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ORIGINAL ARTICLE

Establishment and evaluation of a model for predicting 3-month mortality in Chinese patients with hepatic encephalopathy

Yanping Cui[1] · Shan Guan[1] · Jie Ding[2] · Yukai He[1] · Qingfang Li[1] · Sikui Wang[1] · Huiling Sun[3]

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Abstract

Hepatic encephalopathy (HE) is a serious complication of liver disease. To establish a model for predicting 3-month mortality in patients with HE in China. This retrospective study included 609 patients with HE admitted to the Peoples' Hospital, Liaocheng City, China (August 2006 to January 2016). Patients were allocated to a modeling ($n = 409$) or validation ($n = 200$) group. Demographic/clinical characteristics, laboratory test results, Model for End Stage Liver Disease (MELD) score and Child-Turcotte-Pugh (CTP) score were extracted from medical records. A model for predicting death within 3 months after admission was established using logistic regression analysis (modeling group). Model validity (validation group) was assessed using receiver operating characteristic (ROC) curve analysis. 270/409(66.0%) patients died in the modeling group and 142/203(70.0%) died in the validation group. Compared with survivors, patients who died had more severe HE, and higher MELD score, CTP score, incidence of complications including hepatorenal syndrome (HRS) and upper gastrointestinal bleeding, and values for laboratory parameters including red blood cell count(RBC) and total bilirubin(TBIL)($P < 0.05$). Regression analysis revealed RBC, TBIL, HE stage, HRS and upper gastrointestinal bleeding as independent factors associated with death ($P < 0.05$). The area under the ROC curve (AUC) for the model was 0.931.The model had a higher Youden index than MELD or CTP scores and predicted death in the validation group with a sensitivity of 83.1% and specificity of 93.4%. The established model has superior performance to MELD and CTP scores for predicting mortality in patients with HE.

Keywords Hepatic encephalopathy · Mortality · Prognosis · MELD score · Child-Turcotte-Pugh score

Introduction

Hepatic encephalopathy (HE) is a potentially serious complication of chronic and acute liver disease that can occur in 60–80% of patients with liver cirrhosis (Cichoz-Lach and Michalak 2013; Ferenci et al. 2002; Suraweera et al. 2016). The manifestations of HE include psychomotor, intellectual and cognitive abnormalities that can result in personality changes, irritability, disinhibition, motor abnormalities (e.g. hypertonia and hyperreflexia), extrapyramidal dysfunction (e.g. rigidity, bradykinesia and slow speech) and sleep disturbances (Weissenborn et al. 2005). Although multifactorial, the pathogenesis of HE is thought to include dysregulation of the urea cycle and the accumulation of ammonia, which crosses the blood-brain barrier and leads to the development of brain edema and intracranial hypertension (Parekh and Balart 2015). Current treatment strategies include the provision of adequate nutrition and use of no absorbable disaccharides (such as lactulose and lactitol) and antibiotics (e.g. rifaximin), although liver transplantation remains the only definitive treatment (Suraweera et al. 2016; Vilstrup et al. 2014). HE leads to considerable morbidity and exerts a great burden on patients, caregivers and healthcare systems (Bajaj et al. 2011; Stepanova et al. 2012). Furthermore, overt HE is associated with a poor prognosis, with a 1-year survival rate of 20–42% and a 3-year survival rate of 15–23% (Bustamante et al. 1999; Christensen et al. 1989; Saunders et al. 1981).

Several studies have investigated the factors predicting mortality in patients with liver cirrhosis, and the prognostic factors identified include male gender, HE, Child-Turcotte-Pugh (CTP) score and Model for End Stage Liver Disease (MELD) score

✉ Huiling Sun
sunhuiling0203@163.com

[1] Department of Liver Disease, Liaocheng People's Hospital, Liaocheng, China

[2] Central Laboratory, Liaocheng People's Hospital, Liaocheng, China

[3] Department of Gastroenterology, Liaocheng People's Hospital, Liaocheng 252004, China

(Attia et al. 2008; Botta et al. 2003; D'Amico et al. 2006; Londono et al. 2007; Said et al. 2004; Samada Suarez et al. 2008). The MELD score is calculated using a formula that includes total bilirubin (TBIL), serum creatinine (CRE) and the international normalized ratio (INR) of the prothrombin time (PT) (Malinchoc et al. 2000), while the CTP score considers TBIL, serum albumin (ALB), international normalized ratio of prothrombin time (INR), ascites and HE (with each scored 1–3) (Pugh et al. 1973). However, although these two scoring systems are widely used to assess the severity of liver failure and prioritize patients for transplantation, there has been very little research into the development and validation of a scoring system that could be used specifically to predict the probability of death in patients with HE. An accurate method for predicting prognosis in patients with HE could facilitate decision-making regarding selection of the most appropriate therapeutic strategies, including liver transplantation.

Therefore, the aim of this study was to establish a model for predicting the probability of death within 3 months of admission in patients with HE in China and to compare the prognostic utility of this model with those of the MELD and CTP scores.

Material and methods

Patients

This retrospective study analyzed clinical data extracted from the medical records of 609 consecutive patients with HE admitted to the Peoples' Hospital of Liaocheng City, China, between August 2006 and January 2016. The study was approved by the ethics committee of the Peoples' Hospital of Liaocheng City. Due to the retrospective and anonymized design of the study, written consent from the participants was deemed not to be required.

The inclusion criteria were as follows: 1) age ≥ 18 years; 2) HE had been diagnosed, and its severity graded (from I to IV), based on previously published criteria (Chinese Society of Gastroenterology et al. 2013) (see below); 3) metabolic encephalopathy, toxic encephalopathy, neurologic disease, mental illness and sedative overdose had been excluded; 4) the MELD score had been calculated or sufficient information was available from the medical records for its calculation; and 5) the CTP score had recorded or sufficient information was available from the medical records to enable its determination. Patients were excluded if any of the information required for the analysis (see below) was missing from the medical records.

HE was defined as neuropsychiatric abnormalities during the course of liver disease, including involvement of the cognitive, affective/emotional, behavioral and bioregulatory domains (Chinese Society of Gastroenterology et al. 2013). HE was graded as one of four stages (I–IV) as follows (Conn et al. 1977; Ferenci et al. 2002): stage I: Loss of sleep rhythm, drowsiness, confusion, flapping tremor (asterisk); stage II: features of grade I encephalopathy as well as loss of sphincter control; stage III: unconscious with no response to oral commands, but responding to painful stimuli; or stage IV: deep unconscious state with no response to pain.

All patients received branched-chain amino acids (BCAA), ornithine aspartate and symptomatic treatments to preserve liver function and reduce serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) (Chinese Society of Gastroenterology et al. 2013). For patients with ascites, diuretic therapy was conducted to reduce ascites (using Furosemide, Spironolactone, or Torsemide, with varied doses). Patients with bleeding were provided with somatostatin (250μg as the initial dose, then intravenous infusion at 250 μg/h was continued, or at 500μg/h for severe patients, for 48~72 h after hemostasis) (Vlachogiannakos et al. 2007) or octreotide to reduce the portal vein pressure. The patients with low albumin level were supplemented with albumin (1.5 g/kg on the first day, and 1 g/kg after 48 h). (Simon-Talero et al. 2013)

The patients were randomly allocated to a modeling group or a validation group in ratio of approximately 2:1. Analysis of data from the modeling group (409 of the 609 patients) was used for establishment of the model to predict mortality in patients with HE, while the validation group (the remaining 200 patients) was used to verify the accuracy and performance of the model.

Collection of data

The medical records of all the included patients were reviewed by the first author, and the following data were extracted and recorded for each patient: demographic data including age and gender; disease-related information including etiology, HE stage (I–IV), use of a high-protein diet, history of ascites drainage, and the presence of any complications such as ascites, spontaneous bacterial peritonitis (SBP), upper gastrointestinal (GI) bleeding, hepatorenal syndrome (HRS) and persistent hyponatremia; laboratory test results including leukocyte count (WBC), neutrophil count (NE), neutrophil percentage (NE%), hemoglobin concentration (HGB), blood platelet count (PLT), PT, prothrombin activity (PTA), INR,ALT, AST, TBIL, ALB, CRE, blood urea nitrogen (BUN), serum potassium (K^+)and serum sodium (Na^+); CTP score; and MELD score. The MELD score (Singal and Kamath 2013) was calculated as: $MELD = 3.8 \times \ln[\text{TBIL (mg/dL)}] + 11.2 \times \ln(\text{INR}) + 9.6 \times \ln[\text{CRE (mg/dL)}] + 6.4 \times$ (cause of disease: biliary or alcoholic = 0, other = 1).

Statistical analysis

Statistical analysis was carried out using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). Count data are presented as *n* (%) and were analyzed using theχ^2 test. Continuous data are presented as mean ± standard deviation (SD) and were analyzed using Student's t test. Qualitative data were analyzed

Table 1 Demographic and clinical characteristics of patients in the modeling group, compared with those who died within 3 months of admission and those who survived

	All ($n = 409$)	Survived ($n = 139$)	Died ($n = 270$)	*P* value
Age (years)	52.54 ± 14.67	54.71 ± 12.95	51.42 ± 15.38	0.007
Gender				
Male	295 (72.13%)	100(71.94%)	195(72.22%)	0.952
Female	114 (27.87%)	39(28.06%)	75(27.78%)	
HE stage				
Stage I	44(10.76%)	41 (29.49%)	3 (1.11%)	<0.001
Stage II	113(27.63%)	66 (47.48%)	47 (17.41%)	
Stage II	90(22.0%)	23 (16.55%)	67 (24.81%)	
Stage IV	162(39.61%)	9 (6.47%)	153 (56.67%)	
Etiology				
Hepatitis B	255 (62.35%)	102 (73.38%)	154 (57.04%)	0.001
Hepatitis C	17 (4.16%)	3 (2.16%)	14 (5.19%)	
Alcoholic	68 (16.63%)	11 (7.91%)	57 (21.11%)	
Autoimmune	10 (2.44%)	6 (4.32%)	4 (1.48%)	
Drug induced	3 (0.73%)	1 (0.72%)	2 (0.74%)	
Hepatitis E	3 (0.73%)	1 (0.72%)	2 (0.74%)	
Unknown	52 (12.71%)	15 (10.79%)	37 (13.70%)	
Ascites	239 (58.44%)	68(48.92%)	171(63.33%)	0.006
SBP	202 (49.39%)	44(31.65%)	158 (58.52%)	<0.001
Respiratory infection	30 (7.33%)	13 (9.35%)	17(6.30%)	0.261
Biliary tract infection	24 (5.87%)	10 (7.19%)	14 (5.19)	0.413
Gastrointestinal infection	6 (1.47%)	4 (2.88%)	2 (0.74%)	0.186
Urinary tract infection	5 (1.22%)	2 (1.44%)	3 (1.11%)	1.000
Bloodstream infection	5 (1.22%)	2 (1.44%)	3 (1.11%)	1.000
Upper GI bleed	110 (26.89%)	21(15.11%)	89(32.96%)	<0.001
HRS	182 (44.50%)	27(19.42%)	155(57.41%)	<0.001
Persistent hyponatremia	216 (53.20%)	36(25.90%)	180(66.67%)	<0.001
High-protein diet	16 (3.91%)	14(10.07%)	2(0.74%)	<0.001
Ascites drainage	3 (0.73%)	0(0%)	3(1.11%)	0.554
WBC($\times 10^9$)	11.67 ± 7.67	7.70 ± 5.51	13.72 ± 7.83	<0.001
NE($\times 10^9$)	9.02 ± 6.80	5.41 ± 4.71	10.88 ± 6.97	<0.001
NE%	73.43 ± 14.41	65.96 ± 14.61	77.27 ± 12.72	0.013
RBC ($\times 10^{12}$)	3.18 ± 1.03	3.08 ± 0.80	3.24 ± 1.13	<0.001
HGB(g/L)	103.65 ± 30.01	101.47 ± 25.57	104.77 ± 32.04	0.004
PLT($\times 10^9$)	101.72 ± 70.18	96.45 ± 62.25	104.43 ± 73.89	0.031
TBIL(μmol/L)	268.76 ± 214.60	116.94 ± 62.1	346.92 ± 203.48	<0.001
ALT(IU/L)	180.77 ± 56.0	59.78 ± 36.0	243.06 ± 84.0	<0.001
AST(IU/L)	237.73 ± 106.0	104.61 ± 64	306.26 ± 151.7	<0.001
ALB (g/L)	24.18 ± 6.24	25.03 ± 5.66	23.75 ± 6.49	0.174
K^+(mmol/L)	4.42 ± 1.90	4.27 ± 2.91	4.50 ± 1.05	0.913
Na^+(mmol/L)	129.83 ± 9.91	133.14 ± 6.84	128.12 ± 10.79	0.003
CRE(μmol/L)	164.30 ± 161.81	105.80 ± 89.36	194.42 ± 181.48	<0.001
BUN(μmol/L)	13.25 ± 12.28	9.51 ± 6.20	15.18 ± 12.55	<0.001
PT(s)	29.84 ± 20.08	19.62 ± 8.50	35.10 ± 22.19	<0.001
PTA	37.26 ± 24.41	52.39 ± 22.39	29.48 ± 21.63	0.638
INR	3.90 ± 2.31	1.94 ± 1.56	4.91 ± 4.78	<0.001
MELD score	23.03 ± 14.71	11.95 ± 10.26	28.35 ± 13.51	0.005
CTP score	12.61 ± 1.98	10.75 ± 1.87	13.50 ± 1.28	<0.001

Data presented as mean ± standard deviation or *n* (%). *P*-values are for comparison between patients who died within 3 months of admission and those who survived

ALB, albumin; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *BUN*, blood urea nitrogen; *CRE*, serum creatinine; *CTP*, Child-Turcotte-Pugh; *GI*, gastrointestinal; *HE*, hepatic encephalopathy; *HGB*, hemoglobin concentration; *HRS*, hepatorenal syndrome; *INR*, international normalized ratio of prothrombin time; K^+, serum potassium; *MELD*, Model for End Stage Liver Disease; Na^+, serum sodium; *NE*, neutrophil count; *NE%*, neutrophil percentage; *PLT*, blood platelet count; *PT*, time; *PTA*, prothrombin activity; *RBC*, red blood cell count; *SBP*, spontaneous bacteria peritonitis; *TBIL*, total bilirubin; *WBC*, leukocyte count

using the rank-sum test. The primary short-term outcome measure was death within the first 3 months after primary admission. Univariate non-conditional logistic regression analysis was used to establish a model for predicting death within the first 3 months after admission and derive a formula to calculate the likelihood of death. Death within the first 3 months after admission was used as the dependent variable (0 = no and 1 = yes); and the following 27 factors were used as the independent variables: gender, age, etiology, HE stage, high-protein diet, history of ascites drainage, ascites, SBP, upper GI bleeding, HRS, persistent hyponatremia, WBC, NE, NE%, HGB, PLT, PT, PTA, INR, ALT, AST, TBIL, ALB, CRE, BUN, K^+ and Na^+. Receiver operating characteristic (ROC) curves were plotted and the areas under the ROC curve (AUCs) were calculated to compare the accuracy of CTP score, MELD score and our established model, using the normal distribution Z-test. AUC > 0.7 was taken to indicate good predictive accuracy, and AUC of 0.8–0.9 was taken

Table 2 Demographic and clinical characteristics of patients in the validation group, comparing those who died within 3 months of admission and those who survived

	All ($n = 203$)	Survived ($n = 61$)	Died ($n = 142$)	*P* value
Age (years)	53.45 ± 14.73	55.23 ± 14.14	52.68 ± 14.96	0.31
Gender				
Male	145 (71.43%)	44 (72.13%)	101 (71.13%)	0.885
Female	58 (28.57%)	17 (27.87%)	41 (28.87%)	
HE stage				
Stage I	21(10.5%)	20 (32.79%)	1 (0.70%)	<0.001
Stage II	53(26%)	27 (44.26%)	26 (18.31%)	
Stage III	50(24.5%)	11 (18.03%)	39 (27.46%)	
Stage IV	79(39.0%)	3 (4.92%)	76 (54.29%)	
Etiology				
Hepatitis B	129 (63.55%)	49 (80.33%)	80 (56.34%)	0.016
Hepatitis C	7 (3.45%)	2 (3.28%)	5 (3.52%)	
Alcoholic	36 (17.73%)	2 (3.28%)	34 (23.94%)	
Autoimmune	4 (1.97%)	1 (1.64%)	3 (2.11%)	
Unknown	27 (13.30%)	7 (11.48%)	20 (14.08%)	
Ascites	116 (57.14%)	31(50.82%)	85(59.86%)	0.233
SBP	96 (47.29%)	20(32.79%)	76(53.52%)	0.007
Upper GI bleed	58 (28.57%)	10 (16.39%)	48(33.80%)	0.012
HRS	92 (45.32%)	12 (19.67%)	80(56.34%)	<0.001
Persistent hyponatremia	103 (50.74%)	15(24.59%)	88(61.97%)	<0.001
High-protein diet	7 (3.45%)	6(9.84%)	1(0.70%)	0.001
Ascites drainage	1 (0.49%)	0(0%)	1(0.70%)	0.512
WBC($\times 10^9$)	11.90 ± 8.10	6.82 ± 4.16	14.13 ± 8.40	<0.001
NE($\times 10^9$)	9.45 ± 7.26	4.74 ± 3.67	11.51 ± 7.48	<0.001
NE%	75.31 ± 13.16	66.00 ± 14.05	79.39 ± 10.43	0.003
RBC ($\times 10^{12}$)	3.22 ± 1.01	3.22 ± 0.75	3.21 ± 1.10	0.001
HGB (g/L)	104.87 ± 28.94	105.81 ± 22.44	104.46 ± 31.43	0.005
PLT ($\times 10^9$)	96.31 ± 65.54	82.84 ± 50.25	102.23 ± 70.58	0.016
TBIL (μmol/L)	265.51 ± 210.57	108.14 ± 65.9	334.57 ± 203.55	<0.001
ALT(IU/L)	219.44 ± 56.0	58.04 ± 37.0	290.27 ± 81.0	0.013
AST(IU/L)	281.95 ± 108.0	100.87 ± 71.0	361.41 ± 149.0	0.004
ALB (g/L)	23.73 ± 6.47	25.27 ± 6.14	23.05 ± 6.52	0.36
K^+(mmol/L)	4.48 ± 2.50	4.58 ± 4.30	4.44 ± 0.98	0.17
Na^+(mmol/L)	130.61 ± 10.87	133.63 ± 6.55	129.29 ± 12.08	0.075
CRE (μmol/L)	166.34 ± 160.69	116.04 ± 107.50	188.41 ± 174.93	0.004
BUN (μmol/L)	13.40 ± 11.61	10.29 ± 6.90	14.77 ± 11.38	0.014
PT (s)	33.34 ± 23.56	21.20 ± 11.34	38.66 ± 25.51	<0.001
PTA	33.93 ± 23.97	49.56 ± 24.82	27.06 ± 20.14	0.327
INR	4.23 ± 2.42	2.12 ± 1.59	5.15 ± 3.10	<0.001
MELD score	29.45 ± 13.97	11.07 ± 2.27	13.41 ± 1.67	0.039
CTP score	12.7 ± 2.16	18.82 ± 10.16	34.12 ± 12.84	0.005

Data presented as mean ± standard deviation or *n* (%). *P*-values are for comparison between patients who died within 3 months of admission and those who survived

ALB, albumin; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *BUN*, blood urea nitrogen; *CRE*, serum creatinine; *CTP*, Child-Turcotte-Pugh; *GI*, gastrointestinal; *HE*, hepatic encephalopathy; *HGB*, hemoglobin concentration; *HRS*, hepatorenal syndrome; *INR*, international normalized ratio of prothrombin time; K^+, serum potassium; *MELD*, Model for End Stage Liver Disease; Na^+, serum sodium; *NE*, neutrophil count; *NE%*, neutrophil percentage; *PLT*, blood platelet count; *PT*, time; *PTA*, prothrombin activity; *RBC*, red blood cell count; *SBP*, spontaneous bacteria peritonitis; *TBIL*, total bilirubin; *WBC*, leukocyte count

Table 3 Factors associated with death within 3 months of admission in patients with hepatic encephalopathy, analyzed in the modeling group ($n = 409$) using multivariate non-conditional logistic regression

Factor	*B*	*P*	OR	95% CI of the OR	
				Upper	Lower
RBC	0.435	0.013	1.545	1.097	2.177
TBIL	0.006	<0.001	1.006	1.004	1.008
HE stage	1.526	<0.001	4.600	3.175	6.666
HRS	1.679	<0.001	5.362	2.652	10.844
Upper GI bleeding	1.062	0.006	2.892	1.354	6.176
Constant value	−7.067	<0.001	0.001		

CI, confidence interval; *GI*, gastrointestinal; *HE*, hepatic encephalopathy; *HRS*, hepatorenal syndrome; *OR*, odds ratio; *RBC*, red blood cell count; *TBIL*, total bilirubin

Table 4 Area under the receiver operating characteristic curve for the logistic regression model, MELD score and CTP score when used to predict death within 3 months of admission in patients with hepatic encephalopathy

Method	AUC	95%CI	*P*
MELD score	0.855	0.816–0.893	<0.001
CTP score	0.835	0.797–0.874	<0.001
Logistic regression model	0.931	0.885–0.977	<0.001

AUC, area under the curve derived from receiver operating characteristic curve analysis; *CI*, confidence interval; *CTP*, Child-Turcotte-Pugh; *MELD*, Model for End Stage Liver Disease

to indicate very good predictive accuracy. The Youden index was calculated as an indicator of test performance and was also compared between the three systems. $P < 0.05$ was considered statistically significant.

Results

Comparison of demographic and clinical characteristics between patients who died within 3 months after admission and those who survived

The demographic and clinical characteristics of the patients in the modeling and validation groups are shown in Tables 1 and 2. In the modeling group, 270/409 (66.0%) patients died of whom 195 (72.22%) were men, and 139/409 (34.0%) patients survived of whom 100 (71.94%) were men. In the validation group, 142/203 (70.0%) patients died of whom 101 (71.13%) were men, and 61/203 (30.0%) patients survived of whom 44 (72.13%) were men. In the modeling group, patients who died were younger, more commonly had an alcohol-related etiology, and had more severe HE, higher incidences of complications (ascites, SBP, upper GI bleeding, HRS and persistent hyponatremia), higher values for WBC, NE, NE%, RBC, HGB, PLT, TBIL, ALT, AST, CRE, BUN, PT and INR, and a lower Na^+ as compared with those who survived ($P < 0.05$; Table 1). In the validation group, there were also significant differences between patients who died and those who survived in etiology, HE grade,incidences of most complications (SBP, upper GI bleeding, HRS and persistent hyponatremia) and certain laboratory parameters ($P < 0.05$; Table 2). In both groups, patients who died had significantly higher MELD and CTP scores than those who survived ($P < 0.05$).

Establishment of a model for predicting the probability of death during the first 3 months after admission

Univariate non-conditional logistic regression analysis of the data for the modeling group revealed that RBC, TBIL, HE stage, HR Sand upper GI bleeding were all independent factors associated with death during the first 3 months after admission ($P < 0.05$; Tables 3, 4, and 5). The final logistic regression formula was: logit (Y) =0.435 (RBC) + 0.006 (TBIL) + 1.526 (HE stage, I–IV = 1–4) + 1.679 (HRS, yes = 1, no = 0) + 1.062 (upper GI bleeding, yes = 1, no = 0).

ROC curve analysis to compare the accuracy and performance of the logistic regression model, CTP score and MELD score

The established logistic regression formula was utilized to calculate the probability of death during the first 3 months after admission for the 203 patients in the validation group. Plotting of the ROC curve (Fig. 1) showed that the AUC was 0.931 and that the optimal critical point was 1.19, i.e. ≥ 1.19 was considered as death and < 1.19 as survival. When used to predict death in the 203 patients in the validation group, the logistic regression model had a sensitivity of 83.1%, a specificity of93.4%, a Youden index of 0.765, a positive predictive value of80.3%, a negative predictive value of 93.7%, a positive likelihood ratio of 12.75 and a negative likelihood ratio of 0.21. Comparison of Youden indexes indicated that the

Table 5 Area under the receiver operating characteristic curve for the logistic regression model, MELD score and CTP score when used to predict death within 3 months of admission in patients with different grades of hepatic encephalopathy

HE Grade	AUC	Standard error	Asymptotic Sig.	Asymptotic Sig.	
				Lower	Upper
Grade 1 ($n = 21$)					
MELD	0.868	0.112	0.093	0	1
Child-Pugh	0.816	0.147	0.151	0	1
Logistic equation	0.816	0.099	0.151	0.609	1
Grade 2 ($n = 53$)					
MELD	0.795	0.062	0	0.674	0.916
CTP	0.645	0.073	0.058	0.501	0.789
Logistic equation	0.931	0.031	0	0.87	0.992
Grade 3 ($n = 50$)					
MELD	0.846	0.082	0.003	0.678	1
CTP	0.644	0.12	0.217	0.409	0.879
Logistic equation	0.842	0.106	0.003	0	1
Grade 4 ($n = 79$)					
MELD	0.684	0.152	0.217	0.385	0.982
CTP	0.712	0.151	0.154	0.406	1
Logistic equation	0.649	0.175	0.318	0.306	0.992

AUC, area under the curve derived from receiver operating characteristic curve analysis; *CTP*, Child-Turcotte-Pugh; *MELD*, Model for End Stage Liver Disease

logistic regression model showed the best performance in predicting 3-month mortality, foll owed by the MELD score and CTP score (Fig. 2).

Discussion

An important finding of the present study was that approximately two-thirds of Chinese patients with HE died within 3 months of admission to hospital, and those who died had more severe HE and higher MELD score, CTP score, incidence of complications (including HRS and upper GI bleeding), and values for certain laboratory parameters (including RBC and TBIL) than those who survived. Furthermore, logistic regression analysis showed that RBC, TBIL, HE stage, HRS and upper GI bleeding were independent factors associated with death, and a formula was developed to allow prediction of the probability of death. The area under the ROC curve (AUC) for the logistic regression model (when used to predict 3-month mortality) was 0.931, and the Youden index was higher than that for MELD or CTP score, indicating better performance. The model predicted death in the validation group with a sensitivity of 83.1% and specificity of 93.4%.To the best of our knowledge this is the first model developed specifically to predict mortality in patients with HE. Our model could potentially be useful to clinicians in their decision-making regarding the selection of therapeutic strategies and prioritization of patients for liver transplantation Fig. 3.

Two widely used scales for predicting the prognosis of patients with liver failure are the CTP score and MELD score (Attia et al. 2008; Botta et al. 2003; D'Amico et al. 2006; Londono et al. 2007; Said et al. 2004; Samada Suarez et al. 2008). The CTP score, first proposed by Child and Turcotte around 50 years ago and subsequently revised by Pugh, has been utilized for the evaluation of liver function reserve and prediction of prognosis in patients with severe liver disease. The CTP scoring system assesses liver dysfunction according to clinical and laboratory parameters, including TBIL, ALB, PT, ascites and HE (Pugh et al. 1973). The MELD scoring system was established by Malinchoc and colleagues in 2000 and utilizes a formula that includes TBIL, CRE and INR (Malinchoc et al. 2000). However, the MELD and CTP scales are not without their limitations (Kim and Lee 2013; Samada Suarez et al. 2008). Although the CTP score is easy to calculate in the clinical setting, it has four important limitations: first, not all the variables it considers have an independent effect; second, it includes subjective variables such as ascites and encephalopathy; third, the cutoff points for the quantitative variables may not be optimized; and fourth, certain prognostic factors (e.g. kidney function) are not taken into account. A notable drawback of the MELD scoring system is that CRE and TBIL can be influenced by a variety of factors other than liver disease, including age, sex, body mass, sepsis, hemolysis and therapeutic intervention (e.g. diuretics). In addition to these aforementioned disadvantages, the suitability of the MELD and CTP scoring systems for predicting prognosis in patients with HE remains unknown, as there has been little previous research to validate these scales in this specific setting.

HE is associated with a high mortality (Bustamante et al. 1999; Christensen et al. 1989; Saunders et al. 1981) and has been suggested to provide additional prognostic information independent of MELD score (Stewart et al. 2007). However, there have been few studies of the factors predicting prognosis specifically in patients with HE. One previous investigation

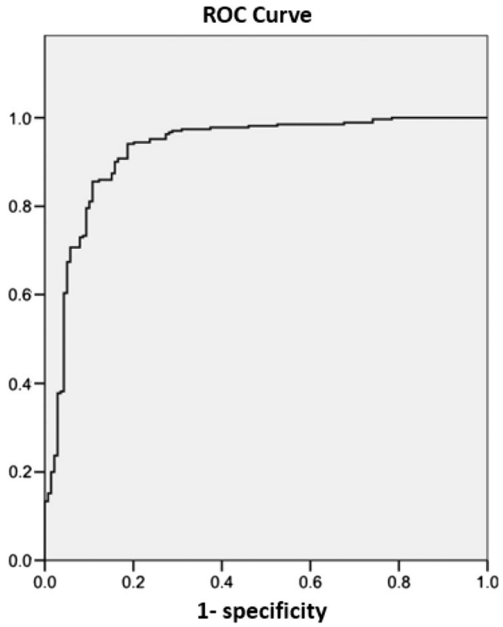

Fig. 1 Receiver operating characteristic curve when using the logistic regression model to predict death within 3 months of admission in patients in the modeling group

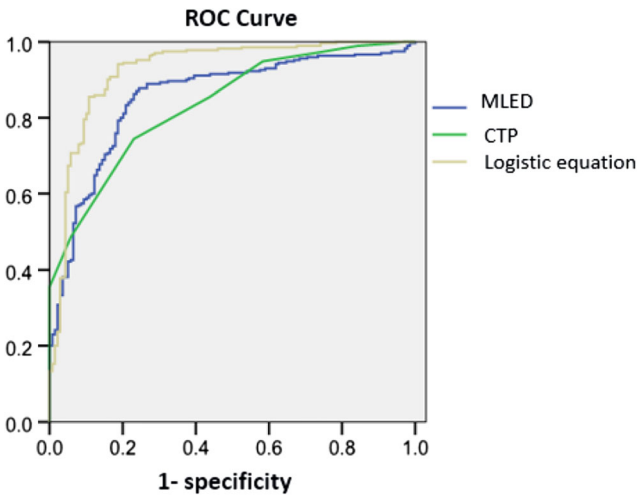

Fig. 2 Comparison of receiver operating characteristic curves between the logistic regression model, MELD score and CTP score when used to predict death within 3 months of admission in patients in the validation group

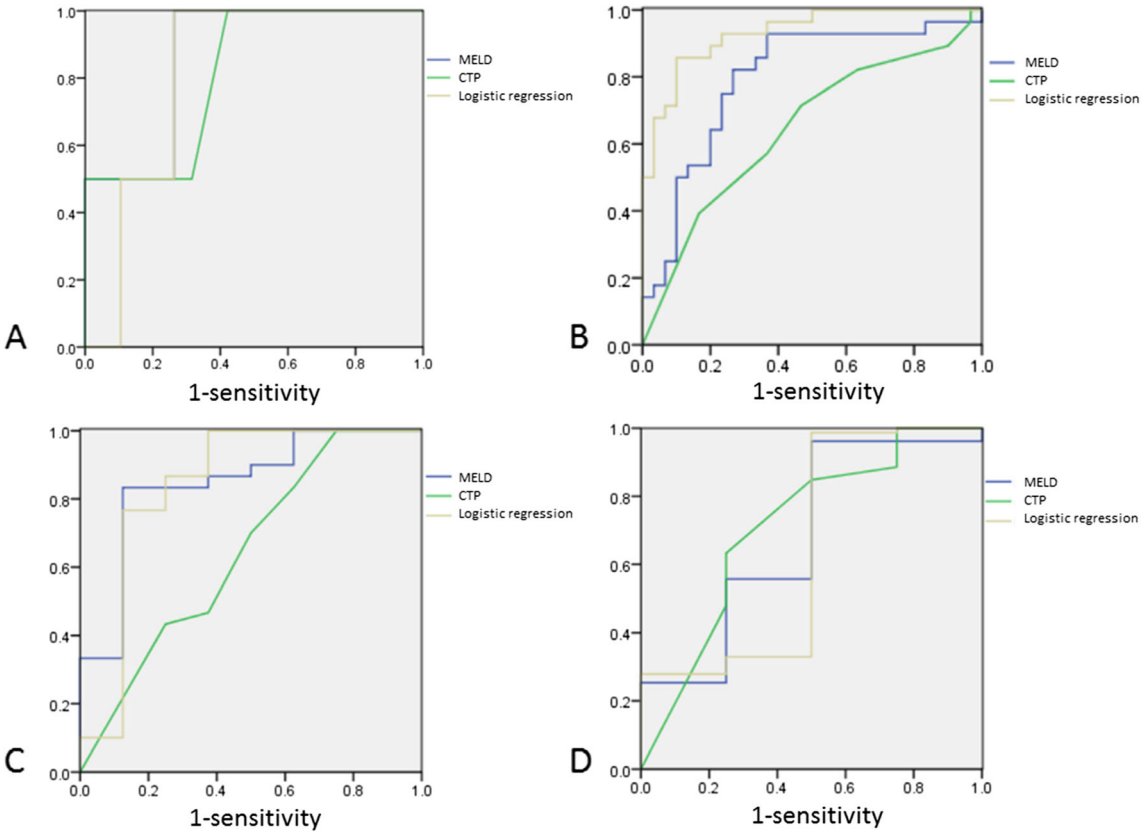

Fig. 3 Comparison of receiver operating characteristic curves between the logistic regression model, MELD score and CTP score when used to predict death within 3 months of admission in patients in the different stages of hepatic encephalopathy

identified male sex, elevated levels of TBIL, alkaline phosphatase, K^+ and BUN, and decreased ALB and PTA as factors associated with poor prognosis in patients with a first episode of acute HE [9], while another study found that a lack of improvement in HE stage during the first week of treatment was predictive of higher mortality (Hassanein et al. 2007). A third study determined that mortality in patients with HE could be predicted by a formula considering CTP score, BUN, WBC, presence/absence of hepatocellular carcinoma, serum lactate dehydrogenase and proteins induced by vitamin K absence (PIVKA-II) (Yoneyama et al. 2004). In more recent research, univariate analysis identified HRS, INR, WBC, TBIL, MELD score, chronic liver failure-sequential organ failure assessment (CLIF–SOFA) score and systemic inflammatory response syndrome (SIRS) as factors associated with 30-day mortality in patients with alcoholic liver cirrhosis and HE, but only CLIF–SOFA and SIRS remained significant in the multivariate analysis (Jeong et al. 2016). However, these previous studies included a relatively small number of participants (111 or fewer). Therefore, the current study was designed to collected at a from a much larger cohort of patients and develop a mathematic model that could be used as a new method for evaluating prognosis in patients with HE.

In the current study, 3-month mortality in the modeling group was 66% overall and 94% for patients with stage IV HE. Multivariate analysis indicated that RBC, TBIL, HE stage, HRS and upper GI bleeding were independent factors associated with 3-monthmortality in patients with HE. Patients with stage IV HE are in a deeper coma than those with stage III HE and have a lower probability of recovering consciousness and thus a poorer prognosis (Ferenci et al. 2002). It was also reported that the invalid treatment and death were 100% for patients with HE stage of IV. Upper GI bleeding, which occurred in approximately one-third of patients who died, can promote ammonia production and absorption from the intestines and thereby aggravate or precipitate HE (Cichoz-Lach and Michalak 2013; Suraweera et al. 2016). Decreased kidney function usually accompanies end-stage liver disease, and HRS was observed in more than half the patients who died in this study; renal dysfunction can increase CRE and BUN, and resultant diffusion of urea into the intestinal lumen can lead to enhanced ammonia uptake from the intestines and worsening of HE.

In the present study, the MELD scores and CTP scores of patients who died were significantly higher than those of patients who survived. ROC curve analysis demonstrated that the logistic regression model, MELD score and CTP score all had an AUC > 0.8, implying very good predictive accuracy, and a Youden index >0.5, implying adequate performance. Therefore, all three systems can be considered good models

for the prediction of short-term prognosis in patients with HE. Although the AUC value did not differ significantly between the three systems, the Youden index was higher for the logistic regression model than for CTP score or MELD score, indicating better performance.

This study has some limitations. First, this was a retrospective analysis, hence selection and reporting bias cannot be excluded. Second, this was a single-center study, so the results may not be generalizable to other regions of China or other countries. Third, although the population sample exceeded 400 in the modeling group, the study may have been underpowered to detect some real differences between groups. Fourth, the study period was only 3 months, so the applicability of our findings to long-term mortality remains unknown. Therefore, multi-center, prospective clinical studies are needed to verify and extend our findings.

In conclusion, the present study has established a new model for predicting 3-month mortality in Chinese patients with HE. The logistic regression model considered 5 factors identified as independent predictors of mortality: RBC, TBIL, HE stage, HRS and upper GI bleeding. The logistic regression model had superior performance to MELD score or CTP score at predicting 3-month mortality. The model we have established could potentially be applied in the clinic to facilitate decision-making regarding selection of therapeutic strategies and prioritization of patients for liver transplantation. Further research is needed to validate and optimize our model for use in the clinical setting.

Compliance with ethical standards

Disclosure of potential conflicts of interest The authors declare that they have no conflict of interest.

Research involving human participants The study was approved by the ethics committee of the Peoples' Hospital of Liaocheng City.

Informed consent Due to the retrospective and anonymized design of the study, written consent from the participants was deemed not to be required.

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