitude less than the primary indicators of bilirubin, creatinine and INR. Jaundice and increased ascitic leukocyte counts are other potential prognostic indicators that deserve further scrutiny in larger studies. Interestingly, abdominal pain and tenderness were of significance in the survivor cohort, but linear regression analysis failed to demonstrate these clinical findigns as significant modifiers of the MELD scores.

A limitation of our study was that it was a cross-sectional observational analysis which did not track outcomes after hospital discharge. Tracking patients longitudinally post-admission would have permitted greater insight as to survival timecourse and survival differences. Additionally, our study did not account for patients that were taking proton-pump inhibitors (PPI) which have been shown to increase the incidence of SBP.[21] PPIs are widely available over the counter and self-prescribing is a common practice in Nepal. Thus, this study was not able to assess PPIs as a potential confounder of mortality outcomes.

Because of the increased mortality associated with SBP, a heightened sense of clinical suspicion should be maintained as the majority of patients with SBP are asymptomatic or have non-specific complaints. Hence, a diagnostic paracentesis is indicated in the majority of patients with cirrhosis and ascites attending outpatient clinics, particularly, if serum protein is low or mild abdominal pain is present.[20-21]

CONCLUSIONS:

Our study evaluated the relationship between MELD scores and mortality in patients with spontaneous bacterial peritonitis. High MELD scores, based on the biochemical findings upon admission, were more likely to be associated with fatal outcomes, reflecting its predictive value in our Nepali population. This tool proved to be reliable in the low-income cirrhotic population with underlying alcohol abuse and hepatitis B that is frequently encountered in Nepal. It also provided a mechanism by which mortality could be predicted with minimal lab parameters—important in this low-resource setting. Our study suggests that age and urea might also be important predictors of mortality. However, our model was limited by the small sample size and future investigations need to assess the validity of using these potential parameters. In summary, our study established a positive correlation between high MELD scores and hospital mortality reinforcing its usefulness as a predictive tool in our low-income, low-resource Nepali setting.

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