A clinical prediction model and its application for bleeding in chronic liver failure patients with esophageal varices

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Abstract. – OBJECTIVES: We aimed to explore the model for end-stage liver disease (MELD), Child-Turcotte-Pugh (CTP) score, endotoxin, bleeding score and dynamic changes of D-dimer in chronic liver failure patients with portal hypertension and esophageal varices, and explored their potential contact with bleeding in short-term prognosis.
PATIENTS AND METHODS: Chronic liver failure patients with esophageal varices were divided into 2 groups: bleeding group (Group A, n=50) and non-bleeding group (Group B, n=50). MELD, CTP score, endotoxin and plasma D-dimer was compared at different time point. The receiver operating characteristic curve (ROC) was drawn. The predictive model based on their cut off value in esophageal varices bleeding patients was evaluated.
RESULTS: Infection and endotoxin levels were related with bleeding and death in chronic liver failure patients with esophageal varices, and affect the patient's coagulation and fibrinolysis activity. The criteria of predictive model for predicting hemorrhage of esophageal varices in patients with chronic liver failure is: MELD ≥ 26; bleeding grading score ≥ 10; and/or plasma D-dimer > 700 ug/L. Plasma D-dimer, MELD score and death rate showed significant differences between two groups. Patients with chronic liver failure occurred bleeding and eventually dead have persistent anomaly plasma D-dimer level. In our model-group patients, the D-dimer and CTP score has statistical difference between surviving and death patients ($p < 0.05$).
CONCLUSIONS: This model could predict the prognosis of bleeding in chronic liver failure patients with esophageal varices. And has the short-term prognostic value for clinical application.

Key Words:
   D-dimer, MELD, Bleeding, Esophageal varices, Chronic liver failure, Patients.

Introduction

Esophageal varices (EV) caused by hypertension is one of common complications in liver cirrhosis, the prevalence ranged from 40 to 80% in patients with cirrhosis[1]. The development of EV lead to bleeding, which is one of the leading causes of death in patients with cirrhosis[2]. Endoscopic screening for EV is currently recommended for patients when the diagnosis of cirrhosis is confirmed, timely pharmacologic or endoscopic treatment can be started to prevent first bleeding in high-risk EV[3]. However, the cost of screening endoscopy is high. Investigators attempted to identify the noninvasive predictor for EV[4-6]. Tafarel et al[7] tested Child–Turcotte–Pugh (CTP) classification, AST to platelet ratio index (APRI), and laboratory indicators in model for end-stage liver disease (MELD), they found high value MELD are associated with EV and thrombocytopenia. Kim et al[8] concluded that P2/MS model is a reliable predictor for bleeding among patients with EV.

D-dimer, a fibrin degradation product of small protein fragment, is a sensitive marker of coagulation and fibrinolysis. For cirrhotic patients, elevated plasma D-dimer has been reported occurred in different degree of liver disease patients, D-dimer is positively related with the severe degree of liver diseases, this indicated the different degrees of hyperfibrinolysis existed in liver disease[9-13]. Dynamic observation of plasma D-dimer level in patients with liver disease has important clinical value[14,15]. Upper gastrointestinal bleeding is a common clinical symptom in chronic liver failure patient with portal hypertension, which is also one of the leading causes of death in patients with chronic liver

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failure. The severity of endotoxin is positively correlated with the severity of liver disease. Infection, the major complication in patients with chronic liver failure, is one of the common causes of death[16]. Currently, few study involved the risk factors of infection, endotoxin and D-dimer in patients with chronic liver failure. We investigated the relationship between dynamic changes of plasma D-dimer, infection, endotoxin, hyperfibrinolysis and the MELD, CTP score in patients with chronic liver failure; hope to predict the risk of massive hemorrhage of EV in patients with chronic liver failure.

Patients and Methods

Patients and Inclusion Criteria

A hospital based case control design was applied in our study. A total of 100 patients (63 males and 37 females, mean age of 58 yr) diagnosed with chronic liver failure were enrolled in Tianjin Medical College Hospital between February and July in 2008.

The study has been approved and registered in Ethics Committee of Tianjin Medical College Hospital, the Ethics Committee approved relating screening and treatment of these patients, all subjects signed written informed consent form. All works were undertaken following the provisions of the Declaration of Helsinki.

The diagnosis of chronic liver failure was adopted guidelines of liver failure (2006) of Chinese Hepatology Medical Association[17]. The diagnosis standards[18]: (1) having ascites or other portal hypertension; (2) having hepatic encephalopathy; (3) increased total serum bilirubin and decreased albumin; (4) having blood coagulation dysfunction, PTA ≤ 40%. The diagnosis of esophageal varices (endoscope, Figure 1)[19] were: (1) mild (G1): esophageal varices is straight or slightly curved without red sign; (2) moderate (G2): esophageal varices is straight or slightly curved with red sign, or esophageal varices is serpentine circuitous uplift without red sign; (3) severe (G3): esophageal varices is serpentine circuitous uplift with red color sign or esophageal varices is beaded, nodular or nodular (with or without red sign). The diagnosis of bacterial infections was according to the symptoms, clinical signs, blood, routine urine, chest X-ray and laboratory test results (Figure 1).
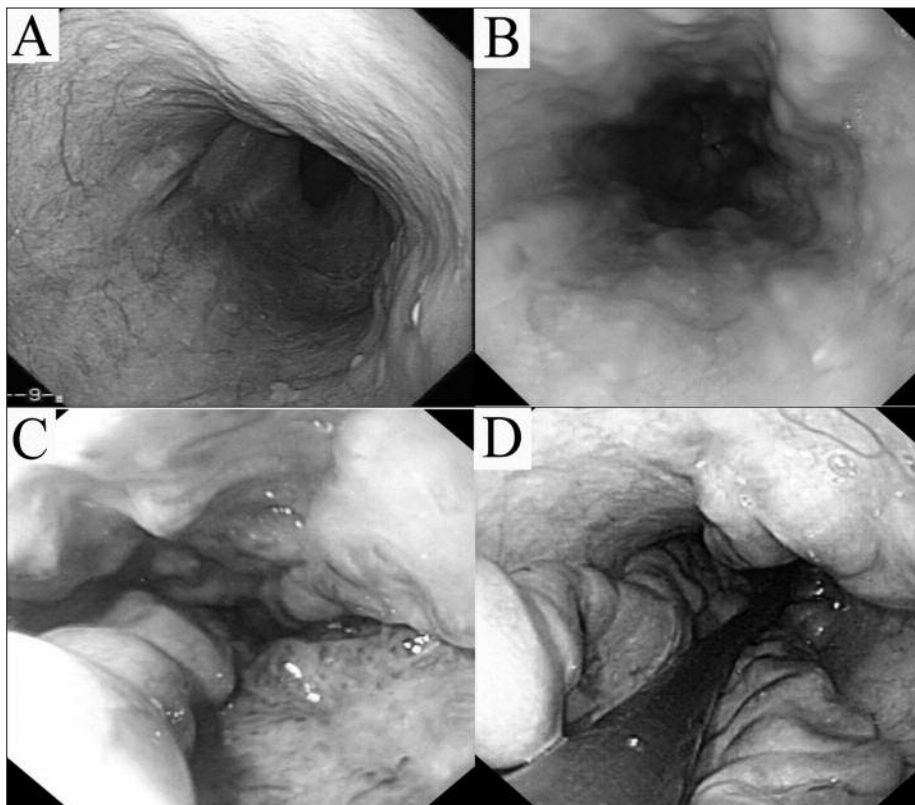

Figure 1. The diagnosis of esophageal varices by endoscope. *A,* Mild varicose vein above the dentate line. *B,* Moderate varicose veins, slightly flexed. *C,* Severe varicose veins with beaded and red color sign. *D,* Severe varicose veins with beaded sign, extending to the cardia.

Table I. The CTP classification in chronic liver failure patients.

Clinical or biochemical index	Score		
	1	2	3
Hepatic encephalopathy	Nil	1-2	3-4
Ascites	Nil	Mild	Moderate or severe
Total bilirubin (μmol/L)	< 34	34-51	> 51
Albumin (g/L)	≥ 35	28-35	≤ 28
Extended INR prothrombin time (s)	1-3	4-6	> 6

INR: international normalized ratio. Total Score: Grade A ≤ 6; Grade B: 7 ~ 9; Grade C ≥ 10.

Patients were excluded if they have: liver carcinoma; previous or current treatment of beta-blockers or nitrates; patient have endoscopic or surgical interventions for portal hypertensions previously were also excluded.

Recruited patients were divided into two groups: bleeding group: patients having esophageal varices bleeding treated by emergency endoscopic hemostasis; and non-bleeding group.

MELD, Bleeding Scoring and CTP Classification

MELD score was calculated according to the level of serum bilirubin, serum creatinine, and the international normalized ratio (INR) of prothrombin time: MELD = 3.8 × total bilirubin (mg/dl) + 11.2 × INR + 9.6 × creatinine (mg/dl) + 6.4 × cause of disease (cholestasis or alcohol is 0; the other is 1). The CTP classification was concluded in Table I; their bleeding score were concluded according to the disease history and clinical examination results (Table II).

Plasma D-dimer Measurement

A total of 2-3 ml peripheral venous blood was drawn at 8 AM to a plastic tubes containing 1.5 ml (0.13 mol/L) sodium citrate. Blood was centrifuged at 2000 g for 10 min at 4°C and the plasma was drawn for testing. D-dimer plasma level was quantified using NycoCard D-dimer assay kit (Axis-Shield PoC AS, Oslo, Norway). For bleeding-group patients, blood was drawn as far as possible when the hemorrhage hemodynamic was stable by sterile venipuncture, and then drawn after 3, 8 and 15 days admission in order to obtain the plasma D-level. Blood samples of non-bleeding patients were taken only at admission.

Statistical Analysis

Statistical analysis was performed using SPSS16.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± SD or n (%), and analyzed using chi-square test, Student's *t*-test or Mann-Whitney U-test when ap-

Table II. The bleeding scoring system in chronic liver failure patients.

	0 score	1 score	2 score
Skin	No bleeding	1-5 ecchymosis	> 5 ecchymosis (diameter > 2 cm) or Intensive petechiae
Oral cavity[a]	No bleeding	1 blood blister or > 5 ecchymosis or bleeding can be stopped automatically	Multiple blood blister or bleeding cannot be stopped automatically
Nasal cavity[a]	No bleeding	Bleeding when blow the nose or nasal bleeding < 5 min	Nasal bleeding > 5 min
Urinary tract[a]	No bleeding	Microscopic hematuria	The naked eye hematuria
Under the conjunctiva a	No bleeding		Bleeding
Duration of liver disease	Nil	< 10 yr	≥ 10 yr
Duration of upper gastrointestinal bleeding	Nil	The previous 1 times or fecal occult blood positive	The previous 1 times or black fecal or visible hemorrhage
The degree of esophageal varices	Nil/G1	G2	G3

[a]In the last 2 weeks G1: mild; G2: moderate; G3: severe. Total score: 0-16.

Table III. The bleeding scoring system in chronic liver failure patients.

Groups	Status	N	Survival (N)	Death (N)	OR (95% CI)
All of the patients	Infection	56	46	10	9.438 (1.148, 76.126)
	Non-infection	44	43	1	
Bleeding group	Infection	32	24	8	5.667 (0.647, 49.616)
	Non-infection	18	17	1	
Non-bleeding group	Infection	24	22	2	
	Non-infection	26	26	0	

[a]In the last 2 weeks G1: mild; G2: moderate; G3: severe. Total score: 0-16.

propriate. Multivariate analysis was performed by means of a stepwise logistic-regression analysis. Receiver operating characteristic curves (ROC) analysis was performed on the available data set for predictive value of the large EVs. The cutoff value was calculated by ROC curve. $p < 0.05$ were considered as statistically significant.

Results

A total of 100 patients were recruited successfully, they were equally divided into two groups: bleeding group (group A, n=50, 29 M, 21 F, mean age of 58.96 ± 12.87 y/o) and non-bleeding group (Group B, n=50, 34 M, 16 F, mean age of 57.34 ± 12.69 y/o), no statistical difference existed in age and sex ratio between the 2 groups.

High Death Risk of Infection and Bleeding in Chronic Liver Failure Patients with Esophageal Variceal

In all patients, a total of 56 case of infection and 10 case of death were reported, the case number of pneumonia, urinary tract infection, spontaneous peritonitis, cholangitis and focal infection were 24, 11, 16, 2 and 3 respectively. We concluded the death number in all patients to Table III. As we can see, in all patients, the OR

of infection was 9.438 (95% CI: 1.148-76.126), which means the infection is a high risk factor for death in chronic liver failure patients with esophageal variceal. However, when hemorrhage was taken into account, the OR decreased to 5.667 with 95% CI ranged from 0.647 to 49.616, which means the infection might not a risk factor for these bleeding patients. Considering there was no infection patients in the death group, this result might not correct for the insufficient clinical cases number.

The death cause of these patients were septic shock (N=4), hemorrhagic shock (N=3) and multiple organ failure (N=4), when compared the death between patients with bleeding and patients without bleeding, there was significant difference between the 2 group patients ($p = 0.025$), bleeding is a risk factor for death.

Comparison of MELD, CTP, Endotoxin and Bleeding Score in Patients with or Without Bleeding

The MELD score, endotoxin level, and bleeding score were concluded in Table IV. Results show that there were significant differences in MELD score, CTP, endotoxin and bleeding score between the survival patients and the death-patients ($p < 0.05$) in the bleeding group; However, difference was found only in the MELD score

Table IV. Comparison of MELD score, endotoxin level, and bleeding score between bleeding and non-bleeding group.

Groups	Cases	Number	MELD	CTP	Endotoxin level	Bleeding grading score
Bleeding group	Survival	41	19.88 ± 7.14	8.34 ± 2.47	93.03 ± 114.73	11.20 ± 1.85
	Death	9	30.61 ± 9.92	10.89 ± 1.62	249.47 ± 141.36	14.22 ± 2.64
p		0.000	0.001	0.001	0.000	
Non-bleeding group	Survival	48	14.13 ± 5.54	8.15 ± 1.80	88.84 ± 124.09	8.75 ± 1.49
	Death	2	40.65 ± 5.35	12.00 ± 1.41	245.80 ± 59.58	10.00 ± 2.83
p		0.000	0.004	0.084	0.265	

and CTP between the survival patients and the death patients ($p < 0.05$) in non-bleeding group. At the meantime, we compared the MELD score, CTP, endotoxin and bleeding score between the survival patients and the dead patients, results showed the difference were all significant ($p = 0.000$).

Predicting Death by MELD Score

The cutoff value of the MELD score to predict death was determined in hemorrhage patients, non-bleeding patients, and all of the patients using ROC curve (Figure 2 A-C). The area under curve (AUC) is 0.810, 1, and 0.889 ($p = 0.004$, 0.017, 0.000) in hemorrhage patients, non-bleeding patients, and all of the patients, respectively, which indicate that there has significance for the MELD predicting death. The possibility of death varied with the MELD score, the 95% CI of the curve area ranged from 0.622 to 0.999, 1 to 1, 0.766 to 1.011, respectively. The cutoff value of the MELD score to predict death was determined

to 26 when the specificity and the sensitivity were taken into account. Which means that the MELD > 26 is a risk factor for death.

Predicating Death by Bleeding Grading Score

ROC curve from Figure 3 showed the area under curve (AUC) is 0.861 ($p = 0.000$) there has significance for bleeding grading score predicting bleeding. The possibility of hemorrhage was positively correlated with the bleeding grading score. Taking into the specificity and the sensitivity account, the cutoff value of bleeding grading score predicting bleeding was 10 with the specificity and sensitivity of 0.71, and 0.82, respectively.

Dynamic Changing of D-dimer Level

The dynamic changing of average D-dimer in bleeding patients were drawn in Figure 4, the plasma D-dimer reached a high peak on the third day after bleeding, and then descend gradually
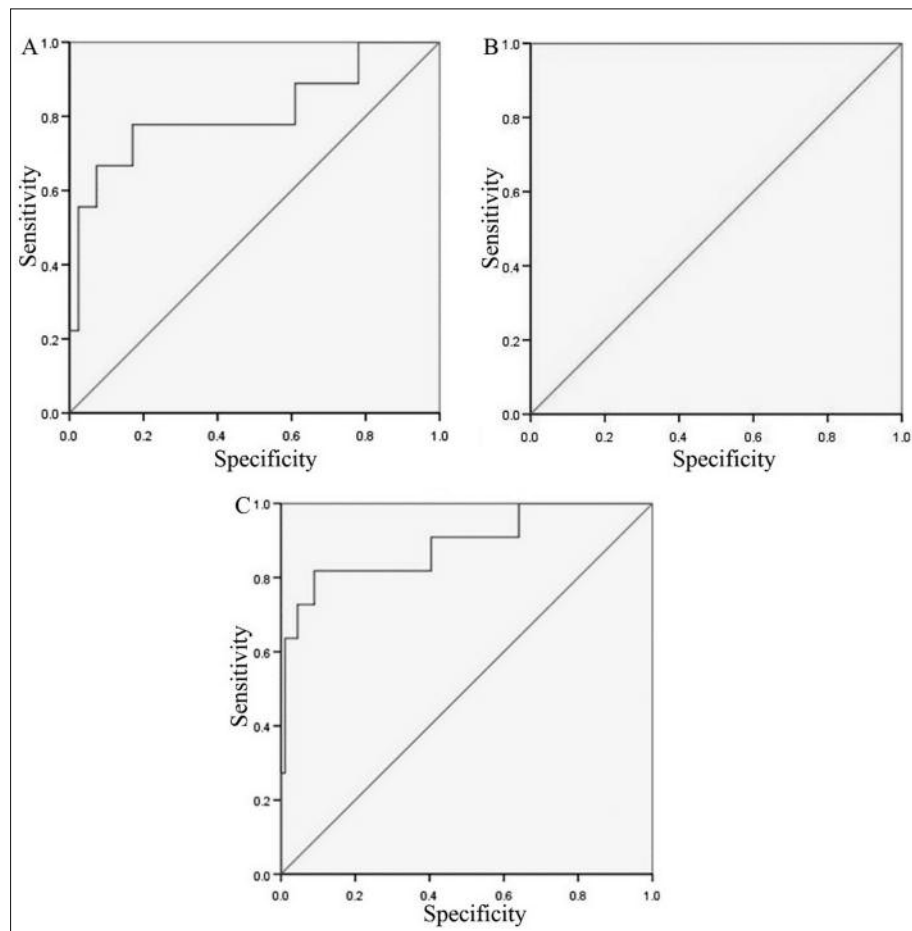

Figure 2. The cutoff value of MELD score to predict death. **A,** In bleeding patients. **B,** In non-bleeding patients. **C,** In all patients.
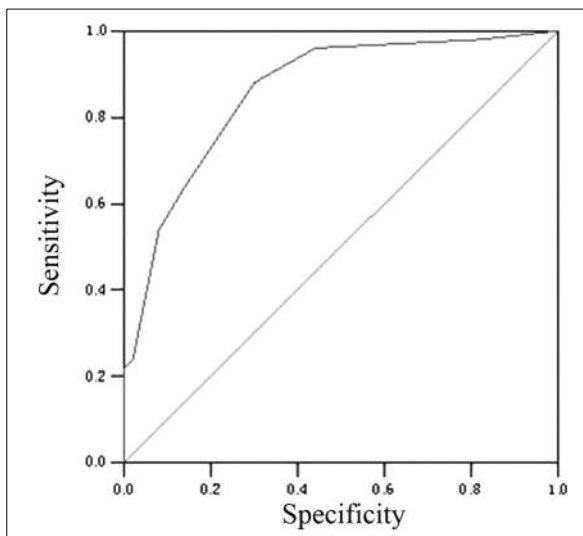
Figure 3. The cutoff value of bleeding grading score to predict bleeding.

until back to the original state around 2 weeks after bleeding. We compared D-dimer level at different time point, results showed there have significant differences at D-dimer level when compared with 3th and 8th day after admission ($p <$ 0.0001 and $p = 0.0018$, respectively), while has no difference in admission and 15th day ($p >$ 0.05).

At different time points, there have significant difference between death group and non-death group at the plasma D-dimer levels; however, there have no difference in the D-dimer levels when compared between patients with or without bleeding and with or without infection.

Predicting Death by Plasma D-dimer Level

ROC curve (Figure 5 A-C) showed the area under curve (AUC) is 0.770, 0.922, 0.791 ($p =$ 0.012, 0.045, 0.002) in hemorrhage patients,
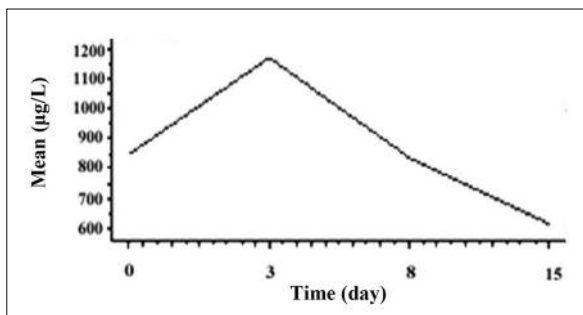

Figure 4. The dynamic changing of average D-dimer in bleeding patients.

non-bleeding patients, and all of the patients, respectively. There has significance for plasma D-dimer (first time from bleeding onset) to predict death. The possibility of death increased when the D-dimer level increased. The 95% CI of the curve area ranges from 0.549 to 0.990, 0.835 to 1.009, and 0.615 to 0.967, respectively. Taking into the specificity and the sensitivity account, the cutoff value of the plasma D-dimer (first time from bleeding onset) to predict death was 700 μg/L.

Clinical Application and Validation of Our Evaluation Model

According to the cut off value we concluded above, another group of chronic liver failure patients with esophageal varice was selected. The MELD score in these patients were ≥ 26. A total of 30 patients (18 M, 12 F, mean age of 58.86±10.69 yr) were selected successfully to model application group; Another 18 esophageal variceal patients with MELD score higher than 26 were chosen as the control, (11 M, 7 F, mean age of 59.17±12.99 yr). Endoscopic examination were performed in model application group patient at the same time, they were given the necessary treatment. Statistical method was performed to compare the MELD, CTP, endotoxin, D-dimer, bleeding grading score, and death rate between model application and the control group.

Table V showed the comparison of model application and control group in MELD, CTP, endotoxin, D-dimer and bleeding grading score. Table 6 showed the comparison of death and survival patients in model application group at MELD, CTP, endotoxin, D-dimer and bleeding score. Results showed the CTP and plasma D-dimer has a significant difference between survival patients and death patients in model group ($p < 0.05$). However, other factors listed in Table VI could not predict death in model group patients; this may due to the insufficient clinical case number.

The chi-square analysis showed there were significant differences between model application group and control group when compared the death rate. The OR between 2 groups was 2.94 with 95% CI of 1.23 to 7.04. This result demonstrate that by actively performing the endoscopy in high-risk patients, and performing preventive medical operation of endoscopic ligation or hardening treatment in chronic liver failure patients with MELD score ≥ 26 could significantly decreased the proportion of death.

Figure 5. The cutoff value of the plasma D-dimer (first time from bleeding onset) to predict death. **A,** In hemorrhage patients; **B,** In non-bleeding patients **(C)** in all of the patients.
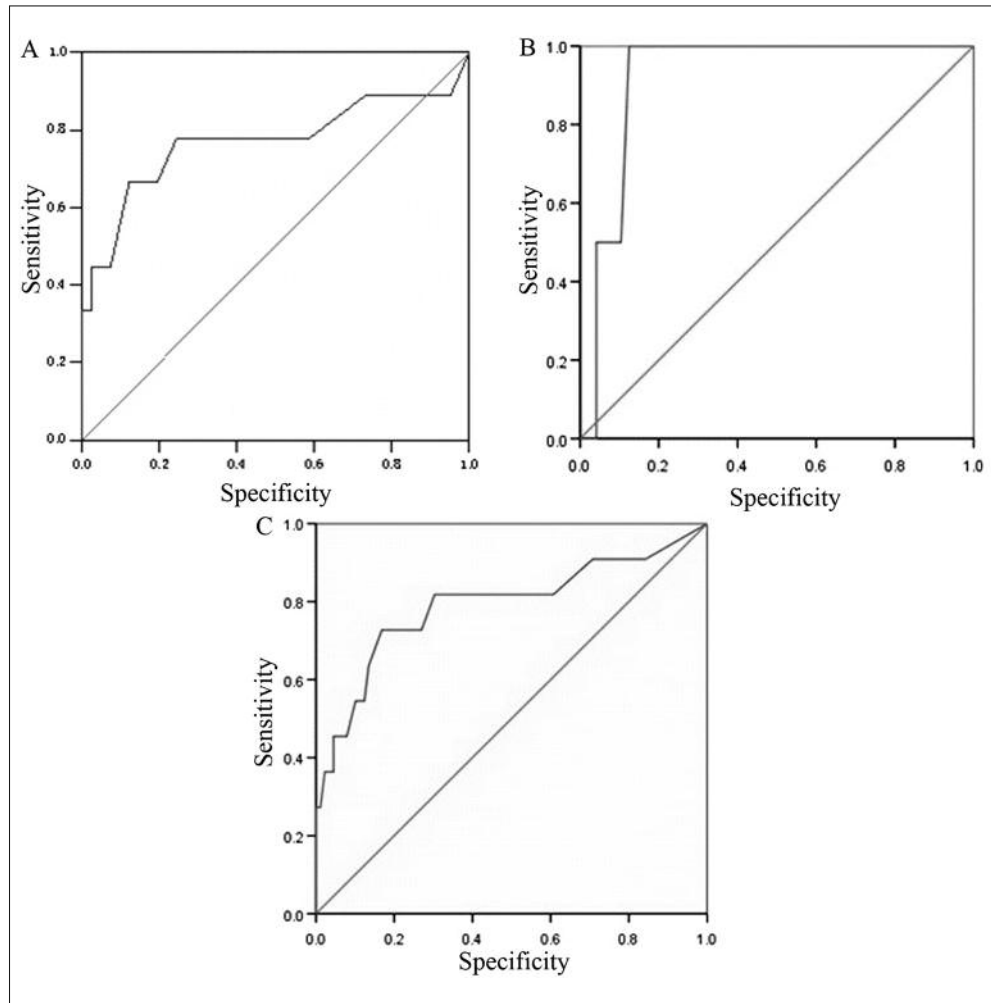
Table V. Comparison of model application and control group in MELD, CTP, endotoxin, D-dimer and bleeding score.

	N	MELD	CTP	Endotoxin	D-dimer	Bleeding grading score
Application	30	33.07 ± 5.78	10.44 ± 1.65	198.61 ± 28.57	1633.33 ± 329.88	13.44 ± 2.57
Control	18	32.31 ± 4.10	10.33 ± 1.47	195.83 ± 19.52	1667.67 ± 486.60	13.20 ± 1.60
t	0.677	0.846	0.856	1.440	0.653	
p	0.558	0.429	0.462	0.335	0.544	

Table VI. Comparison of death and non-death patients in model application group at MELD, CTP, endotoxin, D-dimer and bleeding score.

	N	MELD	CTP	Endotoxin	D-dimer	Bleeding grading score
Live	25	29.47 ± 3.47	10.28 ± 1.34	81.94 ± 105.13	792.00 ± 491.52	12.12 ± 2.67
Death	5	43.51 ± 4.79	8.80 ± 1.64	165.25 ± 173.27	1240.00 ± 240.83	11.44 ± 2.40
t	-2.794	2.179	-1.450	-3.072	0.559	
p	0.09	0.038	0.158	0.010	0.158	

Death rate and death ratio in model application group and control group.

Discussion

Liver failure occurs gradually and over many years. Chronic liver failure usually followed after cirrhosis. Variceal bleeding remains the leading cause of morbidity and mortality in cirrhotic patients, periodic endoscopic screening for EVs and appropriate prophylactic treatments for high-risk cases with the red-color sign or decompensate cirrhosis are currently recommended for all cirrhosis patients[1,2]. Severities of the bleeding episode, failure to control bleeding and early recurrence are indicators of poor outcome. All these factors depend on the severity of the underlying liver dysfunction. Current guidelines suggest that all chronic patients should be screened for varices at diagnosis, and follow up every 2-3 years for patients without varices (depending upon liver disease severity), and 1-2 years for patients with small varices, to assess the enlargement of varices and apply prophylactic treatment [3]. However, a screening strategy involving all cirrhotic patients will lead to a number of unnecessary endoscopies, and may be hampered by a heavy medical and financial burden[8]. Thus, various non-invasive screening tools have been developed, allowing endoscopy to be applied selectively in high-risk patients. Besides, none of these are sufficiently accurate, reproducible, or economical to satisfy the guidelines, and they may be cumbersome to perform[1,20-22]. Thabut et al[23] indicated noninvasive assessment of portal hypertension, emphasized that serum markers and/or radiological examinations would contributed to the diagnosis of EV in the future. Therefore, the ideal marker should be cheaper, with easy access, and high-clinical sensitivity and specificity.

Patients with chronic liver failure are more likely to produce intestinal endotoxemia (IETM). Our study demonstrates the endotoxin level of bleeding group patients is significantly higher than that of control group, this indicate that endotoxin level was related to the severity of the liver function classification. Infection in esophageal varices bleeders with chronic hepatic failure may be a trigger factor for aggravating bleeding, which indicated infection may be an independent predictive index of poor prognosis for esophageal varices bleeders with chronic hepatic failure [24]. However, our study did not find association between infection and death, this may due to the lack of enough case number.

As a symbol of the hypercoagulable state and hyperfibrinolysis, plasma D-dimer with clinical specificity and convenience has replaced t-PA as a superb index of the hyperfibrinolysis in emergency assay[25]. We found that the level of the plasma D-dimer changed a lot in early hemorrhage patients, which indicated that hyperfibrinolysis plays an important role in the pathology of acute bleeding patients. Hyperfibrinolysis is directly associated with esophageal variceal bleeding in chronic liver failure[26]. Measurement of the hyperfunction index can help to evaluate the risk of re-bleeding. In our study, we concluded the cutoff value of D-dimer to predict death is 700 ug/L. The dynamic changes of plasma D-dimer reached high peak on the third day after bleeding and then descend gradually until back to the original state around 2 weeks after. Therefore, high levels of plasma D-dimer at the time of bleeding in patients with massive hemorrhage of esophageal varices in chronic liver failure could directly affected the re-bleeding and death of the patients, which is important for clinicians to judge patient's condition and prognosis in early time. In acute bleeding period, it is difficult to improve the liver function rapidly; however, infection and hyperfibrinolysis can be treated effectively. The pure esophageal varices hemorrhage can be treated with the assistance of antifibrinolytic drug[14]. Antifibrinolytic agents might be more practical than the application of endoscopic variceal ligation, sclerotherapy and vasoactive drugs in patients with massive hemorrhage of esophageal varices in chronic liver failure; however this still needs a wide range of clinical observation.

Complications of chronic liver failure affect the prognosis of patients seriously. Despite of the development of new drugs and the progress of treatments, the death rate of end-stage liver disease/terminal liver failure remains as high as 60%-80%. MELD score has been characterized as dynamic observation and objectivity, MELD can well predict the risk of deaths in end-stage liver disease[27], and provide more information in predicting the prognosis[28]. In our study, the area under curve and the cutoff value of MELD to predict death is 0.810 and 26, respectively. Due to the existence of hemorrhage factors in our research object, the cutoff value of MELD is relatively low. Habib et al[29] indicated in his report that the survival rate was the highest in chronic severe hepatitis patients with MELD ≤ 28, while the patients were all died when MELD ≥ 40. Because we only discussed the death in two weeks

after admission, and didn't perform long-term mortality, the MELD score might be higher than other similar study.

In our study MELD score is associated with the plasma D-dimer, but the plasma D-dimer varied significantly at early level in bleeding died patients. Unfortunately, no association was found among death, infection, MELD, D-dimer, bleeding grading score, and endotoxin in the model group by logistic prediction death, this may due to the application of endoscopy, endoscope band ligation endoscopic injection sclera therapy in high risk patients and, thus, the actual prognostic factors can be affected by medical intervention.

In our study, the appearance of infections is low, because the application of antibiotic treatment for the candidate patients after admission, this could cause the underestimation of the effect of actual infection factors[30]. In addition, indicators were adopted in research objects within 24 hours after admission; therefore, conclusions from our study have certain limitations. Our study could be more comprehensive and objective if the dynamic changes of all kinds of scores were observed after admission, and if more patients with chronic liver failure could be collected.

Conclusions

Our research predicts the short-term prognosis of upper gastrointestinal hemorrhage in EV bleeders with chronic liver failure, and then applied intervention treatment according the cut off value of MELD score; this could provide useful information for the short-term prognosis. Moreover, we will recruited more clinical sample to study further prognosis of the medium-term and long-term prognosis assessment.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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