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Model for End-Stage Liver Disease (MELD) Score as a Useful Prognostic Marker in Cirrhotic Patients with Infection

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ABSTRACT

Objective: To determine the association of Model for End stage liver disease (MELD) score to the outcome of cirrhotic patients with bacterial infection and to compare it with Child-Turcott-Pugh (CTP) score.

Study Design: Descriptive study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from January 2005 to December 2007.

Methodology: Patients with diagnosis of liver cirrhosis and bacterial infection were included. Demographic features, laboratory data and type of infection were recorded. Multiple logistic regression assays were applied to determine the factors associated with poor outcome in cirrhotics with infection. Receiver-Operating Characteristics (ROC) were used to determine the cut-off values of CTP score and MELD score with the best sensitivity and specificity.

Results: A total of 530 patients, 313 male (59%) with a mean age of 53 ± 13 years were analyzed. Spontaneous bacterial peritonitis was the predominant infection seen in 369 (69%) patients. One hundred and eighty six (35%) patients died. Factors associated with poor outcome were a CTP score of more than 11 ($p=0.001$), raised blood urea nitrogen ($p=0.020$), raised creatinine ($p=0.004$), shock ($p=0.002$), and MELD score > 22 ($p=0.03$). An eight percent increase in mortality rate was noticed with every one point rise in MELD score above 22. ROC curve showed that the specificity of CTP and MELD score to predict poor outcome in these patients was 36% and 59% respectively.

Conclusion: Child-Turcott-Pugh score more than 11, raised BUN and creatinine, shock and high MELD score were poor prognostic markers in cirrhotic patients with infection. MELD score had better specificity than CTP score in determining outcome.

Key words: MELD score. Infection. Cirrhosis.

INTRODUCTION

Model for end stage liver disease (MELD) is a scoring system that is used to predict survival in patients with cirrhosis. It is calculated from laboratory values of serum bilirubin, serum creatinine, and the International Normalized Ratio (INR) for prothrombin time.¹ Revised version of MELD is currently used in allocation of organs for liver transplantation. Several online calculators are available to calculate MELD score.² In addition to liver transplantation setting, the MELD scoring system is also used as prognostic marker in selecting patients for trans jugular intrahepatic porto systemic shunts (TIPS), acute liver failure, alcoholic hepatitis, acetaminophen-induced liver injury, hepatorenal syndrome and to assess the surgical mortality risk in patients with liver cirrhosis.³⁻⁸

Bacterial infections are a well-known complication in patients with cirrhosis. About 15-60% of the cirrhotic patients either had infection at the time of admission or

acquired it during the hospital course.^{9,10} Proposed mechanisms of increased susceptibility to infection in cirrhotic patients are defects in the immune response of the host either in the form of changes in the reticuloendothelial system of the body, decreased opsonizing function of ascitic fluid or neutrophil dysfunction. As a result of underlying infections, the patient may develop circulatory, hepatocellular and renal insufficiency leading to morbidity and mortality in cirrhosis.^{11,12} Because of significant morbidity and mortality in cirrhotic patients with infection, it is important to know the predictors associated with poor outcome in these patients.

A study by Terra *et al.* reported renal failure in patients with cirrhosis and sepsis other than spontaneous bacterial peritonitis and value of MELD score.¹³ Another study by Obstein *et al.* determined association of MELD scores with SBP in cirrhotic patients undergoing diagnostic ascitic tap,¹⁴ but the relationship of the MELD score to the outcome of the cirrhotic patients with other infections individually or in combination is not well studied.

The aim of this study was to determine the relationship of MELD scores to the outcome of post-viral hepatitis cirrhosis with infection and to compare it with Child-Turcott-Pugh (CTP) score.

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METHODOLOGY

During the study period, patients records at the Aga Khan University Hospital, Karachi, with diagnosis of cirrhosis and infection were retrieved using International classification of diseases 9th revision with clinical modification (ICD-9-CM-USA). Diagnosis of cirrhosis was made on the basis of clinical features, liver imaging or histology. Patients at admission with infection or acquiring any infection during hospital course were identified. Demographic data, clinical presentation and details of laboratory test results like complete blood count, urine, ascitic or pleural fluid analysis and culture, Hepatitis B, Hepatitis C and other viral serology, metabolic and autoimmune workup, chest X-ray, ultra sound and histopathology of liver biopsy (if done) were noted. Child-Turcott-Pugh (CTP) score were calculated and associated medical illnesses were noted. MELD score was calculated with an online calculator.²

A poor outcome measure was defined as death of the patient during the first admission in the hospital with infection and cirrhosis. Spontaneous Bacterial Peritonitis (SBP) and spontaneous bacterial empyema was diagnosed on polymorpho-nuclear cell count in the ascitic and pleural fluid, equal or higher than 250/cm. A positive pleural or ascitic culture was not necessary for the diagnosis of SBP and spontaneous bacterial empyema.¹⁵

Spontaneous bacteremia was diagnosed when positive blood cultures were obtained in the absence of any other possible cause of bacteremia. If bacteremia was detected in a patient with urinary tract infection, pneumonia, SBP, or other bacterial infection, it was interpreted as secondary to those infections.¹⁶ Urinary tract infection was diagnosed on the basis of positive urine cultures or pyuria (> 10 leukocytes per high-power field).¹⁷ Secondary peritonitis or para pneumonic effusion and infections such as endocarditis, cellulitis or biliary infections were made as per diagnostic criteria.¹⁸ Mixed infection was considered when features of more than one infection were present in individual patient at the same time. Septic shock was diagnosed on the basis of a decrease in systolic blood pressure below 90 mmHg, or a reduction of more than 40 mmHg from the baseline despite adequate fluid resuscitation, accompanied by tachycardia and oliguria (urine output less than 20 mL/h) or anuria in the absence of other causes of shock.¹⁹

Spontaneous bacterial peritonitis and empyema were considered as community acquired when the infection was present at admission and as nosocomial when it developed during hospitalization in a patient with normal ascitic or pleural fluid at admission. Other infections were considered as community acquired when they were diagnosed during the first 48 hours of hospitalization and nosocomial when the diagnosis was made after this period.^{20,21}

Spontaneous bacterial peritonitis, empyema, bacteremia and urinary tract infections were empirically treated with intravenous third generation cephalosporin in standard dose. The remaining infections were treated according to the guidelines of treating infections.²⁰⁻²¹ Initial antibiotic therapy was modified on the basis of the results of cultures, and clinical course. SBP and spontaneous bacterial empyema were considered resolved when all clinical signs of infection disappeared, polymorpho nuclear cell count in ascitic or pleural fluid decreased to less than 250 cells/mm³ total, differential white blood cell count normalized, and blood and ascitic or pleural fluid cultures become negative. The resolution of the remaining infections was established on the basis of conventional criteria. All organisms isolated in positive cultures were tested for antimicrobial sensitivity.

A descriptive analysis was done for demographic, clinical and radiographic features and results were presented as mean \pm standard deviation for quantitative variables and number (percentage) for qualitative variables. In univariate analyses, differences in proportions were assessed by using the chi-square test. For contrasts of continuous variables, an independent sample t-test was used to assess the difference of means. Variables found to be statistically significant in the univariate analysis were included in a multivariate stepwise logistic regression model. The model was constructed to identify independent predictors of mortality and to obtain the odds ratio.

Receiver-Operating Characteristics (ROC) curve was used to determine the cut-off values of Child-Turcott Pugh score and MELD score with the best sensitivity and specificity in discriminating between patients who survived and those who died.

All analyses were conducted by using the Statistical Package for Social Science (SPSS 11.5.0). All p-values were two sided and considered statistically significant if < 0.05.

RESULTS

Among the total of 1598 cirrhotic patients admitted during the study period, 530 had infection as the main cause of admission. The rest of the patients admitted with other problems such as porto-systemic encephalopathy and gastrointestinal bleeding without infection, therapeutic paracentesis of ascitic fluid, trans-arterial chemo-embolization (TACE), variceal sclerotherapy, band ligation and various surgical procedures or percutaneous ethanol injection for hepatoma were excluded.

Out of 530 cirrhotic patients with infection, 313 (59%) were male and the mean age of the patient was 53 \pm 13 years. Hepatitis C was the major underlying cause of cirrhosis seen in 341 (64%) patients, non-B, non-C cirrhosis was seen in 81 (15%) hepatitis B in 68 (13%),

Table I: Clinical characteristics of survived versus deceased cirrhotic patients with infection.

Characteristics	Survived patients n=344 n (%)	Deceased patients n=186 n (%)	p-value
Mean age (years)	53.45 ± 13.0	54.70 ± 13.8	0.30
Female	145 (42.2)	72 (38.7)	0.34
Male	199 (57.8)	14 (61.3)	0.44
CTP score	11.4 ± 2.04	13.2 ± 2.04	0.03
MELD Score	22 ± 8.06	26.05 ± 7.87	0.03
Encephalopathy	293 (85)	144 (77)	0.02
Upper GI bleed	52 (15)	42 (22)	0.03
SBP	253 (74)	116 (62)	0.002
UTI	120 (35)	70 (38)	0.02
SBP and UTI	68 (20)	33 (17.8)	0.05
Pneumonia	25 (7)	18 (10)	0.25
Septic shock	23 (7)	42 (23)	0.001
Cellulitis	14 (4)	3 (2)	0.26
Spontaneous bacteremia	16 (9)	7 (2)	0.21

CTP= Child-Turcott-Pugh score; SBP= spontaneous bacterial peritonitis; UTI= Urinary tract infection; p < 0.05 is significant.

combined hepatitis B with hepatitis C in 25 (5%) and hepatitis B along with hepatitis D in 15(3%) patients. Child-Turcott-Pugh (CTP) class C was present in 441 (83%): 74 (14%) had class B and 15(3%) patients had Child class A. Mean Child-Turcott-Pugh score was 11.4 ± 2.04 and mean MELD score was 22.4 ± 8.06 and ranged from 6 to 47.

Spontaneous Bacterial Peritonitis (SBP) was the predominant infection seen in 369 (69%) patients. Urinary Tract Infection (UTI) was found in 190 (36%), sepsis in 65 (12%), pneumonia in 43 (8%), spontaneous bacteremia in 23 (4%), SBP with UTI in 101 (19%), cellulitis in 17 (3%) and meningitis in 4 (0.7%). Five hundred and five patients had community acquired infection and 25 (5%) patients had hospital acquired infection.

A total of 186 (35%) patients died on first admission with infection and 344 (65%) patients responded to treatment and recovered. Demographic, clinical, and biochemical data of the survived and deceased patients are shown in Tables I and II.

On univariate analysis, CTP score more than 11, raised white cell count, neutrophilia, impaired renal function, raised total and direct bilirubin level, septic shock and MELD score more than 22 were associated with poor outcome. The predictors of poor outcome in cirrhosis with infection were CTP score more than 11 (p= 0.02), raised serum BUN (p=0.03), high creatinine (p= 0.003), septic shock (p=0.001) and MELD score more than 22 (p=0.001). With every one point rise in the MELD score above 22, there was 8% increase in mortality. However, individual infections alone or in combination were not significant as regard the poor outcome (Table III).

Receiver Operating Characteristic (ROC) curve for MELD score and CTP score is shown in Figure 1. The

Table II: Laboratory parameters of survived versus deceased cirrhotic patients with infection.

Parameters	Survived patients n=344 n (%)	Deceased patients n=186 n (%)	p-value
Hb gm/dl			
< 12	276 (80.2)	148 (79.6)	0.85
≥ 12	68 (19.8)	38 (20.4)	
TLC x 10 ³ /cmm			
< 18	308 (89.5)	133 (71.5)	0.001
≥ 18	36 (10.5)	53 (28.5)	
Neutrophil %			
40-75	157 (45.6)	57 (30.6)	0.001
> 75%	187 (54.4)	129 (69.4)	
RBS mg/dl			
< 200	302 (87.8)	164 (88.2)	0.89
≥ 200	42 (12.2)	22 (11.8)	
BUN mg/dl			
6-16	119 (34.6)	39 (21)	0.001
> 16	225 (65.4)	147 (79)	
Creatinine mg/dl			
0.85-1.35	135 (39.2)	45 (24.2)	0.001
> 1.35	209 (60.8)	141 (75.8)	
Total bilirubin mg/dl			
0.2-1.25	99 (28.8)	45 (24.2)	0.25
> 1.25	245 (71.2)	141 (75.8)	
ALT I.U/L			
0-55	252 (73.3)	128 (68.8)	0.27
> 55	92 (26.7)	58 (31.2)	
AST I.U/L			
< 37	22 (18.5)	11 (20.8)	0.72
≥ 37	97 (81.5)	42 (79.2)	
GGT I.U/L			
3-50	77 (22.4)	30 (16.1)	0.08
> 50	267 (77.6)	156 (83.9)	
Alkaline phosphatase I.U/L			
28-124	219 (63.7)	115 (61.8)	0.67
> 124	125 (36.3)	71 (38.2)	
Total protein gr/L			
< 7.7	259 (75.3)	157 (84.4)	0.01
≥ 7.7	85 (24.7)	29 (15.6)	
Albumin gr/L			
< 3.2	302 (72)	116 (84)	0.02
≥ 3.2	42 (90)	70 (52)	
Globulin gr/L			
< 3	33 (9.6)	12 (6.5)	0.21
≥ 3	311 (90.4)	174 (93.5)	
PT seconds			
9-11	29 (8.4)	17 (9.1)	0.78
> 11	315 (91.6)	169 (90.9)	
APTT seconds			
< 33	41 (15.1)	17 (10.8)	0.20
≥ 33	230 (84.9)	141 (89.2)	

Hb=Hemoglobin; TLC=Total leukocytes count; RBS= Random blood sugar; BUN= Blood urea nitrogen; ALT Alanine aminotransferase; AST= Aspartate aminotransferase; GGT= Gama glutamyltranspeptidase; PT= Prothrombin time; APTT Activated partial thromboplastin time; p < 0.05 is significant.

cut-off value for MELD scores to predict the poor outcome was 22 with a sensitivity of 68% and a specificity of 59% where as the cut-off value for the CTP score in our study was 11 with a sensitivity of 73% and a specificity of 36% (p=0.001).

Certain factors such as raised white blood count neutrophilia and raised bilirubin level were significant on univariate analysis but not in multivariate analysis.

Table III: Factors associated with poor outcome in cirrhotic patients with infections on multivariate analysis.

Factors of poor outcome	Adjusted OR	95% CIs	p-value
Creatinine			
< 1.1	1.0		
> 1.1	2.23	1.30 – 3.82	0.003
BUN	1.008	1.001- 1.01	0.030
Diagnosis			
SBP	0.44	0.24 - 0.80	0.008
UTI	0.86	0.46 - 1.62	0.650
SBP and UTI	1.65	0.77-3.51	0.190
Septic sock	3.69	1.96-6.94	0.001
CTP score less than 11	1.0	-	-
CTP score more than 11	1.71	1.07- 2.75	0.020
MELD Score < 22	1	-	-
MELD Score > 22	2.27	1.43 3.62	0.001

BUN= Blood urea nitrogen; SBP= spontaneous bacterial peritonitis; UTI= Urinary tract infection; CTP= Child-Turcott-Pugh score; MELD=Model for end stage liver disease; $p < 0.05$ is significant.

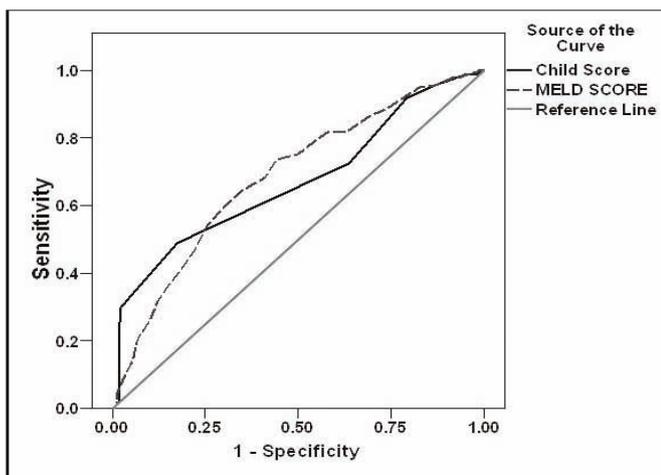


Figure 1: The ROC curve of MELD score and Child-Turcott-Pugh (CTP) score.

The cut-off value for MELD scores is 22 with a sensitivity of 68% and a specificity of 59% and cutoff value for CTP score was 11 with sensitivity of 73% and specificity of 36% for in hospital mortality in the patients with cirrhosis and infection.

Area under the curve: Child score=0.67, MELD score=0.68.

DISCUSSION

The utility of MELD score system is well studied for assessing the overall prognosis of the patients with cirrhosis, for various associated complications and specifically for prioritizing patients for liver transplantation.³⁻⁷ This study highlights the usefulness of MELD score as a prognostic marker in cirrhotic patients with infection. It was found that in cirrhotic patients with infection, a higher the MELD score was independently related with an increase in hospital mortality in these patients. Mortality increased by 8% with a one degree rise in MELD score, a possible explanation being that increase in MELD score may be the cause or effect of severe liver dysfunction in infection and hence is associated with adverse outcome. One should not exclude bad outcome in patients with a MELD score less than 22, as 16 (3%) of the patients who died also had MELD score ≤ 22 .

In this cohort of patients sensitivity of MELD score in determining the outcome in cirrhotic patients with infection was better than the CTP score. The possible reason may be that CTP score is calculated from characteristics some of which are subjective and may change from observer to observer. Moreover, the CTP score cannot go beyond 15 and laboratory parameters are grouped as categorical variable. On the other hand, variables in the MELD score are objective, continuous and have no defined upper limit. Therefore, the variability and range of score in the MELD system is a better representative of severity of liver disease compared to the CTP score.

Elevated serum bilirubin level is an important prognostic marker in parenchymal liver disease.²² Patients with acute hepatitis and a high serum bilirubin level take longer to recover²³ and in the King's College Criteria for acute liver failure, serum bilirubin of more than 18 mg/dL is regarded as a poor prognostic marker. Similarly, a higher serum bilirubin concentration is associated with a poor prognosis in alcoholic hepatitis and primary biliary cirrhosis.^{24,25} However, the outcome of the patient does not always correlate with level of bilirubin.

In the present study it was found that raised bilirubin level was significantly associated with poor prognosis on univariate analysis and surprisingly it did not remain a significant factor on multivariate analysis. However, when combined with other two parameters i.e. creatinine and INR in the MELD score system, it remained significant on multivariate analysis also. This highlights the fact that combinations of laboratory parameters in the MELD score are more important than certain laboratory values on individual basis.

Another interesting observation in this cohort of patients is increased mortality in those cirrhotic patients with infection that had hemodynamic instability in the form of shock irrespective of underlying infection. Such patients should be managed robustly by starting broad spectrum antibiotics immediately on presentation along with aggressive resuscitative measures. It was observed in the present series that despite starting appropriate treatment, the outcome was not usually favourable in this subgroup of patients.

One limitation of the study is single centre retrospective design and also that one had to rely upon the documented information. However, the primary aim of explaining the usefulness of the MELD score in this study was not affected with retrospective study design. Secondly in this study, the majority of patients had cirrhosis due to chronic viral hepatitis because 99% of the patients admitted with this complication during the study period had post-viral hepatitis cirrhosis and hence the group is homogenous but the value of the MELD score in predicting the outcome in patients with cirrhosis other than chronic viral hepatitis was not appropriately evaluated.

CONCLUSION

A CTP score more than 11, MELD score more than 22, raised serum BUN and creatinine and hemodynamic instability are poor prognostic markers for cirrhotic patients with infection. Moreover, a one point rise in MELD score above 22 increases the mortality by 8%. MELD could be a useful and better alternative to the existing methods used in predicting the poor outcome in cirrhotic patients with infection.

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