

Prediction of Hepatorenal Syndrome by Model of End Stage Liver Disease Score

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Abstract: Background: Hepatorenal Syndrome (HRS) is a severe complication of liver cirrhosis with ascites. Model for End-stage Liver Disease (MELD) is a widely accepted objective scoring system for patients with chronic liver disease. The aim of this study is to investigate if MELD score can predict the short term development of HRS or not. **Method:** A prospective follow up study of a 51 patients with known advanced chronic liver disease for the development of HRS. MELD score was calculated initially for all patients. Patients were followed during their admission for development of HRS. 33% of the patients developed type 1 HRS (group 1), 37% developed type 2 HRS (group 2) and 29% did not develop HRS (group 3). Forward logistic regression analysis was done to detect the predictors of HRS. Receiving Operation Characteristic (ROC) was constructed to detect the cut off value for the best predictor of HRS. **Results:** MELD score was found to be differ significantly among the 3 groups (25.26 ± 5.42 for group 1, 21.01 ± 3.35 for group 2 and 16.78 ± 2.00 for group 3), $P < .001$. Forward logistic regression analysis and ROC curve showed that MELD score can shortly predict the development of type 1 HRS at cut off value 23.4 and HRS in general with cut off value 17.7 with good sensitivity, specificity, negative and positive predictive values. **Conclusion:** MELD score can be helpful in the short term prediction of HRS which allows early initiation of therapy and improvement of prognosis.

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1. Introduction:

Hepatorenal syndrome (HRS) is a serious complication of end-stage liver disease (ESLD) or fulminant hepatic failure and without liver transplantation has a dismal prognosis. The only effective treatment for HRS is a liver transplantation (LT) (1). HRS is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. It is characterized by marked reduction in GFR and renal plasma flow (RPF) in the absence of other cause of renal failure. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilation. Tubular function is preserved with the absence of proteinuria or histologic changes in the kidney (2). The diagnosis depends mainly on exclusion of other causes of renal impairment and unresponsiveness to a volume expansion. The diagnostic criteria were first developed by international ascites club in 1996 and were updated in 2007 (3-4). Two types of HRS have been described; type 1 HRS is a rapidly progressive functional renal failure with doubling of serum creatinine to > 2.5 ($226 \mu\text{mol/L}$) mg/dl in less than 2 weeks with clinical pattern of acute renal failure; Type-2 hepatorenal syndrome is a moderate renal failure with serum creatinine ranging from 1.25 to 2.5 mg/dl ($113\text{--}226 \mu\text{mol/L}$) with a steady or slowly progressive course

and clinically presented as refractory ascites (5). Without liver transplantation, the mortality of untreated type 1 HRS is 80% in 2 weeks and only 10% of patients survive more than 3 months (3). Patients with type 2 HRS have a better mean survival of approximately 6 months (6). Model for end-stage liver disease (MELD) is a widely accepted objective scoring system for patients with chronic liver disease (7). MELD was initially created to predict survival following elective placement of transjugular intrahepatic portosystemic shunting (TIPS) (8). MELD was established after that as a basis for priorities for liver transplantation (9). The objective of this study is to investigate the possibility of using MELD score at a certain cut off values as a short term predictor of the development of HRS.

2. Patients and methods:

The protocol for this study followed the ethical standards and approved by the ethical committee of our institution and all subjects gave informed consent to participate in this study. This study was conducted on 51 patients with decompensated liver cirrhosis 34 (66.6 %) males and 17 (33.4 %) females who were admitted to the Internal Medicine Department, Menofia University Hospital. All patients were hepatitis c positive and the diagnosis of decompensated liver cirrhosis was done depending on

long standing history of chronic liver disease secondary to hepatitis c, clinical examination with picture of decompensated liver cirrhosis and on ultrasound findings. Patients were followed up during their admission for rising serum creatinine to > 1.5 mg/dl. For patients admitted with serum creatinine above 1.5 mg/dl, the measures to diagnose HRS were applied directly. The diagnosis of HRS was made when there is no improvement in serum creatinine (decrease to a level of < 1.5 mg/dl) after at least 2 days with diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/day). The patients were followed for the next two weeks, if there is rapid deterioration of kidney function with doubling of serum creatinine to a level > 2.5 mg/dl or death the patient was defined as type 1 HRS. If there is moderate reduction of kidney function and serum creatinine ranging from 1.25 – 2.5 mg/dl the patient was defined as type 2 HRS. Patients with the following criteria were excluded, shock, current or recent treatment with nephrotoxic drugs, Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, micro-hematuria (< 50 RBCs/high power field) and/or abnormal renal ultrasonography (3). Also patients with spontaneous bacterial peritonitis, hepatocellular carcinoma and congestive heart failure were excluded. Patients with rising creatinine to > 1.5 mg/dl and responded to diuretic withdrawal and volume expansion were excluded from the study. According to the development of HRS patients were divided into three groups. Group 1; 17 patients with type 1 HRS (12 males and 5 females), group 2; 19 patients with type 2 HRS (13 males and 6 females) and group 3; 15 patients with decompensated liver disease and absence of HRS (10 males and 5 females). All patients underwent full history taking and clinical examination. Laboratory investigations including liver function tests (ALT, AST, serum albumin, total bilirubin and INR), serum sodium and kidney functions tests (serum creatinine (Scr) and blood urea), urine analysis and spot sample protein/creatinine ratio for determination of 24 hours urinary protein. Abdominal ultrasound was done to confirm ascites, liver cirrhosis and exclude possibility of malignancy. MELD score was calculated using the following formula; $[3.8 \times \log \text{bilirubin (mg/dl)} + 11.2 \times \log \text{INR} + 9.6 \times \log \text{creatinine (mg/dl)} + 6.43]$ (10).

Statistical Evaluation

We used the statistical package of social signs (SPSS, version 16) to perform the analysis. Results are expressed as mean values \pm standard deviation and categorical variables as count and percentage. One way anova test was used for comparison of quantitative variables among more than two

independent groups.. Chi-square test was used for non-quantitative variables. Forward logistic regression analysis was used to determine the possible predictor of HRS. Receiving operation characteristic (ROC), curve was generated to determine the cut off values with sensitivity and specificity of the best predictor of HRS. P value < 0.05 was considered significant.

3. Results:

This study included 51 patients with decompensated liver cirrhosis 34 (66.6 %) males and 17 (33.4 %) females. The cohort was divided according to the development of HRS into three groups. Group 1; type 1 HRS included 17 patients 12 (70.5 %) male and 5 (29.5 %) female, group 2; type 2 HRS included 19 patients 13 (68 %) male and 6 (32 %) female and group 3; Decompensated liver cirrhosis without HRS included 15 patients 10 (66.6 %) male and 5 (33.4 %) females. Baseline characteristics and comparison of the studied groups were shown in table 1. The groups were matched regarding age and sex. MELD score showed highly significant difference among the studied groups. MELD score was found to be 25.26 ± 2.42 , 21.01 ± 3.35 and 16.87 ± 2.00 for type 1 HRS, type 2 HRS and decompensated liver cirrhosis without HRS respectively (Figure 1). Scr, serum albumin, INR, bilirubin, serum sodium and mean arterial blood pressure showed significant difference among the studied groups. Forward logistic regression analysis demonstrated that MELD score and Scr significantly can predict the development of type 1 HRS when type 1 HRS compared with other 2 types, however MELD score showed higher significance 0.000 than Scr 0.024 and also MELD score and blood urea can predict the development of HRS in general (without differentiation of both types) when group 3 (Decompensated liver cirrhosis without HRS) was compared with both groups of HRS, however MELD score showed higher significance 0.000 than blood urea 0.008. ROC curve was constructed to determine the cut off values of MELD score for predicting development of type 1 HRS and HRS in general. MELD score can predict type 1 HRS at cut off value of 23.4 with area under the curve (AUC) of 0.910 (95% CI: 0.826 - 0.994), $P < 0.001$, (Figure 2). It showed sensitivity of 94 %, specificity of 88 %, positive predictor value (PPV) of 80 % and negative predictor value (NPV) of 97 % (Table 2). ROC curve was constructed again to detect the cut off value of MELD score for prediction of development of HRS in general showed that MELD score can predict the development of HRS in general at cut off value 17.7 with AUC of 0.924 (95 % CI: 0.851 – 0.997), $P < 0.001$ (Figure 3). It showed sensitivity of 92 %,

specificity 87 %, PPV of 94 % and NPP of 81 %) (Table 3). We did Regression analysis comparing type 2 HRS (Group 2) with decompensated cirrhotic patients without HRS (Group 3) to detect if MELD

score can predict development of type 2 HRS and it showed that MELD score cannot predict the development of type 2 HRS.

Table 1: Baseline characteristics and comparison of the studied groups

Variables	Group 1 type 1 HRS	Group 2 type 2 HRS	Group 3: Decompensated liver cirrhosis without HRS	Anova /Chi square test	P value
*Age in years	61.41 ± 5.94	60.53 ± 7.46	57.33 ± 6.76	1.58	> 0.05
**Sex (M/F)	12/5	13/6 (68.4/31.6%)	10/5 (66.6/33.4%)	0.22	> 0.05
*Mean ABP mmHg	(70.6/29.4%)	76.05 ± 6.36	82.22 ± 6.77	13.47	< 0.001
*Serum Alb (mg/dl)	69.71 ± 7.32	2.54 ± 0.29	2.72 ± 0.31	5.97	< 0.005
*ALT (IU)	2.34 ± 0.35	32.26 ± 19.23	34.80 ± 15.00	0.19	> 0.05
*AST(IU)	36.71 ± 27.99	47.37 ± 19.58	48.47 ± 19.08	0.45	> 0.05
*Bilirubin (mg/dl)	42.88 ± 14.99	3.10 ± 0.70	2.50 ± 0.45	11.80	< 0.001
*INR	4.01 ± 1.29	1.94 ± 0.52	1.75 ± 0.20	7.92	< 0.005
*Scr (mg/dl)	2.40 ± 0.61	1.43 ± 0.27	1.08 ± 0.14	21.39	< 0.001
Urea (mg/dl)	1.56 ± 0.18	82.95 ± 30.17	63.00 ± 15.61	10.50	< 0.001
*Na (mmol/L)	103.41 ± 25.17	125.42 ± 5.17	129.60 ± 4.21	10.72	< 0.001
*Hb (gm/dl)	122.53 ± 3.22	9.13 ± 1.49	10.29 ± 1.84	2.34	> 0.05
*Platlets	9.22 ± 1.74	139.53 ± 70.08	142.00 ± 66.02	0.06	> 0.05
*MELD Score	133.82 ± 60.71	21.01 ± 3.35	16.78 ± 2.00	39.25	< 0.001
	25.26 ± 2.42				

*: Mean ± Standard Deviation, **: Number and percentage, M/F: Male/Female, HRS: Hepatorenal syndrome, APB: Arterial blood pressure, Alb: Albumin, ALT: Alanine transaminase, AST: Aspartate transaminase, INR: International normalized ratio, Scr: Serum creatinine, Hb: Hemoglobin, MELD: Model of end stage liver disease

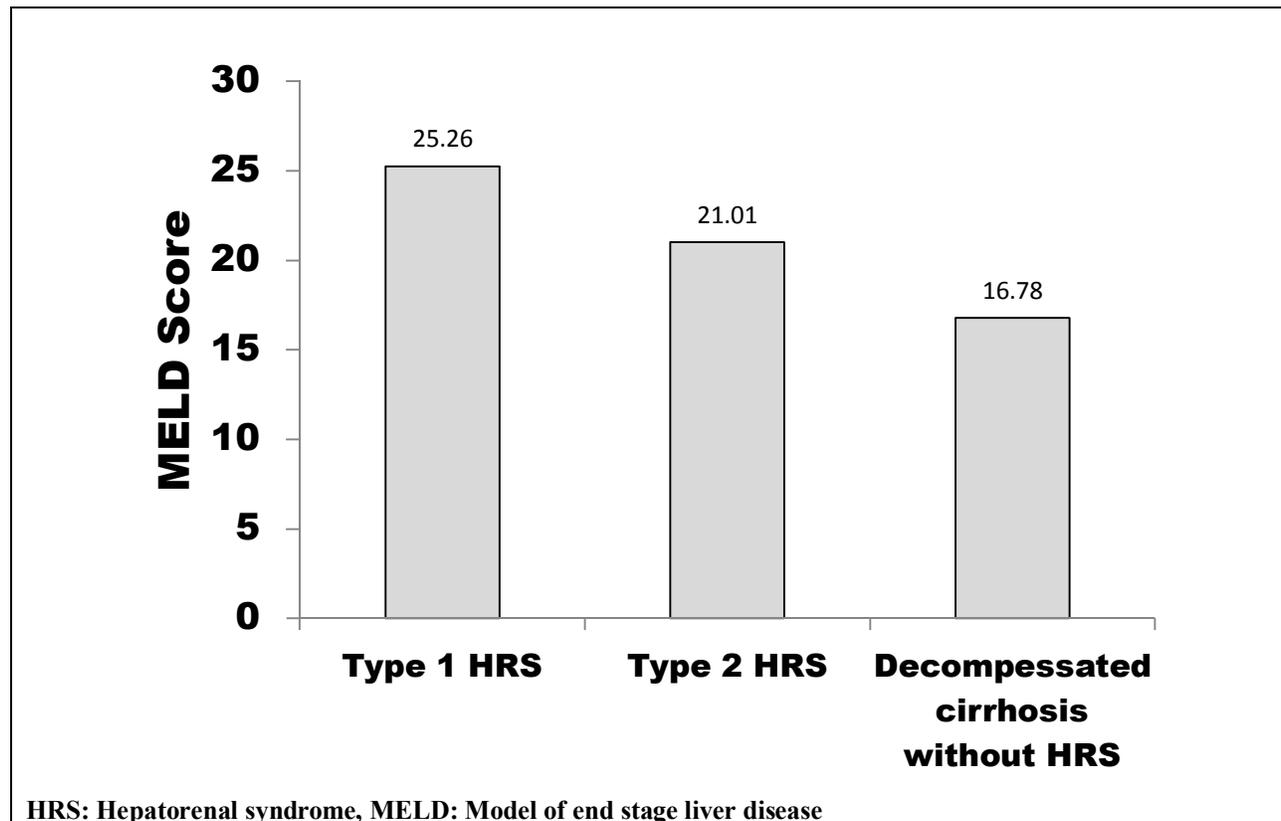
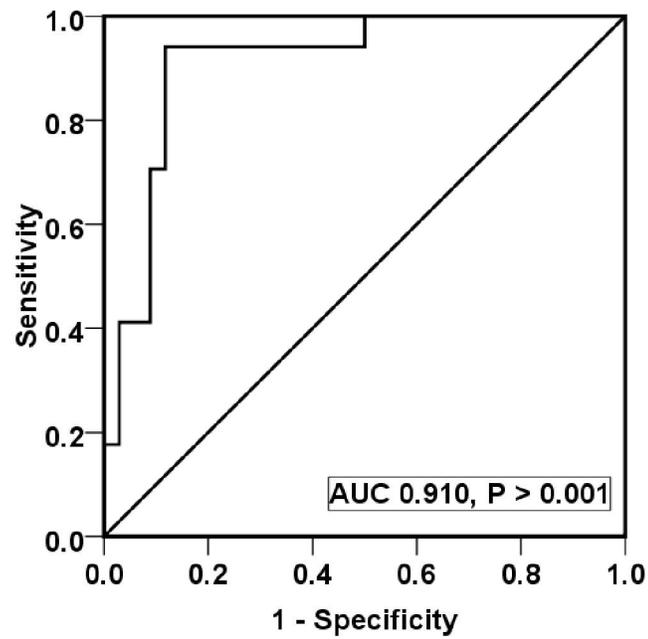
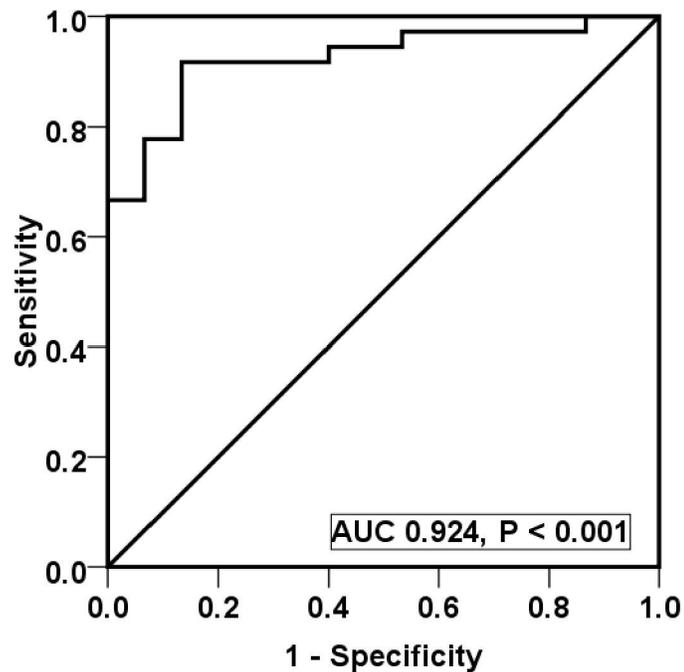


Figure 1: Comparison of MELD Score among the studied groups



ROC: Receiving operation characteristic, MELD: Model of end stage liver disease, HRS: Hepatorenal Syndrome, AUC: Area under the curve.

Figure 2: ROC Curve for MELD score as a predictor of development of type 1 HRS



ROC: Receiving operation characteristic, MELD: Model of end stage liver disease, HRS: Hepatorenal Syndrome, AUC: Area under the curve.

Figure 3: ROC Curve for MELD score as a predictor of development of HRS

Table 2: Sensitivity, specificity, positive and negative predictor values of MELD score as a predictor of type 1 HRS and HRS in general

	Sensitivity	Specificity	Positive predictor value	Negative predictive value
MELD score at cut off value 23.4 to predict type 1 HRS	94 %	88 %	80 %	97 %
MELD score at cut off value 17.7 to predict HRS in general	92 %	87 %	94 %	81 %

MELD: Model of end stage liver disease

4. Discussion:

HRS is a sever complication of liver cirrhosis with ascites. The diagnostic criteria were first developed by international ascites club in 1996 and were updated in 2007 (3-4). A rapid diagnosis of HRS and a prompt initiation of the treatment with terlipressin and albumin are mandatory because this leads to an improvement of prognosis (11, 12). The MELD score was initially created to predict survival following the elective placement of TIPS (Transjugular intrahepatic portosystemic shunt) but has now been validated as a predictor of survival in patients with a wide variety of liver diseases (13). Some studies demonstrated that initial MELD scores were important predictors of survival in HRS patients. Alessandria et al., demonstrated that type of HRS and MELD score were associated with an independent prognostic value and found that all patients with type 1 HRS had a high MELD score (> or =20) and showed an extremely poor outcome (median survival: 1 month). By contrast, the survival of patients with type 2 HRS was longer and dependent on MELD score (> or =20, median survival 3 month; <20, median survival 11 month (14). Also Schepke et al. concluded that meld score has relevant prognostic value to type 1 HRS (15) and Bambaha et al concluded that current MELD is the single most important determinant of mortality risk on the waiting list for liver transplant patients (16). Other studies showed that change in MELD scores over time is more important than initial MELD score and concluded that mortality risk on the liver transplant waiting list is predicted more accurately by serial MELD score determinations than by medical urgency status or single MELD measurements (17-18). The use of MELD score as a short term predictor of HRS has not been studied extensively. In the current study we found that MELD score can predict the short term development of type 1 HRS and HRS in general. ROC curve showed that MELD score can predict type 1 HRS at cut off value of 23.4 and HRS in general at cut off value 17.7 with good sensitivity, specificity, positive and negative predictor values. There were no enough studies addressed the issue of prediction of HRS. In one study Janičko and coworkers retrospectively studied 82 patients with decompensated liver cirrhosis among whom 18 developed HRS, like our results he found significant

difference regarding serum sodium, Scr, bilirubin and MELD score however in contrast to our results he founded that sodium together with creatinine are the strongest HRS predictors, followed by bilirubin or MELD score (19). Also Ahn et al. found that cystatin C, MELD score and serum sodium were the independent predictive factors for hepatorenal syndrome (20) As mentioned before we could not find any other work studied the MELD score for prediction of HRS, however other markers was studied as a predictor for HRS. Sharaway and coworkers evaluated the clinical significance of cystatin C as a predictor of HRS in patients with liver cirrhosis, ascites, and normal serum creatinine level on a number of 80 patients and concluded that cystatin C level was the most independent predictive factor for HRS (21). In another study, the low cardiac output was also found as a predictor of the development of HRS and survival in patients with cirrhosis and ascites (22). We can consider our work is the first study to address the admission calculated MELD score as a predictive for short term development of HRS during the same admission. As early initiation of therapy for HRS is very important and can greatly improve outcome it gives our work a great value as we can initiate therapy so early before the diagnosis of HRS depending on prediction using admission calculated MELD score.

Conclusion:

Calculated MELD score at admission is a simple noninvasive method that can be helpful for short term prediction of HRS in general and type 1 HRS. MELD score of 17.7 can predict development of HRS without differentiation between type 1 or type 2 and value of 23.4 or more means that patient either has type 1 HRS or shortly he will develop during this admission. As early diagnosis and initiation of therapy for HRS is crucial and improve prognosis. It is recommended to initiate therapy without delay for HRS with such value of MELD score at admission. Other studies are needed to confirm our results and also to confirm that initiation of therapy depending on our prediction may improve outcome compared to those started therapy depending on diagnostic criteria.

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1. Olivera-Martinez M, Sayles H, Vivekanandan R, D' Souza S, Florescu MC. Hepatorenal syndrome: are we missing some prognostic factors? *Dig Dis Sci*. 2012 Jan; 57(1):210-4.
2. Wadei HM, Mai ML, Ahsan N, and Gonwa TA. Hepatorenal Syndrome: Pathophysiology and Management. *Clin J Am Soc Nephrol*. 2006 Sep;1(5):1066-79.
3. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, Ring-Larsen H, Schölmerich J. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *International Ascites Club. Hepatology*. 1996 Jan;23(1):164-76.
4. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of Hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310–1318.
5. Angeli P, Merkel C. Pathogenesis and management of hepatorenal syndrome in patients with cirrhosis. *J Hepatol*. 2008;48 Suppl 1:S93-103.
6. Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. *Lancet*. 2003; 362:1819–1827.
7. Darwish Murad S, Kim WR, de Groen PC, Kamath PS, Malinchoc M, Valla DC, Janssen HL. Can the model for end-stage liver disease be used to predict the prognosis in patients with Budd-Chiari syndrome? *Liver Transpl*. 2007 Jun; 13(6): 867-74.
8. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PCJ. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; 31:864-871.
9. Wiesner RH, Kamath PS, Malinchoc M, Kremers WK, Krom RAF, Kim WR. MELD and PELD: Application of survival models to liver allocation. *Liver Transpl* 2001;7:567-580.
10. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001 Feb; 33(2):464-70.
11. Angeli P, Merkel C. Pathogenesis and management of hepatorenal syndrome. *J Hepatol* 2008;48:S93–S103.
12. Ginès P, Schrier RW. Renal failure in cirrhosis. *New Engl J Med* 2009;361:1279–1290.
13. Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A, *et al*. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol* 2004;40:897–903.
14. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jimenez W, Arroyo V, *et al*. MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 2004;41:1282–1289.
15. Schepke M, Appenrodt B, Heller J, Zielinski J, Sauerbruch T. Prognostic factors for patients with cirrhosis and kidney dysfunction in the era of MELD: results of a prospective study. *Liver Int* 2006;26:834–839.
16. Bambha K, Kim WR, Kremers WK, Therneau TM, Kamath PS, Wiesner R, *et al*. Predicting survival among patients listed for liver transplantation: an assessment of serial MELD measurements. *Am J Transplant* 2004;4(11):1798–804.
17. Huo TI, Wu JC, Lin HC, Lee FY, Hou MC, Lee PC, *et al*. Evaluation of the increase in model for end-stage liver disease (Delta MELD) score over time as a prognostic predictor in patients with advanced cirrhosis: risk factor analysis and comparison with initial MELD and Child-Turcotte-Pugh score. *J Hepatol* 2005;42:826–832.
18. Merion RM, Wolfe RA, Dykstra DM, Leichtman AB, Gillespie B, Held PJ. Longitudinal assessment of mortality risk among candidates for liver transplantation. *Liver Transplant* 2003;9:12–18.
19. Janičko M, Veseliny E, Abraldes JG, Jarčuška P. Serum Sodium Identifies Patients with Cirrhosis at High Risk of Hepatorenal Syndrome. *Z Gastroenterol*. 2013 Jul;51(7):628-634. Epub 2013 May 21.
20. Ahn HS, Kim YS, Kim SG, Kim HK, Min SK, Jeong SW, Jang JY, Lee SH, Kim HS, Kim BS, Park JM. Cystatin C is a good predictor of hepatorenal syndrome and survival in patients with cirrhosis who have normal serum creatinine levels. *HepatoGastroenterology*. 2012 Jun;59(116):1168-73.
21. Sharawey MA, Shawky EM, Ali LH, Mohammed AA, Hassan HA, Fouad YM. Cystatin C: a predictor of hepatorenal syndrome in patients with liver cirrhosis. *Hepatol Int*. 2011 Mar 12. [Epub ahead of print]
22. Krag A, Bendtsen F, Henriksen JH, Møller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut*. 2010 Jan;59(1):105-10. doi: 10.1136/gut.2009.180570

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