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Plasma D-dimer as a novel biomarker for predicting poor outcomes in HBV-related decompensated cirrhosis

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Abstract

This study aim was to evaluate whether plasma D-dimer levels could serve as a novel prognostic biomarker for 1-month mortality in patients with HBV-related decompensated cirrhosis (HBV-DeCi).

This was a retrospective study that enrolled 132 HBV-DeCi patients. Univariate and multivariate regression models were used to identify risk factors for mortality. The area under the receiver operating characteristic curve was calculated to estimate and compare the predictive values of different prognostic markers.

In the present study, the plasma D-dimer levels were higher in the nonsurviving group than in the surviving group. Additionally, the D-dimer level was positively correlated with the model for end-stage liver disease (MELD) score. The results of multivariate analysis showed that both the MELD score and D-dimer level are independent predictors of 1-month mortality in HBV-DeCi patients (both $P < .01$).

Plasma D-dimer can be considered a new additional prognostic marker for 1-month mortality in HBV-DeCi patients.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUCs = areas under the curve, DeCi = decompensated cirrhosis, HBV = hepatitis B virus, HE = hepatic encephalopathy, HR = hazard ratio, HRS = hepatorenal syndrome, INR = international normalized ratio, MELD score = model for end-stage liver disease score, PVT = portal vein thrombosis, ROC = receiver operating characteristic.

Keywords: coagulation, decompensated cirrhosis, fibrinolysis, hepatitis B virus, plasma D-dimer

1. Introduction

Chronic infection with hepatitis B virus (HBV) is a major health problem due to its worldwide distribution and its long-term effects. Patients with chronic HBV infection have a high risk of progressive liver fibrosis, cirrhosis and even hepatocellular carcinoma. The natural history of cirrhosis is characterized by the decompensation of the disease, which is associated with high morbidity and mortality, with a 5-year survival rate of only 19% to 35%, in contrast to the 84% 5-year survival rate in compensated cirrhosis.[1–3] Currently, the most effective therapy for decompensated cirrhosis (DeCi) is liver transplantation. However, the shortage of donor livers and the considerable cost has limited the clinical application of liver transplantation. Therefore, identifying an objective, accurate and specific biomarker for HBV-DeCi prognosis and disease monitoring is urgently needed.

Plasma D-dimer is a degradation product of cross-linked fibrin, which is indicative of the activation of coagulation and fibrinolysis. In the past decade, increased D-dimer has been confirmed as a risk factor in patients with various carcinomas, such as gastric cancer,[4,5] colorectal cancer,[6] breast cancer,[7] and lung cancer.[8–10] Some research has also shown that there are elevated D-dimer levels in patients without significant thrombosis but with infection[11] or autoimmune diseases.[12] Recently, Li et al indicated that elevated D-dimer levels are associated with worse outcomes among cirrhotic patients.[13] Furthermore, Qi and his colleagues reported that high D-dimer levels can serve as a new marker for predicting short-term mortality in patients with acute-on-chronic liver failure.[14] Despite these correlations, D-dimer in the context of HBV-DeCi remains poorly understood. Therefore, in the present study, we investigated the prognostic value of D-dimer in HBV-DeCi patients.

2. Materials and methods

2.1. Patients

This retrospective study consecutively enrolled 190 newly diagnosed HBV-DeCi patients from the Shengzhou People's

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Hospital (Zhejiang, China), between April 2017 and December 2018. We recruited patients who were HBsAg-positive and for whom decompensation appeared for the first time while they were in the hospital. DeCi was defined as the presence of one or more of the major complications (i.e., ascites, hepatic encephalopathy [HE], gastrointestinal hemorrhage and hepatorenal syndrome [HRS]) of liver disease.[15] All patients received standard treatment, including antiviral therapy, bed rest, intravenous albumin, nutritional support, and the prevention and treatment of complications. The exclusion criteria included the following:

1. patients with alcoholic liver disease, autoimmune hepatitis, drug-induced liver injury or other viral infections (hepatitis A, C, E virus, or HIV infection);
2. HCC or other malignancies;
3. patients who received antiviral or immunosuppressive medication in the 6 months before the study; and
4. patients with other known blood coagulation disorders or complications involving portal vein thrombosis (PVT).

Finally, 132 patients were enrolled in the current study. The primary outcome was 30-day mortality.

The study was performed according to the Declaration of Helsinki, and the procedures were approved by the Ethics Committee of the Shengzhou People's Hospital.

2.2. Data collection

The laboratory data, including total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, blood urea nitrogen, plasma D-dimer, international normalized ratio (INR) and platelet counts, were collected within the first 24 h after the diagnosis of HBV-DeCi. All biochemical indices were measured using a Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan). The D-dimer and INR were measured with a Sysmex CA1500 full-automatic analyzer (Sysmex Corp, Hyogo, Japan). Platelet counts were analyzed by an autoanalyzer (Sysmex XE-2100, Kobe, Japan). The normal plasma D-dimer level at our hospital laboratory is < 0.170 mg/L fibrinogen equivalent units (FEU). Demographic and clinical characteristics (i.e., age, gender, and complications related to liver disease, such as ascites, HE, and HRS) were obtained from the electronic medical records. In addition, the Model for End-Stage Liver Disease (MELD) score was used to assess the severity of liver disease, which was calculated using the following formula: MELD score = $3.78 \times \ln$ (total bilirubin, mg/dL) + $11.2 \times \ln$ (INR) + $9.57 \times \ln$ (creatinine, mg/dL) + 6.4.

2.3. Statistical analysis

Statistical analyses were performed using SPSS 19.0 (SPSS Inc, Chicago, IL) and MedCalc version 12.7 (Mariakerke, Belgium). Data are expressed as the means and standard deviations, medians and interquartile ranges (IQR), or counts, as appropriate. Differences in the variables were analyzed using Student's *t* tests or Mann–Whitney *U* tests. Categorical variables were compared with a χ^2-test, as appropriate. Spearman's correlation test was used for the correlation analyses. Logistic regression analyses were performed to identify independent indicators for 1-month mortality in patients with HBV-DeCi. The diagnostic accuracy of prognostic variables was evaluated by receiver operating characteristic (ROC) analysis. A P value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

In this retrospective study, 132 patients with HBV-DeCi were enrolled. The baseline characteristics of all participants are listed in Table 1. Among the patients, 27 (20.5%) were female, and the mean age was 52.3 years (range: 27–74 years). HBV-DeCi was accompanied by ascites in 98 patients, HE in 2 patients, HRS in 20 patients, jaundice in 16 patients and bacterial infections in 36 patients. A significant positive correlation was seen between the plasma D-dimer levels and the MELD score ($r = 0.246$, $P = .005$), but there was no correlation between the plasma D-dimer levels and age ($r = -0.153$, $P = .081$). In addition, D-dimer levels were not different between men and women (median 2.37, IQR 1.13–4.16 vs 2.38, 1.53–3.81, $P = .934$). The D-dimer ranged from 0.18 to 22.14 mg/L FEU (median: 2.38 mg/L FEU) in our patients at admission.

3.2. Comparison of plasma D-dimer levels between nonsurvivors and survivors among the HBV-DeCi patients

During this period, the patients were divided into the survivor and nonsurvivor groups according to 1-month mortality. The comparisons of the demographic, clinical, and laboratory parameters between the two groups are shown in Table 2. D-dimer levels were observed to be significantly higher in the nonsurvivor group than in the survivor group (median 4.23, IQR 2.34–6.66 vs 2.32, 1.07–3.53, $P < .001$). Furthermore, compared to the survivors the nonsurvivors also had a higher MELD score ($P < .001$), serum BUN level ($P < .001$), serum creatinine ($P < .001$), INR ($P < .001$) and a lower albumin level ($P = .001$), while the other biochemical variables (i.e., age, gender, total protein, total bilirubin, ALT, AST, and platelet counts) were similar between the two groups.

Table 1.

Demographics and laboratory findings in patients with HBV-DeCi.

	HBV-DeCi patients (n = 132)
Gender (male/female)	105/27
Age (years)	52.3 ± 10.3
Total protein (g/L)	60.2 ± 8.3
Albumin (g/L)	28.9 ± 5.5
ALT (U/L)	30.0 (15.3–54.3)
AST (U/L)	43.0 (28.3–71.8)
Total bilirubin (μmol/L)	43.0 (25.0–102.0)
INR	1.46 ± 0.30
Creatinine (μmol/L)	74.0 (62.0–94.8)
Blood urea nitrogen (μmol/L)	5.9 (4.3–8.2)
Platelet counts ($\times 10^9$/L)	65.0 (40.8–97.3)
HE (n)	2
HRS (n)	20
Ascites (n)	98
Jaundice (n)	16
MELD score	12.5 (8.8–17.5)
D-dimer (mg/L FEU)	2.38 (1.15–4.12)

Data are expressed as n, the mean ± SD, or median (interquartile range).
ALT = alanine aminotransferase, AST = aspartate aminotransferase, HE = hepatic encephalopathy, HRS = hepatorenal syndrome, INR = international normalized ratio, MELD score = model for end-stage liver disease score.

Table 2.

Demographics and laboratory findings in survivors and nonsurvivors among the patients with HBV-DeCi.

	Nonsurviving patients (n = 27)	Surviving patients (n = 105)	*P*
Age (years)	52.8 ± 11.7	52.2 ± 9.9	.782
Gender (male/female)	23/4	82/23	.584
Total protein (g/L)	59.1 ± 10.4	60.5 ± 7.6	.434
Albumin (g/L)	25.9 ± 5.5	29.7 ± 5.3	.001
ALT (U/L)	26.0 (13.3–51.0)	30.0 (16.8–55.3)	.297
AST (U/L)	41.0 (27.0–68.8)	46.0 (29.0–73.0)	.294
Creatinine (μmol/L)	111.0 (87.3–123.5)	73.0 (61.0–82.0)	<.001
Total bilirubin (μmol/L)	74.0 (32.3–129.8)	40.0 (24.5–84.5)	.071
INR	1.63 ± 0.40	1.42 ± 0.26	<.001
Blood urea nitrogen (μmol/L)	9.00 (7.20–14.0)	5.50 (4.28–7.40)	<.001
Platelet counts ($\times 10^9$/L)	63.0 (36.3–87.0)	70.0 (43.0–98.8)	.345
MELD score	17.84 (15.45–21.40)	11.43 (7.81–14.66)	<.001
D-dimer (mg/L FEU)	4.23 (2.34–6.66)	2.32 (1.07–3.53)	<.001

Data are expressed as n, the mean ± SD, or median (interquartile range).
ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = international normalized ratio, MELD score = model for end-stage liver disease score.

Table 3.

Cox proportional hazards analysis for the predictors of 1-month mortality in patients with HBV-DeCi.

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.006	0.965–1.048	.780			
ALT (U/L)	0.993	0.983–1.003	.154			
Albumin (g/L)	0.872	0.799–0.951	.001	0.992	0.825–1.031	.156
Urea nitrogen (μmol/L)	1.007	0.992–1.022	.387			
MELD score	1.257	1.138–1.389	<.001	1.238	1.113–1.326	.001
D-dimer (mg/L FEU)	1.589	1.247–2.024	<.001	1.477	1.136–1.920	.004

ALT = alanine aminotransferase, CI = confidence interval, HR = hazard ratio, MELD score = model for end-stage liver disease score.

3.3. Increased plasma D-dimer levels are a predictor of prognosis in HBV-DeCi patients

Univariate and multivariate analyses were performed to identify risk factors for poor prognosis in HBV-DeCi. In the univariate analysis, a higher MELD score, D-dimer, and lower albumin were risk factors for 30-day mortality. In the multivariate analysis, only the MELD score and the D-dimer level were associated with mortality (Table 3). ROC curve analysis was performed to evaluate the relative efficiencies of the D-dimer and MELD scores for predicting mortality (Fig. 1). The MELD score had a cut-off value of 14.7, with a sensitivity of 81.5% and a specificity of 75.2%. D-dimer had a cut-off value of 3.80 mg/L FEU, with a sensitivity of 63.0% and a specificity of 77.1%. The AUC values for predicting mortality were 0.834 ± 0.034 for the MELD score and 0.736 ± 0.056 for the D-dimer level. The predictive powers of the MELD score and D-dimer for mortality were not significantly different ($P = .103$).

4. Discussion

Coagulation and fibrinolysis markers have the potential to serve as the predictors of disease and disease severity. This study aimed to investigate the prognostic role of the fibrinolytic biomarker D-dimer in HBV-DeCi patients. Our study indicated that the nonsurvivors had a higher plasma D-dimer level compared with that in the survivors, and the D-dimer level could predict the 1-month mortality in HBV-DeCi patients. The MELD score has been widely used for organ allocation in liver transplantation and is a current useful prognostic tool for assessing the 3- to 6-month survival in patients with liver failure.[16,17] Multivariate analyses showed that D-dimer levels and MELD scores were independent predictors of 30-day mortality and predicted the mortality with

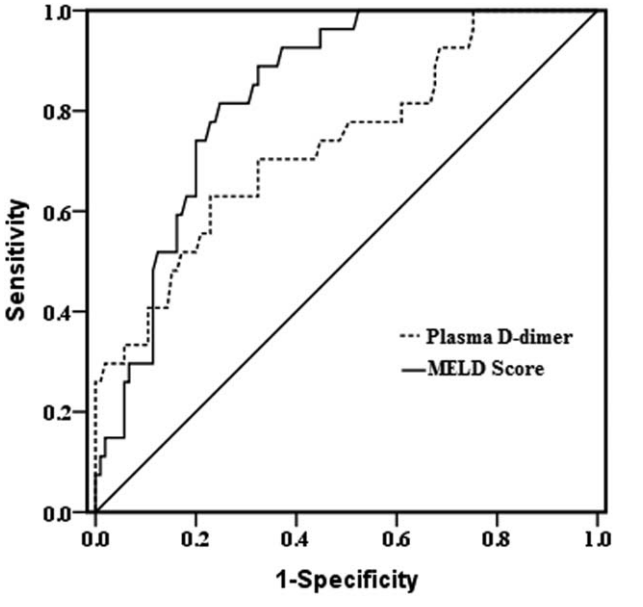

Figure 1. Receiver operating characteristic curve indicating the relative efficiencies for the prediction of 1-month mortality by the D-dimer level (▪▪▪▪) and MELD Score (▬▬) at admission.

similar power in our study. Nevertheless, the D-dimer level involved only a single index, which could be easily acquired. In line with our results, Li et al also reported that the plasma D-dimer level has a predictive role in cirrhotic patients, although their research was designed to determine in-hospital mortality and did not examine a definite time period.[13] In our study, we mainly focused on DeCi caused by HBV infection. Whether these findings are applicable to other etiologies of DeCi needs further study.

The underlying mechanisms enabling the plasma D-dimer to indicate possible outcomes in HBV-DeCi patients have not been well elucidated. D-dimer is produced by fibrin degradation, and the analysis of D-dimer can help with the diagnosis of thrombosis, such as deep vein thrombosis or pulmonary embolism.[18] A previous study reported that patients with DeCi have an increased risk of PVT and that D-dimer might be regarded as a diagnostic biomarker for PVT formation in cirrhotic patients.[19–21] However, Zocco et al pointed out that D-dimer was neither associated with nor predictive of PVT formation in cirrhotic patients.[22] Another study by Nery et al demonstrated that the development of PVT and cirrhosis progression were did not have a cause-and-effect relationship.[23] In our study, we found that the incidence of PVT was low, and only one patient was excluded as a result of PVT. Therefore, we speculate that the increase of D-dimer in HBV-DeCi patients is unlikely to be caused by PVT. Coagulation is closely related to liver function because most factors in the coagulation and fibrinolytic systems are produced and regulated by the liver.[24] Liver function impairment is generally associated with adverse alterations in the coagulation and anticoagulation systems. The impaired liver synthesis of both pro- and anticoagulants maintains a hemostatic balance in advanced liver disease, but this balance is relatively unstable, and patients are prone to bleeding or thrombosis and to the formation of a hypercoagulable state under certain stress conditions.[25] Previous reports have suggested that low-grade disseminated intravascular coagulation often occurs in cirrhotic patients.[26] In addition, hepatic hypercoagulation and fibrin deposition were also observed in explanted liver tissue and mouse models of acute liver failure.[27,28] Therefore, we speculate that the clearing ability of activated fibrinolytic factor is reduced due to liver cell impairment, resulting in the degradation of fibrin and an elevated D-dimer level in patients with HBV-DeCi. In our study, D-dimer levels were significantly higher in the nonsurvivor group than in the survivor group. These data may reflect the hepatic clearing capacity, which was worse in the nonsurvivors than in the survivors. Additionally, we found that the plasma D-dimer level was positively correlated with the MELD score, the increased D-dimer level is closely associated with disease severity and liver damage in HBV-DeCi patients, leading to high mortality. In contrast, systemic inflammation plays a pivotal role in the pathogenesis of chronic HBV infection. Previous studies have reported that systemic inflammation occurs frequently in patients with advanced cirrhosis and may be associated with worse outcomes.[29] Schwameis et al demonstrated that D-dimer can serve as an additional biomarker in the early stage of bacteremia.[30] Another study reported by Levi et al showed that high levels of D-dimer were predictive of a poor clinical outcome in sepsis.[31] Furthermore, Robson et al found that D-dimer could activate monocytes to release proinflammatory cytokines such as interleukin-6 in vitro.[32] In our study, there were 98 patients with ascites, of whom 36 had bacterial infections. Various inflammatory mediators activate the coagulation systems, thus down-regulating the natural anticoagulant mechanisms.[33] Hence, the activation of coagulation in concert with inflammatory activation can result in microvascular thrombosis, which might be attributed to the increased plasma D-dimer levels. Therefore, we propose that increased D-dimer levels may be related to the complex pathogenesis of HBV-DeCi. D-dimer is not only a biomarker of the activation of fibrinolysis but may also indicate systematic inflammation. Therefore, we believe that D-dimer could be helpful in the assessment of the prognosis of patients with HBV-DeCi. More studies are needed to further investigate the underlying mechanism.

Our study has several limitations. First, it was conducted retrospectively, which could have led to increased selection bias. Therefore, the findings of this study need to be validated by prospective and multicenter studies. Second, we failed to examine some inflammatory biomarkers, such as CRP or proinflammtory cytokine, which might be helpful in establishing a mechanism that explains these results. Finally, we did not give virological data in our study, such as viral loads or genotypes, which could confound the association between D-dimer levels and adverse outcome. Previous studies have indicated that hepatic fibrosis, but not hepatitis viral load, was associated with higher D-dimer levels in hepatitis B/C co-infected individuals.[34] Of course, further research is needed to explore the role of virological on D-dimer levels in HBV-DeCi patients.

In summary, our data suggest that higher D-dimer levels are associated with worse outcomes in HBV-DeCi patients. This readily available and low-cost marker may help improve the clinical management of HBV-DeCi. However, due to the retrospective design of the study and small sample size, more studies are warranted to further clarify this issue.

Author contributions

Data curation: WeiLin Mao, LiangJun Shen.
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Investigation: LiangJun Shen.
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Writing – original draft: Jing Zhou.
Writing – review & editing: HongGuang Huang.

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