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D-dimer is a prognostic marker for 1-year mortality in patients with chronic liver failure and hepatic encephalopathy

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Abstract

Background and Aim: Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver failure with poor outcomes. The present study aimed to evaluate the predictive values of D-dimer in patients with HE.

Materials and Methods: Patients with chronic liver failure (CLF) and HE were enrolled. Univariate and multivariate logistic analysis was performed to investigate the risk factors for 1-year mortality of HE.

Results: During the first year after diagnosis, 39.2% (65/166) of the patients died. D-dimer was significantly higher in non-survivors (Z=2.617, p<0.01). Both D-dimer and international normalized ratio (INR) positively correlated with Child-Pugh and MELD scores, and negatively correlated with sodium (all p<0.01). Moreover, there was a negative relationship between D-dimer and HE grades (r=-0.168, p=0.031), while the relationship between INR and HE grades was not significant (r=0.083, p=0.289). Multivariate analysis showed that age (odds ratio (OR):1.035, 95% CI:1.004–1.067, p=0.03), D-dimer (OR=1.138, 95% CI:1.030–1.258, p=0.01), ALT (OR=1.012, 95% CI:1.001-1.022, p=0.03), and sodium (OR=0.920, 95% CI:0.858–0.986, p=0.02) were independent risk factors for 1-year mortality. Then, a new model Model(Age_DD_ALT_Na) incorporating age, D-dimer, ALT, and sodium was developed. AUROC of Model(Age_DD_ALT_Na) was 0.732, which was significantly higher than MELD and Child-Pugh scores (AUROC: 0.602 and 0.599, p=0.013 and 0.022).

Conclusion: D-dimer is a prognostic marker for 1-year mortality in patients with CLF and HE.

Keywords: ALT; Child-Pugh; D-dimer; hepatic encephalopathy; MELD; sodium

Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric complication of decompensated cirrhosis (DC) or liver failure. Approximately 20% of patients with DC experienced recurrent HE.[1,2] It is also a common side effect of a transjugular intrahepatic portosystemic shunt. Patients with DC and HE have high mortality, decreased life quality, and a heavy economic burden.[1]

In case a suspicious HE was considered, HE should be classified based on four criteria, including underlying liver disease, severity of clinical manifestations, time course, and precipitating factors.[3] It is widely accepted that ammonia and inflammation, resulting from variceal bleeding and infection, are major triggers for HE.[4] While in some cases, it is difficult to confirm the precipitating factors, and it is uncertain to attribute neurological disturbances to a normal level of ammonia. So, other factors, such as worse liver function, sarcopenia, and a history of previous HE, should also be evaluated to improve the management and prognosis of HE.[3,5]

Coagulation disorder is an indicator of severe liver diseases, including acute or chronic liver failure (CLF). Tan et al.[6] reported that a higher international normalized ratio (INR) was an independent risk factor for HE incidence, and clinicians should pay attention to continuous changes in INR. A similar study by Shi et al.[7] showed that increased INR predicts accelerating deterioration and high short-term mortality in patients with liver cirrhosis or advanced fibrosis. Apart from insufficient liver function, variceal bleeding is another important risk factor for HE development and poor prognosis.[8] It is recently recognized that the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score incorporating INR and HE is better than the Child-Pugh score and model for end-stage liver disease (MELD) in predicting mortality of DC.[9]

Abnormalities of blood coagulation and fibrinolysis coexist in liver failure.[10] D-dimer, which is an index of fibrinolysis, is associated with short-term mortality in patients with acute-on-chronic liver failure (ACLF).[11] Serum D-dimer level at admission can be used to stratify patients at high risk of ACLF-related death.[11] For patients with liver cirrhosis (LC), increased D-dimer is an independent risk factor for portal vein thrombosis (PVT), which increases complications of LC and aggravates LC progression.[12] To date, knowledge about D-dimer in the prognosis of HE remains limited.

Herein, we investigated the relationship between D-dimer and the severity of HE, and compared the predictive value of D-dimer and INR in patients with CLF and HE.

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Table 1. Characteristics of patients with chronic liver failure and hepatic encephalopathy

Variables	Survivor (n=101)	Non-survivor (n=65)	Z or χ^2	p
Age (years)	63.0 (54.0–70.0)	66.0 (57.0–72.5)	1.844	0.07
Male, n (%)	67 (66.3)	41 (63.1)	0.185	0.67
HBV infection, n(%)	51 (50.5)	26 (40.0)	1.752	0.19
Diabetes, n(%)	19 (18.8)	14 (21.5)	0.185	0.67
ALT, U/L	24.0 (16.0–35.5)	33.0 (23.4–49.5)	3.239	<0.01
AST, U/L	36.0 (25.5–54.5)	47.0 (32.0–75.0)	3.453	<0.01
TBil, μmol/L	34.8 (20.1–52.0)	45.9 (26.5–77.3)	2.217	0.03
Albumin, g/L	30.2 (26.8–36.3)	30.5 (26.9–35.5)	0.318	0.75
Creatinine, μmol/L	79.2 (65.8–96.0)	84.6 (71.7–101.7)	1.975	0.05
Serum sodium, mmol/L	140.3 (137.2–142.3)	138.0 (134.2–141.2)	2.668	<0.01
Ammonia (μmol/L)	82.0 (57.8–103.8)	74.5 (36.5–134.0)	0.349	0.73
INR	1.3 (1.1–1.5)	1.4 (1.2–1.7)	1.266	0.21
D-dimer	1.5 (0.6–2.7)	2.6 (0.7–4.8)	2.617	<0.01
MELD score	13.0 (10.0–16.5)	15.0 (12.0–20.0)	2.220	0.03
Duration of follow-up, months	32.1 (16.7–56.3)	1.6 (0–6.7)	10.773	<0.01

Comparison was conducted by Mann-Whitney U test (median and IQR) for continuous variables, and Chi-square test for categorial values. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin; INR: International normalized ratio; MELD: Model for end-stage liver disease.

Materials and Methods

Patients

From October 2010 to December 2021, data from 189 patients with CLF and HE admitted to our hospital were retrospectively collected. CLF was diagnosed according to the Chinese Guideline for Diagnosis and Treatment of Liver Failure (2019 version).[13] HE was diagnosed according to underlying LC, clinical cognitive damage, and ammonia, and then was graded using the West Haven Criteria.[14,15] Cerebral CT scans were performed routinely to exclude cerebrovascular accidents and intracranial tumors. Patients who suffered from malignant tumors or developed hepatocellular carcinoma (HCC) in the first year after diagnosis were excluded.

Demographic, clinical, and laboratory data, including age, sex, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBil), albumin, INR, creatinine, D-dimer, and complications, were collected at the first time of admission.

The study complied with the Declaration of Helsinki, 2013 (NMUEC (2018) 506). The study was approved by the Ethics Committee of Changzhou Third People's Hospital. Informed consent was obtained from participants in the study.

Score Systems

The non-invasive risk score MELD was calculated as described before.[16] MELD=11.2×ln(INR)+9.6×ln[creatinine (mg/dl)]+3.8×ln[TBil (mg/dl)]+6.4.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were presented as median with interquartile range (IQR), and were analyzed using Mann-Whitney U tests. Categorical values were presented as frequencies and were compared using the chi-square test or Fisher's exact test. Correlation analysis was performed using the Spearman correlation test. Independent risk factors for mortality were identified using logistic regression analysis. Predictive accuracy of different scoring systems was evaluated based on the area under the receiver operating characteristic curve (AUROC) by MedCalc version 15.2.2 software for Windows (MedCalc Software, Mariakerke, Belgium). $p<0.05$ was considered statistically significant.

Results

Characteristics of Patients

Among the 189 patients, 23 patients were excluded, including 15 patients with indefinite outcomes, 5 patients with insufficient data for analysis, and 3 patients who developed HCC in the first year after diagnosis. Data from 166 patients were analyzed, including 77 individuals with hepatitis B virus-related LC, five with hepatitis C virus-related LC, 17 with alcoholic LC, 10 with autoimmune hepatitis, nine with primary biliary cholangitis, 20 with schistosomiasis cirrhosis, and the remaining 28 patients with indefinite etiology.

During the first year after diagnosis, 39.2% (65/166) of the patients died. Survivors had lower ALT, AST, and TBil, and higher serum sodium than non-survivors ($z=3.239$, 3.453, 2.217, and 2.668, all $p<0.05$). There was no significant difference in INR between survivor and non-survivor groups ($z=1.266$, $p=0.21$), while D-dimer was significantly higher in non-survivors ($z=2.617$, $p<0.01$) (Table 1).

Moreover, D-dimer was significantly higher in patients with spontaneous bacterial peritonitis (SBP) ($z=2.234$, $p=0.03$), and there was no significant difference in INR ($z=1.771$, $p=0.08$) between patients with and without SBP. Both D-dimer ($z=1.382$, $p=0.17$) and INR ($z=0.386$, $p=0.70$) showed no significant difference between patients with and without upper gastrointestinal bleeding.

Correlation Between D-Dimer and Other Laboratory Parameters

D-dimer positively correlated with AST, TBil, Child-Pugh, MELD, and INR ($r=0.204$, 0.275, 0.412, 0.444, and 0.414, all $p<0.01$), and INR also positively correlated with AST, TBil, Child-Pugh, and MELD ($r=0.179$,

0.596, 0.821, 0.840, all p<0.05). Both D-dimer and INR negatively correlated with sodium (r=-0.216 and -0.237, both p<0.01). Moreover, there was a negative relationship between D-dimer and HE grades (r=-0.168, p=0.031), while the relationship between INR and HE grades was not significant (r=0.083, p=0.289) (Fig. 1).

Independent Risk Factors for 1-Year Mortality of HE

As shown in Table 2, the univariate logistic analysis showed that age, ALT, AST, MELD, sodium, and D-dimer were associated with 1-year mortality. Multivariate analysis showed that age (odds ratio (OR):1.035, 95% CI:1.004–1.067, p=0.03), D-dimer (OR=1.138, 95% CI:1.030–1.258, p=0.01), ALT (OR=1.012, 95% CI:1.001–1.022, p=0.03), and sodium (OR=0.920, 95% CI:0.858–0.986, p=0.02) were independent risk factors for 1-year mortality. Then, a new model incorporating age, D-dimer, ALT, and sodium was developed: Model(Age_DD_ALT_Na) (y=1) . The AUROC of Model(Age_DD_ALT_Na) was 0.732, which was significantly higher than MELD and Child-Pugh scores (AUROC: 0.602 and 0.599, p=0.013 and 0.022) (Fig. 2).

Risk Stratification for Cumulative Mortality of HE

With an optimal cut-off value of 0.32, Model(Age_DD_ALT_Na) achieved 83.08% sensitivity, 59.41% specificity (Youdan index=0.425). Then the patients were divided into two groups: the low-risk group (Model(Age_DD_ALT_Na) <0.32) and high-risk group (Model(Age_DD_ALT_Na) ≥0.32). Kaplan-Meier survival analysis showed that patients with HE in the high-risk group had a poor prognosis (χ^2=25.63, p<0.01) (Fig. 3).

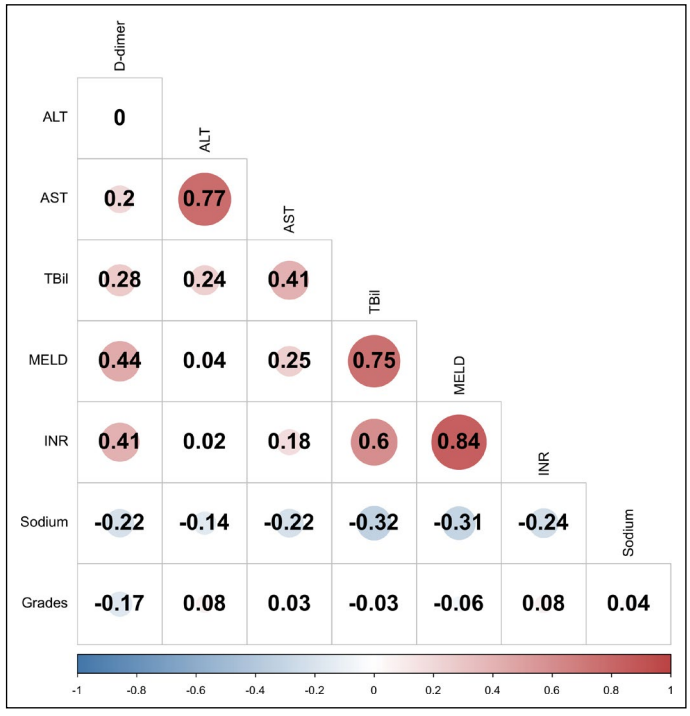

Figure 1. Correlation analysis between D-dimer and other laboratory parameters.

INR: International normalized ratio; MELD: Model for end-stage liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin.

Discussion

In the present study, approximately 39.2% (65/166) of the patients died during the first year after diagnosis. D-dimer was significantly higher in non-survivors, while INR did not differ significantly between survivor and non-survivor groups. Both D-dimer and INR positively correlated with Child-Pugh and MELD scores and negatively correlated with serum sodium. Multivariate analysis showed that age, D-dimer, ALT, and sodium were independent risk factors for 1-year mortality. A new model incorporating age, D-dimer, ALT, and sodium had better accuracy than Child-Pugh and MELD scores in predicting 1-year mortality of HE.

ALT, which is the most frequently used marker of liver injury, has been reported to be a risk factor for several chronic diseases, including liver disease, cancer, ischemic heart disease, and diabetes during 20 years of follow-up.[17] The pathophysiology mechanism of HE is comprehensive, including brain energy metabolic irregularities, blood-brain barrier disturbance, and systemic inflammation in liver failure.[18] Although both ALT and AST were not very high in patients with CLF, non-survivors had higher ALT and AST than survivors in the present study. It

Table 2. Risk factors for mortality in patients with hepatic encephalopathy

Baseline variables	Univariate			Multivariate		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Age	1.027	0.999–1.056	0.06	1.035	1.004–1.067	0.03
Male	1.154	0.601–2.212	0.67			
HBV infection	1.530	0.814–2.876	0.19			
Diabetes	0.844	0.389–1.830	0.67			
ALT	1.010	1.001–1.020	0.03	1.012	1.001–1.022	0.03
AST	1.007	1.000 –1.015	0.04			
Albumin	0.994	0.949–1.040	0.78			
MELD	1.077	1.015–1.143	0.02			
Serum sodium	0.917	0.861–0.978	<0.01	0.920	0.858–0.986	0.02
D-dimer	1.134	1.029–1.250	0.01	1.138	1.030–1.258	0.01

CI: Confidence interval; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MELD: Model for end-stage liver disease.

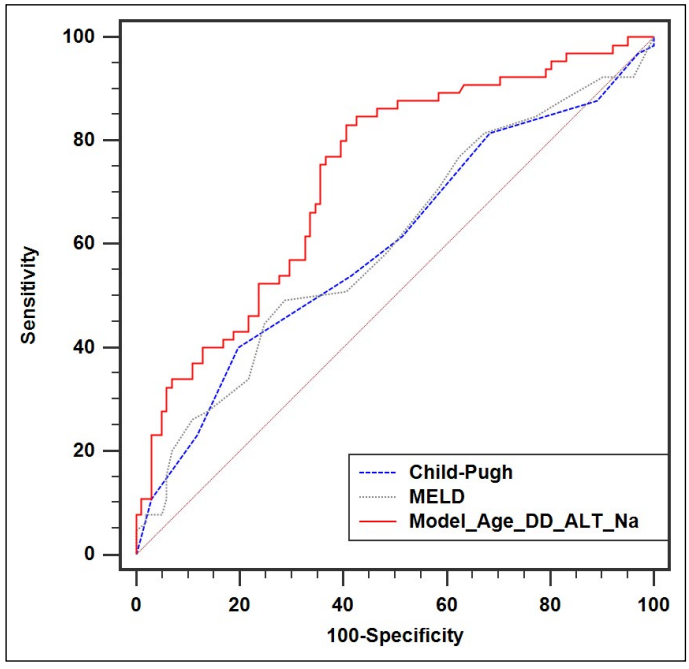

Figure 2. Comparison of AUROC between Model(Age_DD_ALT_Na), MELD and Child-Pugh scores. AUROC, area under the receiver operating characteristic curve; DD, D-dimer; Model(Age_DD_ALT_Na), a model consisting of age, D-dimer, ALT and sodium; MELD, model for end-stage liver disease.

indicates that liver inflammation may play a role in the progression of HE, and patients with HE may benefit from maintaining ALT at a relatively lower level. Regardless of etiology, liver function protection and monitoring should be recommended during follow-up.

According to previous studies, elevated D-dimer on admission is related to a poor prognosis in several diseases.[19–21] In addition, D-dimer >1.1 g/L has been reported to be the only factor associated with mortality in patients with LC and coronavirus disease 2019.[22] In the present study, raised D-dimer was related to the severity of LC, as it positively correlated with MELD and Child-Pugh scores. Interestingly, D-dimer, which is one of the independent risk factors of HE mortality, negatively correlated with HE grades. Collectively, outcomes of HE may primarily hinge on the severity of LC, but not the grades of HE. D-dimer was higher in patients with SBP, indicating that infection may cause D-dimer elevation, and patients with infections should be paid more attention.

In the present study, the relationship between INR and HE grades was not significant, and there was no significant difference in INR between survivors and non-survivors. Tan et al.[6] reported that increased INR was an independent risk factor for HE development in patients with LC. It should be noted that both INR>1.5 and HE were included in the diagnostic criteria of liver failure.[23] Based on the present study, INR was inferior to D-dimer in predicting 1-year mortality of HE. Thus, clinicians should pay more attention to D-dimer in clinical practice, especially for patients with suspected HE.

To note, there are several limitations to our study. First, the mechanisms of coagulation dysfunction, including increased D-dimer and INR in patients with HE, remain unclear. Second, data about PVT were limited in patients with high D-dimer, so the effect of PVT on outcomes of HE could not be evaluated. Third, it is a retrospective study, and the sample size is relatively small, so a prospective and multi-center study with a

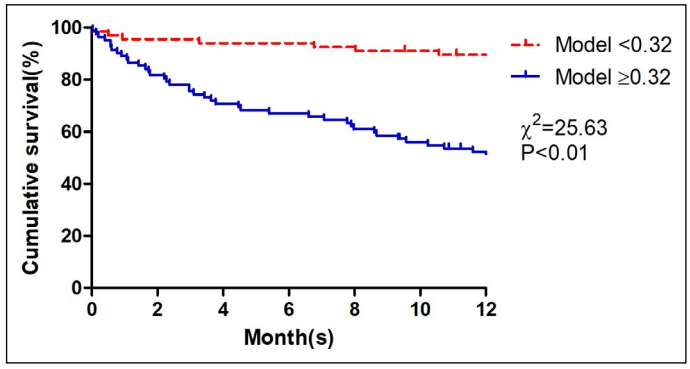

Figure 3. Kaplan-Meier analysis of Model(Age_DD_ALT_Na) in patients with hepatic encephalopathy.

large sample size is needed to substantiate these findings. Fourth, the new model has a specificity of 59%, which is somewhat low. For HE, which is a severe complication of liver failure, a sensitivity of 83% may be more important than low specificity, because high sensitivity is useful to detect patients who are at high risk of death and send them for timely treatment.

In conclusion, D-dimer is a prognostic marker for 1-year mortality in patients with CLF and HE.

Ethics Committee Approval: The study was approved by the Ethics Committee of Changzhou Third People's Hospital (date: 22.02.2018, number: NMUEC (2018) 506).

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