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ORIGINAL ARTICLE

Relationship between D-Dimer to Lymphocyte Ratio and the Mortality in HBV-Associated Decompensated Cirrhosis

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SUMMARY

Background: **HBV-associated decompensated cirrhosis (HBV-DC) is hallmarked by high short-term mortality. Accurate non-invasive prognostic tools for these patients are urgent clinical need. Thus, we aimed to explore the relationship between the plasma D-dimer to lymphocyte ratio (DLR) and mortality in HBV-DC patients.**
Methods: **A retrospective analysis was conducted on 152 patients with HBV-DC. To estimate disease severity and outcomes, the Model for End-Stage Liver Disease (MELD) score was utilized. The predictive value of the DLR in assessing mortality risk was assessed using multivariate logistic regression analysis and receiver operating characteristic curve analysis.**
Results: **During the 30-day follow-up period, 20 patients died. The DLR was markedly different between non-survivors and survivors and higher DLR was found to be linked with adverse consequences. Furthermore, logistic regression demonstrated DLR as an independent predictive factor of 30-day mortality in HBV-DC patients and the prognostic value of DLR was very similar to that of MELD score, the combinations of DLR and MELD score show a better predictive value than that of a single index.**
Conclusions: **The DLR was a reliable tool to predict 30-day mortality in HBV-DC patients.**
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KEYWORDS

hepatitis B virus, D-dimer to lymphocyte ratio, decompensated cirrhosis, predictor, mortality

LIST OF ABBREVIATIONS

AUC - Area under the curve
CI - Confidence interval
DC - Decompensated cirrhosis
DLR - D-dimer to lymphocyte ratio
HBV - Hepatitis B virus
MELD score - Model for End-stage liver disease score
ROC - Receiver operating characteristic

INTRODUCTION

Liver cirrhosis is a major public health issue and carries a high mortality risk. It ranks as the 11th leading cause of death worldwide, with increasing mortality in recent

decades. Liver cirrhosis is primarily caused by hepatitis B virus (HBV) infection in Asian-Pacific countries [1, 2]. Most causes of death among cirrhotic patients are due to complications that occur during the transition to decompensation [3]. Patients with decompensated cirrhosis (DC) have much lower survival rates than those with compensated cirrhosis, with median survival times ranging from 2 - 4 years versus 10 - 12 years, respectively, according to one study [4]. Given the high mortality, finding an effective and objective indicator for HBV-DC prognosis is urgently needed in clinical practice, which might be associated with a reduction in mortality.

The pathogenesis of HBV-DC is complex and involves many factors. Accumulating evidence suggests that persistent inflammatory response and immune dysfunction are the key mechanisms in HBV-DC pathophysiology that determine the liver damage severity and patient prognosis [5-8]. It is well known that lymphocytes play pivotal roles in cell-mediated immunity. A recent study revealed that a low lymphocyte count may be associated with malnutrition and immune dysregulation in liver disease [9]. In addition, plasma D-dimer is a marker of fibrinolytic activation and may also indicate systemic inflammation. For instance, several studies have reported increased D-dimer levels in patients with infections [10] or autoimmune disorders [11] despite the absence of significant thrombosis. Increased D-dimer levels have been observed in various clinical scenarios, and have been linked to adverse outcomes in critically ill patients [12,13]. Moreover, several reports also indicated that high D-dimer can predict unfavorable outcome in liver diseases [14-16]. Thus, it is hypothesized that a combined assessment of D-dimer and lymphocyte count could provide valuable information on the prognosis of liver disease. Recently, the D-dimer to lymphocyte ratio (DLR) has been shown to be correlated with prognosis in several clinical scenarios, including acute aortic dissection [17] and colorectal cancer liver metastases [18]. However, few studies have investigated whether DLR can predict mortality in HBV-DC. Therefore, this study aimed to assess the prognostic value of DLR in these patients.

MATERIALS AND METHODS

Patients

We conducted an analysis of data from 218 patients with HBV-DC who were admitted to the Department of Gastroenterology between November 2019 and October 2021. The institutional ethics committee approved this study. The diagnosis of DC was based on the occurrence of variceal bleeding, ascites, hepatic encephalopathy, and/or hepatorenal syndrome [19]. Of the initial cohort, 66 patients were excluded due to ongoing steroid therapy (n = 7), malignancy (n = 6), hematological disease (n = 5), incomplete clinical data (n = 6), autoimmune hepatitis (n = 4), drug-induced liver injury (n = 5), age older than 80 years (n = 10) or hepatitis A, C, or HIV infection (n = 23). Ultimately, our analysis included 152 patients, with the endpoint being 30-day mortality.

Data extraction

Demographic and clinical data were extracted retrospectively from medical records, and laboratory variables were measured in all patients within the first 24 hours after admission. Serum levels of albumin, total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine were measured using the Hitachi 7600 analyzer (Hitachi, Tokyo, Japan). The international normalized ratio (INR) and D-dimer were determined using the Sysmex CA-1500 full-automatic analyzer (Sysmex Corp, Hyogo, Japan). Hemoglobin, platelet count, white blood cell count, neutrophil count, and lymphocyte count were measured using the Sysmex XE-2100 analyzer (Sysmex, Kobe, Japan). In addition, complications associated with liver disease such as hepatorenal syndrome, ascites, encephalopathy, and variceal hemorrhage were collected for each patient. The DLR was calculated as the ratio of D-dimer to lymphocyte count, while liver disease severity was assessed using the Model for End-Stage Liver Disease (MELD) score [20].

Statistical analysis

Data analyses were performed using SPSS (v. 20.0) and MedCalc (v. 15.2.2). Variables are expressed as median (P25, P75) and numbers where appropriate. Differences between patients were assessed using the Mann-Whitney U-test or the χ^2 test. Univariate and multivariate logistic regression analyses were conducted to identify independent indicators of mortality. The receiver-operator characteristic (ROC) curve was used to evaluate the predictive accuracy of variables. Discriminatory ability was estimated based on the area under the ROC curve (AUC). Statistical significance was set at $p < 0.05$.

RESULTS

Demographic data

A total of 152 HBV-DC patients were recruited, of whom 122 were male (80%). The median age was 53 years. The most common reasons for hospitalization were ascites (n = 120, 79%), gastrointestinal bleeding (n = 45, 30%), hepatorenal syndrome (n = 18, 12%), and hepatic encephalopathy (n = 2, 1%). The DLR ranged from 0.70 to 3.96, with a median of 1.99.

The 30-day in-hospital mortality rate was 13.2%. Based on their 30-day survival, patients were divided into survivors (n = 132) and non-survivors (n = 20). Detailed information is presented in Table 1. The non-survivors had a higher DLR than the survivors (median [P25, P75]: 5.38 [2.33 - 8.94] vs. 1.71 [0.63 - 3.35], $p < 0.001$). In addition, several laboratory data differed significantly between the groups, including total protein,

Table 1. Patient characteristics at baseline.

	All patients (n = 152)	Non-survivors (n = 20)	Survivors (n = 132)	p
Gender (female/male)	32/120	5/15	27/105	0.201
Age (years)	53.0 (46.0 - 63.0)	57.0 (49.0 - 64.0)	52.0 (46.0 - 62.5)	0.191
Total protein (g/L)	60.8 (56.1 - 66.7)	56.7 (52.0 - 62.9)	61.4 (56.5 - 66.9)	0.027
Albumin (g/L)	30.4 (26.4 - 33.7)	28.9 (22.9 - 30.6)	31.1 (26.8 - 34.5)	0.011
Alanine aminotransferase (U/L)	30.5 (16.0 - 55.0)	38.5 (14.0 - 69.0)	30.0 (16.5 - 54.0)	0.715
Aspartate aminotransferase (U/L)	46.0 (29.0 - 73.0)	53.0 (33.5 - 166.0)	45.0 (28.5 - 73.0)	0.371
Serum creatinine (μmol/L)	72.0 (59.5 - 86.5)	94.5 (70.5 - 127.0)	69.5 (58.5 - 82.5)	0.002
Total bilirubin (μmol/L)	42.0 (19.0 - 119.0)	119.6 (70.5 - 293.5)	36.0 (17.5 - 103.0)	0.001
INR	1.37 (1.20 - 1.63)	1.69 (1.43 - 1.94)	1.33 (1.18 - 1.55)	0.001
Blood urea nitrogen (mmol/L)	5.7 (4.2 - 7.3)	7.7 (6.0 - 10.2)	5.4 (4.1 - 6.9)	0.002
D-dimer (mg/L FEU)	2.04 (0.79 - 3.83)	3.62 (1.91 - 6.87)	1.76 (0.66 - 3.47)	0.001
Hemoglobin (g/L)	103.5 (85.5 - 121.0)	94.5 (74.0 - 112.5)	104.5 (86.0 - 121.5)	0.082
Platelet (x 10^9/L)	72.0 (45.0 - 113.0)	67.0 (45.0 - 138.0)	74.5 (45.0 - 111.5	0.857
White blood cell (x 10^9/L)	4.2 (2.7 - 5.8)	5.2 (2.8 - 7.3)	4.0 (2.7 - 5.4)	0.068
Neutrophil count (x 10^9/L)	2.4 (1.4 - 3.4)	3.4 (1.8 - 5.5)	2.2 (1.4 - 3.2)	0.011
Lymphocyte count (x 10^9/L)	1.0 (0.7 - 1.4)	0.7 (0.6 - 1.2)	1.0 (0.7 - 1.4)	0.106
DLR	1.99 (0.71 - 3.69)	5.38 (2.23 - 8.94)	1.71 (0.63 - 3.35)	< 0.001
MELD score	11.6 (7.3 - 17.3)	21.5 (14.8 - 23.7)	11.1 (6.8 - 15.5)	< 0.001

Data are expressed as number or median.
Abbreviations: INR - international normalized ratio, DLR - D-dimer to lymphocyte ratio, MELD - Model for End-stage Liver Disease.

Table 2. Factors associated with mortality of HBV-DC patients identified by logistic regression analyses.

	Univariate			Multivariate		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Total protein (g/L)	0.930	0.870 - 0.993	0.026			
Albumin (g/L)	0.893	0.814 -0.979	0.013			
Neutrophil count (x 10^9/L)	1.147	1.006 - 1.308	0.024			
D-dimer (mg/L FEU)	1.238	1.071 - 1.430	< 0.001			
Lymphocyte count (x 10^9/L)	0.659	0.280 - 1.555	0.318			
DLR	1.340	1.162 - 1.546	< 0.001	1.485	1.180 - 1.876	0.001
Blood urea nitrogen (mmol/L)	1.080	1.013 - 1.152	0.018			
MELD score	1.242	1.128 - 1.367	< 0.001	1.367	1.164 - 1.604	0.001

Abbreviations: DLR - D-dimer to lymphocyte ratio, MELD - Model for End-stage Liver Disease.

albumin, total bilirubin, creatinine, blood urea nitrogen, INR, D-dimer, neutrophil count, and MELD score ($p < 0.01$ for all).

Factors associated with mortality

Table 2 displays the risk factors for mortality that were identified by univariate and multivariate analyses. After adjusting for confounding variables, both DLR and MELD score were identified as independent risk factors for mortality. The ROC curves for MELD score and DLR for predicting mortality are shown in Figure 1. The cutoff value for MELD score was 18.2, with a sensitivity of 75% and specificity of 89%. For DLR, the cutoff value was 4.78, with a sensitivity of 65% and

Table 3. Clinical data according to DLR values.

	High group (DLR > 4.78, n = 32)	Low group (DLR ≤ 4.78, n = 120)	p
Gender (female/male)	7/25	25/95	0.908
Age (years)	54.0 (46.5 - 61.0)	53.0 (46.0 - 63.0)	0.867
Total protein (g/L)	58.4 (54.0 - 61.7)	61.8 (56.3 - 67.1)	0.021
Albumin (g/L)	27.2 (23.9 - 29.9)	31.3 (28.4 - 34.8)	0.001
Total bilirubin (μmol/L)	53.0 (25.0 - 108.0)	37.5 (17.5 - 126.0)	0.496
INR	1.55 (1.32 - 1.74)	1.32 (1.18 - 1.57)	0.007
Serum creatinine (μmol/L)	76.5 (64.0 - 118.0)	71.0 (58.0 - 83.0)	0.043
Blood urea nitrogen (mmol/L)	7.0 (5.6 - 9.9)	5.2 (4.1 - 7.0)	0.001
D-dimer (mg/L FEU)	4.65 (3.16 - 6.71)	1.32 (0.52 - 2.65)	< 0.001
Hemoglobin (g/L)	94.5 (81.0 - 110.0)	107.0 (86.0 - 124.0)	0.023
White blood cell (x 10^9/L)	4.1 (2.5 - 5.1)	4.2 (2.8 - 6.0)	0.292
Neutrophil count (x 10^9/L)	2.6 (1.5 - 3.6)	2.4 (1.4 - 3.4)	0.673
Lymphocyte count (x 10^9/L)	0.7 (0.4 - 0.8)	1.1 (0.8 - 1.5)	< 0.001
Platelet (x 10°/L)	39.0 (27.5 - 71.0)	82.0 (55.0 - 120.5)	< 0.001
MELD score	13.1 (10.6 - 17.8)	11.1(6.6 - 16.9)	0.031
30-day mortality (yes/no)	13/19	7/113	< 0.001

Data are expressed as number or median.
Abbreviations: DLR - D-dimer to lymphocyte ratio, INR - international normalized ratio, MELD - Model for End-Stage Liver Disease.

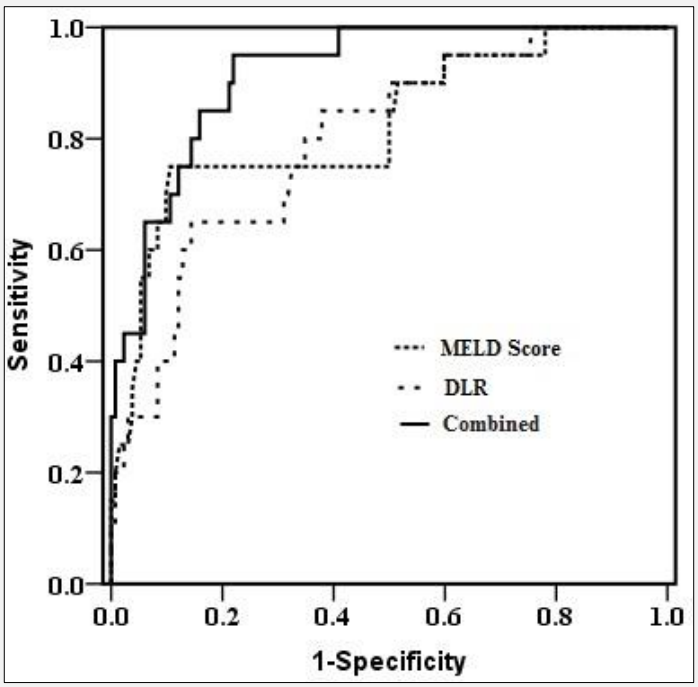

Figure 1. Receiver operating curves showing the relative prognostic performances of MELD score, DLR, and their combination for prediction of mortality in HBV-DC.

specificity of 87%. The MELD score and DLR showed comparable ability to predict mortality, as indicated by their similar AUCs (0.823 for MELD score vs. 0.796 for DLR; Z = 0.302, p = 0.763). Moreover, the combination of DLR and MELD score further improved prognostic accuracy for poor outcomes (AUC: 0.917), compared to the AUCs of DLR (p = 0.029) or MELD score alone (p = 0.043).

Subgroup analyses

We divided the study cohort into two groups based on the DLR cutoff value: DLR ≤ 4.78 (n = 120) and DLR > 4.78 (n = 32). Patients with DLR > 4.78 had higher mortality than those with DLR ≤ 4.78. We also observed significant differences in total protein, albumin, creatinine, blood urea nitrogen, INR, D-dimer, lymphocyte count, hemoglobin level, platelet count, and MELD score between patients with DLR > 4.78 and those with DLR ≤ 4.78 (Table 3).

DISCUSSION

In our study, 13.2% of patients died within 30 days. This proportion is similar to previous studies, in which approximately 11.0% of decompensated cirrhosis patients died within 28 days [21-23]. To reduce high mortality, identification of high-risk patients is essential, and timely and effective treatment should be provided. Currently, the MELD score system is the most useful predictive model in such patients in clinical practice, and the score is determined using three components: total bilirubin, creatinine, and INR. However, the MELD score cannot accurately predict the prognosis in approximately 15% to 20% of cases [24]. This may be due to the fact that the MELD score does not incorporate some important factors such as ascites, portal hypertension, and systemic inflammation that can affect the prognosis of patients. Therefore, we investigated the relationship between DLR and clinical outcomes in HBV-DC patients. Our results showed that the DLR was higher in non-survivors than in survivors, and the DLR was identified as an independent indicator of 30-day poor prognosis in multivariate analyses. Additionally, the prognostic accuracy of the DLR was similar to that of the MELD score. From a clinical perspective, the DLR is determined using two simple markers, making it easier to use than the MELD score. Furthermore, the combination of DLR and MELD score was a better predictor of mortality in HBV-DC patients than either indicator alone.

The underlying mechanism behind the high DLR predicting poor outcomes for HBV-DC patients might be explained by the following. Regarding the first component of DLR, D-dimer was obviously higher in non-survivors than in survivors. D-dimer is a fibrin degradation product, and its levels can aid in the diagnosis of thrombosis, including deep vein thrombosis or pulmonary embolism [25]. The liver plays an important role in regulating hemostasis [26]. Most of the clotting and fibrinolytic factors and inhibitors are produced by the liver, and it is also responsible for clearing activated clotting or fibrinolysis enzymes from the blood, which protects against both hemorrhage and improper coagulation activation [26,27]. Disruption of the hemostatic system can cause intravascular coagulation, which may lead to venous thromboembolism [28]. Previous research has shown that cirrhotic patients often experience low-grade disseminated intravascular coagulation [29]. Therefore, we hypothesize that the liver damage reduces the clearance ability of activated fibrinolytic factors, leading to increased fibrin breakdown and higher D-dimer levels in HBV-DC patients. In addition, systemic inflammation is common in people with advanced cirrhosis and is associated with poor outcomes. There is strong evidence indicating a close interaction between inflammation and coagulation. Inflammation triggers coagulation, while coagulation significantly impacts inflammatory activity [30]. Several studies have shown that elevated D-dimer levels not only indicate underlying hypercoagulability but also signify the presence of an inflammatory process [31-34]. The activation of both coagulation and inflammation can result in the formation of microvascular clots, which may be associated with an increase in plasma D-dimer levels.

Regarding the second component of DLR, lymphocyte count was slightly lower in non-survivors compared with survivors. Earlier research has demonstrated that a reduction in lymphocyte count is linked to the apoptosis or malfunction of immune cells [35,36], indicating a weakening of the host's antivirus response. Research conducted in the past has shown that patients with chronic hepatitis B and cirrhosis tend to have a lower count of lymphocytes, which can result in unfavorable outcomes [37]. Furthermore, the pretransplant lymphocyte count has been revealed to be one of the prognostic markers in liver transplant recipients [38,39]. The prevalence of lymphocytopenia was 40% in our cohort (lymphocyte count < 0.8 x 10^9/L). However, D-dimer or lymphocytes were not found to be an independent prognostic factor in a multivariate analysis in our study. This could be due to the fact that DLR as a ratio is more stable than its individual characteristics, which can be influenced by factors such as hydration level or specimen handling. Furthermore, our study revealed a correlation between higher DLR and poorer prognosis among the patients in our cohort. This indicates that DLR may provide a comprehensive assessment of immune status, organ dysfunction, and systemic inflammation, effectively reflecting overall physiological function within the body. As a result, DLR can serve as a valuable prognostic biomarker for HBV-DC.

CONCLUSION

In this retrospective study, we have confirmed that DLR, which combines two simple laboratory parameters, can be effectively used in daily practice to predict short-term mortality in HBV-DC patients. Moreover, our findings demonstrate that the combination of DLR and the MELD score significantly enhances the prognostic accuracy for mortality, providing a more effective approach for managing these patients, particularly in primary hospitals, and helps reduce the patient's medical burden. Our study provides valuable insights into the development of a simple and practical prognostic model for HBV-DC patients. However, it is important to note that the study was limited by its single-center design, small sample size, and lack of external validation. Therefore, further prospective research is necessary to confirm the veracity of these results. Future studies should consider multi-center research with larger sample sizes to validate our findings.

Declaration of Interest:

None of the authors have any commercial or other association that might pose a conflict of interest.

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