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IMPACTS OF PROGNOSTIC SCORES ON SHORT TERM MORTALITY IN LIVER CIRRHOTIC PATIENTS WITH HEPATORENAL SYNDROME

Gastroenterology

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ABSTRACT

Background/Aims: This study was designed to evaluate the role of new scoring systems which are recommended for predicting of mortality in end-stage liver disease, and in predicting short-term prognosis of Hepatorenal Syndrome (HRS).

Material and Methods: A total of 380 patients, were retrospectively investigated using medical records.New scoring systems continue to be developed using various mathematical formulas obtained by combining Model for end-stage liver disease (MELD) score with Na: Model for end-stage liver disease with incorporation of serum sodium (MELD-Na, MELDNa), changes of MELD-Na on day 14 of the medical therapy MELD-Na (Delta MELD-Na), the integrated MELD (iMELD), The United Kingdom Model for End-Stage Liver Disease (UKELD), Update MELD, MELD to Na ratio (MESO).

Results: Forty four of 380 liver cirrhosis patients were diagnosed with HRS. There were 25 patients with type 1 HRS and 19 patients with type 2 HRS. As a post-treatment response, there was positive correlation between Child-Turcotte-Pugh (CTP) classification score, MELD, MELDNa, MELD-Na, iMELD, MESO, UKELD, and Updated MELD scores, whereas negative correlation between all scores and Delta MELD-Na for both type 1 and type 2 HRS. Mortality rate was significantly higher in type 1 HRS (68% (17/25)) than type 2 (31.5% (6/19)) HRS in the course of three months follow up period (p=0.01).All prognostic scores were significantly convenient for predicting three months survival in type 1 and type 2 HRS patients.

Conclusion: The present study has investigated short-term efficacy of currently recommended prognostic factors in liver cirrhosis with HRS; it was determined that dilutional hyponatremia and age have significant effect on short-term mortality.

KEYWORDS

Survival Analyses, liver cirrhosis, hepatorenal syndrome

Introduction

Hepatorenal syndrome (HRS) is characterized by renal dysfunction due to notable abnormalities in arterial circulation and activation of endogenous vasoactive system in the patients with advanced hepatic failure and portal hypertension. International Ascites Club defined criteria, which were modified in 2007 (1, 2). HRS was divided into two subgroups according to the laboratory findings and prognosis as type 1 and 2. Type 1 HRS is a condition with high mortality and rapid loss of renal functions usually in the presence of a precipitating factor. In general type 2 HRS is a quietly progressive condition with ascites resistant to diuretic therapy (1). The prevalence of HRS among hospitalized cirrhosis patients is 10%. One-year and five-year incidence of HRS in the course of follow-up period in the patients with ascites has been reported to be 18% and 40%, respectively (3). The mean survival in untreated type 1 HRS patients is approximately 1 month, whereas survival after liver transplantation has been reported to be 65% (4).

Various models can be used to predict prognosis in the patients with hepatic diseases. The first model "Child-Turcotte-Pugh (CTP)" scoring is widely used by the clinicians to determine the prognosis of patients with chronic liver disease as it gives opinion about survival of cirrhosis patients (5). However, CTP has been replaced by "Model for end stage liver disease (MELD) " classification in most recent years since the criticisms about CTP that the evaluation of hepatic encephalopathy and abdominal ascites is not objective enough and it cannot precisely distinguish the patients divided into limited number of subgroups. MELD scoring is completely based on objective laboratory markers (serum creatinine, bilirubin, and prothrombin time, etc.). Some papers are reported that serum Na is associated with mortality in HRS patients and reported that MELD score predicts mortality more accurately when combined with serum Na level (6-8). Hence, new scoring systems continue to be developed using various mathematical formulas obtained by combining MELD score with Na: Model for end-stage liver disease with incorporation of serum sodium (MELD-Na, MELDNa), changes of MELD-Na on day 14 of the medical therapy MELD-Na (Delta MELD-Na), the integrated MELD (iMELD), The United Kingdom Model for End-Stage Liver Disease (UKELD), Update MELD, MELD to Na ratio (MESO) etc.) (8).

This study was designed to evaluate the influence of prognostic scoring systems in cirrhotic patients with HRS.

Methods

Patients

A total of 380 patients, who had been admitted between January 2008 and September 2009 to Ege University Gastroenterology Department for liver cirrhosis, were retrospectively investigated using medical records. Demographic characteristics, etiological factors, precipitating factors, laboratory tests and responds to therapy were evaluated in 57 patients (15%) with elevated creatinine level and azotemia. Thirteen (3.4%) of the patients were excluded because of detecting pre-renal, renal and post-renal causes. Finally, 44 patients (11.5%), which have been diagnosed with HRS according to the new criteria, were enrolled in the study (2). Twenty five (6.5%) patients with rapid and progressive renal failure (reaching to a higher value than 2.5 mg/dl as compared to baseline values in less than 2 weeks) were type 1 HRS. Nineteen patients (4.7%) with stable and slowly progressive renal dysfunction were type 2 HRS. Serum creatinine, serum total bilirubin, international normalized ratio (INR), serum Na, and serum albumin levels were assessed to quantify pre-treatment and post-treatment prognostic scores of the patients with HRS. Presence of ascites and likely renal pathology were determined by ultrasonographic examination of the patients performed in supine position. Disease outcomes (recovery, death, liver transplantation, bridge therapies until liver transplantation) obtained from the clinical files of patients were evaluated. The endpoint was three months for follow-up. Study protocol was approved by the local ethics committee.

Prognostic Models

List of prognostic models were following (9, 10).

CHILD-PUGH SCORE: Presence and degree of ascites and encephalopathy, INR, Total Bilirubin, albumin

MELD: 9.57 x ln (creatinine (mg/dL)) + 3.78 x ln (bilirubin (mg/dL)) + 11.2 x ln (INR) + 6.43

MELD-Na: MELD + 1.59x (135 – Na (mmol/L)); (Na range = 120 - 135 mmol/L)

MELDNa : MELD–Na (mmol/L) –(0.025 x MELD x (140 –Na (mmol/L)) +140; (Na range = 125 – 140 mmol/L)

MESO: (MELD / Na (mmol/L)) x 100

iMELD: MELD + (age (years) x 0.3) – (0.7 x Na (mmol/L)) + 100

UKELD: 5 x {1.5 x ln (INR) + 0.3 x ln (creatinine (µmol/L)) + 0.6 x ln (bilirubin (µmol/L)) - 13xln (Na (mmol/L) + 70}

Update MELD: 1.27 x ln (1+creatinine (mg/dL)) + 0.94 x ln (1+bilirubin (mg/dL)) +1.66 x ln (1 + INR)

Delta MELD-Na: MELD-Na on Day 14 of the medical therapy - MELD-Na at the beginning of treatment

Statistical Analysis

All analyses were performed using Statistical package for Social Sciences (SPSS) for Windows 16.0 program. The distribution of continuous variables was determined using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as means ± standard deviations (SD). Variables with skew distributions were expressed as median (minimum-maximum) and categorical variables expressed as proportions. Categorical variables were compared using the Chi-squared test, normally distributed numeric variables compared using the independent samples Students t test, and skewed numeric variables compared using the Mann Whitney U test. Pearson or Spearman's correlation, where appropriate, was used to explore the associations between study parameters. Two-sided values of P<0.05 and 95% Confidence Interval were considered statistically significant. In order to obtain scoring output of each model, Receiver –operating characteristic (ROC) curve was drawn separately for each of type 1 and type 2 HRS. Validity of each model was measured statistically [equivalent of the area under the ROC curve (AUC)]. The best cut-off values for the best sensitivity, specificity and prognostic scores were determined and used in the ROC curves. AUC > 0.7 was considered efficient and AUC >0.8 was considered excellent.

Results

Forty four (12 (30%) female and mean age: 57±10 years) of 380 hepatic cirrhosis patients were diagnosed with HRS. There was no statistically significant difference between type 1 and type 2 HRS groups regarding to age and sex (p=NS). Twenty five patients had type 1 and 19 patients had type 2 HRS. Etiological factors of cirrhosis patients were, hepatitis B virus (HBV) (18 patients and 3 patients had hepatitis delta virus (HDV)), alcohol (13 patients), hepatitis C virus (HCV) (7 patients), and other factors (2 Budd-Chiari, 2 autoimmune hepatitis and 2 primary biliary cirrhosis). Precipitating factors in patients were gastrointestinal system (GIS) hemorrhage (23%), Spontaneous bacterial peritonitis (SBP) (22%), infection (10%), and esophageal variceal bleeding (EVB) + SBP (5%). No precipitating factor was determined in 19 patients. Demographic features of the patients are shown in Table 1.

Table 1. Demographic characteristics of Type 1 and Type 2 HRS patients

	Type 1 (n=25)	TYPE 2 (n=19)	p
Sex (F/M)	6/19	6/13	0,57
Age Mean	59.96 ± 9.85	63.63 ± 11.99	0.27
T. bilirubin	17.05±18.09	7.01±10.98	0.03*
INR	1.78± 0.65	1.55±0.35	0.17
Creatinine	3.31±1.09	2.02±0.40	0.00*
Na	133.20±3.62	129.74±5.29	0.02*
Ascites	2.56±0.71	2.16±0.83	0.09
Encephalopathy	2.24±0.97	1.79±1.18	0.17

* Statistically significant
F: female; M: male; INR: international normalized ratio; Na:sodyum

All patients were administered medical therapy composed of terlipressin and albumin for 5 days. As a post-treatment response, there was positive correlation between CHILD, MELD, MELD-Na, MELDNa, MESO, iMELD, UKELD, and Updated MELD scores, whereas negative correlation between all scores and Delta MELD-Na for type 1 and type 2 HRS.

Mortality rate was significantly higher in type 1 HRS (68% (17/25)) than type 2 (31.5% (6/19)) HRS in the course of three months follow up period (p=0.01) A total of 3 patients (2 type 1 HRS, 1 type 2 HRS) underwent transplantation. There was no mortality in patients underwent transplantation. All prognostic scores were significantly convenient for predicting three months survival in type 1 and type 2 HRS patients (Table 2).

Table 2. Comparison between mean values of all prognostic scores used to predict 3-month survival in Type 1 and Type 2 HRS patients

	Type 1 (n=25)			**TYPE 2 (n=19)**		
	Alive (n=8)	**Ex (n=17)**	**p**	**Alive (n=8)**	**Ex(n=17)**	**p**
CTP	8.88± 1.45	12.94 ± 1.63	0.000	8.31 ± 1.31	12.50 ± 1.04	0.001
MELD	15.7 ±5.39	32.64 ± 8.84	0.000	10.6 ± 5.51	27.16±11.23	0.002
UPTADE MELD	3.78 ±0.72	5.99 ± 1.28	0.001	3.36 ± 0.84	5.21 ± 1.52	0.005
MELD-Na	17.2 ±7.40	40.46±10.51	0.000	13.6 ± 7.60	44.91 ± 9.17	0.001
DELTA MELD-Na	-10.0±4.44	7.047 ± 7.91	0.000	-7.6 ± 7.91	19.31±11.75	0.001
MELDNa	18.7 ± 5.38	34.49 ± 6.69	0.000	14.9 ± 4.64	32.25 ± 6.80	0.001
MESO	11.6 ± 4.19	25.11 ± 6.99	0.000	8.02 ± 4.19	21.81 ± 8.82	0.002
UKELD	51.3 ± 3.60	62.05 ± 5.92	0.001	50.3 ± 4.93	62.85±6.32	0.002
iMELD	37.5 ± 6.31	60.27 ± 9.27	0.000	39.3±13.03	60.08±10.42	0.007
SerumNa (mmol/L)	135.0 ± 3.46	130.11±3.51	0.006	133.6 ± 3.42	123.66±2.73	0.001

Values are presented as mean ± standart deviation or numbers.
CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease; MeldNa, MELD-Na: incorporate Na into MELD; DELTA MELD-Na: Changes of MELD-Na on day 14 of the medical therapy; MELDNa: the MELD score combined with the serum sodium concentration;
MESO: MELD to Na ratio ; UKELD: The United Kingdom Model for End-Stage Liver Disease; iMELD: the integrated MELD; Na:Sodyum

A pair-wise comparison of the AUROC showed no significant difference between CHILD, MELD, MELD-Na, MELDNa, MESO, iMELD, UKELD, Delta MELD-Na and Updated MELD scores both type 1 and type 2 HRS (p<0,05); ROC analysis, which was performed to determine the effect of post-treatment prognostic scores in predicting three month mortality in HRS patients, revealed that area under the ROC curve was the highest for iMELD in type 1 HRS patients but has lower value than the other tests in type 2 HRS patients even though it is already a better score. (AUC: 0.99 and 0.89 for type 1 and type 2 HRS, respectively) (Table 3, Figure 1-2).

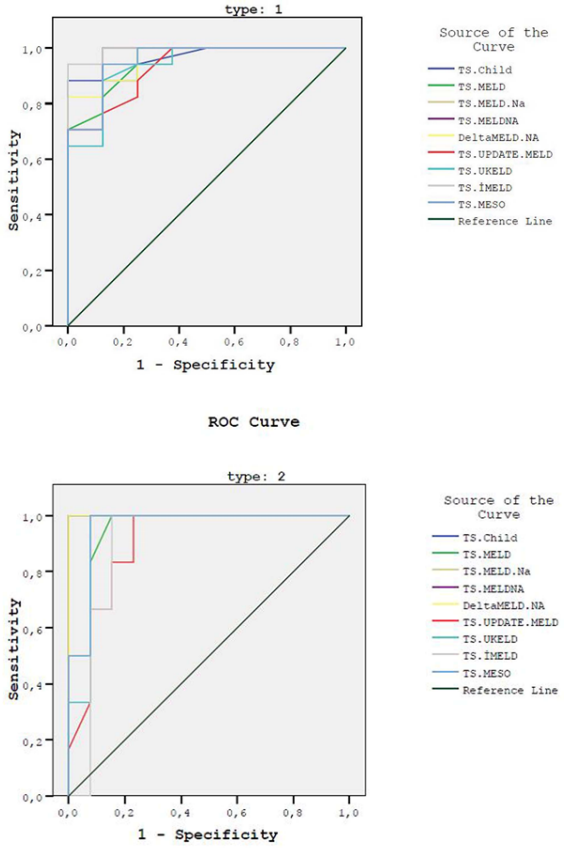
Table 3: Estimated accuracy of post-treatment prognostic scores in predicting 3-month mortality in Type 1 and Type 2 HRS patients

	Variables	Cut-off	Sensitivity	Specificity	95%CI
Type 1	CHILD*	9.50	0.94	0.25	0.96 (0.89–1.02)
	MELD*	19.0	0.94	0.25	0.95(0.87–1.03)
	MELD.Na*	25.6	0.94	0.12	0.95(0.86–1.04)
	MELDNA*	24.2	0.94	0.12	0.96(0.88–1.04)
	DELTA MELD - Na*	-6.6	0.94	0.25	0.96(0.89–1.01)
	UPDATE. MELD**	4.0	0.88	0.25	0.93(0.83–1.02)
	UKELD**	53.1	0.94	0.37	0.93(0.84–1.03)
	iMELD*	48.4	0.94	0.12	0.99(0.96–1.01)
	MESO*	14.3	0.94	0.25	0.95(0.87–1.03)
Type 2	CHILD**	10.5	1.00	0.00	1.00 (1.00–1.00)
	MELD**	17.0	0.83	0.77	0.95(0.86–1.04)
	MELD.Na**	36.0	0.83	0.00	1.00(1.00–1.00)
	MELDNA**	26.5	0.83	0.00	1,00(1.00–1.00)
	DELTAMELD-Na**	7.90	0.83	0.00	1.00(1.00–1.00)
	UPDATE. MELD**	3.6	0.83	0.23	0.90(0.76–1.04)
	UKELD**	57.3	0.83	0.77	0.94(0.84–1.05)
	iMELD**	48.4	0.83	0.15	0.89(0.74–1.05)
	MESO**	13.9	0.83	0.77	0.96(0.87-1.04)

Type 1: *P <0.001 vs CHILD, MELD, MELD.Na, MELDNA, DeltaMELD.NA, iMELD, MESO **P <0.05 vs UPDATE.MELD, UKELD

Type:2: **P <0.05 vs CHILD, MELD, MELD.Na, MELDNA, DeltaMELD.NA ,UPDATE.MELD, UKELD, iMELD, MESO
CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease; MeldNa, MELD-Na: incorporate Na into MELD; DELTA MELD-Na: Changes of MELD-Na on day 14 of the medical therapy; MELDNa: the MELD score combined with the serum sodium concentration; MESO: MELD to Na ratio ; UKELD: The United Kingdom Model for End-Stage Liver Disease; iMELD: the integrated MELD; Na:Sodyum

Figure 1.2.



ROC Curve

Discussion

In this single-center study, a large database of cirrhosis patients with hepatorenal syndrome, were evaluated. We demonstrated that all prognostic scores were significantly convenient for predicting three months survival in type 1 and type 2 HRS patients. Hepatorenal syndrome is the severest condition with fatal course in cirrhotic patients who needed hepatic transplantation. Hepatorenal syndrome or refractory ascites is the most critical factors affecting mortality in the patients with hepatic failure who needed hepatic transplantation (11).

CTP has been widely used for the prediction of survival in the patients that underwent surgical procedure for portal hypertension and then in the patients that underwent TIPS. In the United States of America, it has been used for years before 2002 by United Network for Organ Sharing (UNOS), which takes CHILD scoring and the necessity of intensive care stay as the basis, in determining priority for transplantation and hepatic reserve (12).

In the present study, CTP score as well as other tests showed positive correlation in the analyses performed to predict three months survival in both type 1 and type 2 HRS patients. The analysis used to investigate efficacy of prognostic scores in predicting short-term mortality in the present patients revealed that CTP is ideal with regard to its specificity and sensitivity particularly in type 2 HRS patients. This has to be confirmed in multicenter studies that will be performed in larger patient population. Limitation of CTP classification includes the degree of ascites and encephalopathy, which are subjective parameters, and inter-observer and intra-observer variability. Comprising subjective criteria such as failure in evaluating esophagus varices bleeding and renal functions poses a problem (13).

MELD score is a mathematical model being used since 2002. First, it was used to assess prognosis in the cases that underwent TIPS (14). Increase in MELD score is related to the intensity of hepatic failure and the risk of three months mortality. It is different from CTP as it includes renal functions and comprises objective variables (INR, serum bilirubin, and creatinine) rather than subjective assessment of the clinical abnormalities depending on the observer's opinion. It distinguishes the patients with similar clinical condition more objectively (15). Botta et al. (16) stated that MELD is over to CTP in assessing short and mid period of survival in cirrhotic patients with either UNOS status 2A (eg. CTP score ≥10; varices bleeding accompanied by cirrhosis-related complications, refractory ascites/ hepatic hydrothorax, Hepatorenal syndrome or stage 3 or 4 hepatic encephalopathy) or UNOS status 2B (eg. CTP score ≥10 or ≥7 together with complications). Nevertheless, superiority of MELD over CTP system has been demonstrated in only 4 (4512 patients) of the recent 11 studies, whereas 7 studies (8020 patients) determined no statistically significant difference (17). MELD score is being widely used in many transplant centers according to the severity of liver disease, excluding fulminant hepatic failure such as UNOS status 1, for the patients who are in the waiting list for transplantation (18).

With regard to the limitations of MELD, different laboratory methods used for measuring serum creatinine may lead to critical differences in MELD score (19). It is yet unclear whether total or direct fraction of bilirubin will be used to predict mortality. The fact that different steps of coagulation pathway are influenced in the coagulopathy of cirrhosis raises questions about the accuracy of INR, which represents the coagulation status (15). Effect of hepatic encephalopathy on mortality is prominent particularly when severe; however, hepatic encephalopathy, esophagus varices bleeding, spontaneous bacterial peritonitis and hepatopulmonary syndrome are not included in MELD scoring (20). Besides MELD score, additional points are given for tumor size and number to the patients with hepatocellular carcinoma (HCC) who meet the Milan criteria (21). Moreover, MELD score remains inadequate in determining short-term survival also in some conditions such as Budd Chiari Syndrome, malnutrition, polycystic liver disease, hepatopulmonary syndrome, hereditary hemorrhagic telangiectasia, cystic fibrosis and recurrent biliary sepsis (22). MELD score is inadequate in determining survival in approximately 15-20% of the cases.

Dilutional hyponatremia is typical complication of cirrhosis resulting from the change in vascular hemodynamics. It is usually related to refractory ascites, hepatorenal syndrome and higher mortality (23). Serum Na level <126 meq/L is independent determinant of three and six months mortality and may enhance the validity of MELD (24). Cut-off value for serum Na remains debatable. Heuman et al. (25) stated that presence of ascites together with a serum Na level < 135 mEq/L is more accurate than MELD and an independent risk factor in predicting 3- and 6-month mortality. They found that, persistent ascites or hydrothorax) together with decreased serum Na is an independent risk factor for six months survival particularly in the patients with MELD score <21. In the present study, serum Na was found to be an important risk factor for mortality independent from MELD score. We demonstrated increased risk of mortality with decreasing serum Na level. This result is consistent with the studies in the literature.

Some articles suggested that MELD-Na, which is a MELD-based scoring. MELD-Na scoring was created by mathematical integration of serum Na into the traditional MELD parameters. It was propounded that MELD-Na predicts 6-month survival better than MELD scoring (26, 27). Kim et al. (28) recommended MELDNa score by another calculation method and stated that the new method is better in predicting 3-month mortality. It was propounded that effect of Na on mortality is low in the patients with MELD score higher than 30 but considerable in the patients with moderate MELD scores. In the present study, contrary to the literature, MELDNa calculated by either formula did not show significant superiority over CHILD or MELD in predicting 3-month mortality in type 1 HRS patients. However, MELDNa calculated either formula was found equivalent to CHILD but superior to MELD in type 2 HRS. This may result from remarkably low Na level and ascites in type 2 HRS as compared to type 1 HRS.

Luca et al. (29) and subsequently Huo et al. (30) suggested iMELD score and included age in the formula in addition to MELD and serum Na values; they published in the literature that the new formula is superior over MELD in predicting three, six and twelve months

mortality. In the present study, it is observed that patients at advanced ages should be treated immediately due to the contribution of comorbidities, particularly in the event of diseases with high mortality such as type 1 HRS.

Although different formulas created by various mathematical integration of MELD and Na such as UKELD, Delta MELD-Na, updated MELD and MESO index MELD are almost excellent tests in predicting short-term mortality in type 1 and type 2 HRS patients, the present study failed to demonstrate superiority of any formula over the others.

The major limitation of the present study is the fact that, effects of the tests within constant values determined by us on mortality could have been investigated separately for each prognostic factor in either group. For this purpose, a prospective randomized study that will be conducted in larger patient population for longer follow-up period may give more explicit outcomes.

In conclusion, the present study has investigated short-term efficacy of currently recommended prognostic factors in liver cirrhosis patients who were on the waiting list for transplantation and developed HRS; it was determined that dilutional hyponatremia and age have significant effect on short-term mortality and these parameters have been highlighted taking emergency for transplantation into account.

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