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# Evaluation of five lymphocyte-based scores for prediction of mortality in hepatitis B virus-associated decompensated cirrhosis

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ABSTRACT

*Background:* Lymphocytes are generally accepted to be a key component of the immune response, and an inadequate immune response is closely associated with disease severity and adverse outcomes in hepatitis B virus (HBV)-infected patients. The present study aimed to determine and compare the prognostic values of five lymphocyte-based scores (monocyte-to-lymphocyte ratio [MLR], mean platelet volume-to-lymphocyte ratio [MPVLR], neutrophil-to-lymphocyte ratio [NLR], red cell distribution width-to-lymphocyte ratio [RLR], and C-reactive protein-to-lymphocyte ratio [CLR]) for HBV-associated decompensated cirrhosis (HBV-DC).
*Methods:* Data were extracted from an institutional database. The outcome was 30-day mortality. Receiver operating characteristic curve analyses were conducted, and the resulting area under the curve (AUC) values were used to evaluate the predictive capabilities of the five lymphocyte-based scores for mortality in HBC-DC relative to Model for End-Stage Liver Disease (MELD) score.
*Results:* The study included 273 patients, and the 30-day mortality was 20.9%. Lymphocyte counts were slightly lower in non-survivors than in survivors. The prognostic values of CLR, NLR, MLR, MPVLR, and RLR for mortality in HBV-DC were different. The predictive powers of NLR and MLR were superior to those of the other three scores and similar to that of MELD score. Multivariate analyses identified NLR, MLR, and MELD score as independent prognostic predictors.
*Conclusion:* High NLR and MLR are easily accessible and reliable indicators for predicting 30-day mortality in HBV-DC and have superior prognostic ability compared with other lymphocyte-based scores.

## 1. Introduction

Hepatitis B virus (HBV) infection is a major health issue that can progress to cirrhosis, which carries a high risk of mortality [1].

*Abbreviations:* AUCs, Areas under the curve; CI, Confidence interval; DC, Decompensated cirrhosis; HBV, Hepatitis B virus; INR, International normalized ratio; MELD score, Model for end stage liver disease score; RDW, Red cell distribution width; CLR, CRP-to-lymphocytes ratio; NLR, Neutrophils-to-lymphocytes ratio; MLR, Monocytes-to-lymphocytes ratio; MPV, Mean platelet volume; MPVLR, MPV-to-lymphocytes ratio; RLR, RDW-to-lymphocytes ratio; NPV, Negative predictive value; PPV, Positive predictive value; ROC, Receiver operating characteristic.

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Patients with cirrhosis can be divided into those with compensated disease and those with decompensated disease. The mortality rate dramatically increases when patients shift into the state of decompensated cirrhosis (DC) [2,3]. Currently, the only effective therapy for patients with HBV-DC is liver transplantation. However, liver transplantation is limited by the lack of available donors, risk of surgical complications, and high cost. Therefore, the identification of objective and accurate scoring systems for the prognosis of HBV-DC patients remains an active challenge in clinical practice, with a view to helping clinicians identify high-risk patients and adjust treatment strategies.

The status of the host immune response is closely associated with the pathogenesis and clinical outcomes of hepatitis B [4,5]. Multiple immune cells, particularly lymphocytes, play pivotal roles in cell-mediated immunity. Previous studies revealed that a decreased lymphocyte count was associated with immune cell apoptosis or dysfunction [6,7], suggesting attenuation of the host antivirus response. Keefe et al. [8] reported that development of advanced cirrhosis may be associated with a gradual decrease in lymphocyte count. Meanwhile, low lymphocyte count prior to liver transplantation was identified as a risk factor for mortality in recipients [9,10]. Recently, the usefulness of lymphocyte-based scores, including mean platelet volume (MPV)-to-lymphocyte ratio (MPVLR), neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW)-to-lymphocyte ratio (RLR), C-reactive protein (CRP)-to-lymphocyte ratio (CLR), and monocyte-to-lymphocyte ratio (MLR), has been reported in different clinical scenarios [11–13]. Although previous studies investigated these parameters in patients with liver disease, no studies have simultaneously explored the prognostic values of these lymphocyte-based scores in HBV-DC. Therefore, we aimed to determine and compare the prognostic performances of these five lymphocyte-based scores in HBV-DC.

## 2. Materials and methods

### 3.1. Participants

This study retrospectively assessed 335 HBV-DC patients who were admitted to our hospital from May 2019 to May 2022. DC was defined by the presence of gastrointestinal bleeding, encephalopathy, ascites, and/or hepatorenal syndrome [14]. The inclusion criteria were: age of 18–75 years and positivity for hepatitis B surface antigen. The exclusion criteria were: co-infection with other hepatitis viruses or HIV, alcohol-related diseases, autoimmune liver diseases, hematological diseases, hepatocellular carcinoma, and incomplete data. Patients who had received immunomodulatory therapy within the previous 6 months were also excluded. All patients received antiviral therapy from the start date (Lamivudine, Entecavir or Tenofovir). Finally, 273 patients participated in the study (Fig. 1). The primary outcome was 30-day mortality. This study was approved by the Ethics Committee of the Kunshan Hospital of Chinese Medicine (approval number: KZYYJH2022-SB016-01), which waived the requirement for informed consent due to the use of pre-existing data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

### 3.2. Data collection

The baseline demographic, clinical, and laboratory findings of the patients were extracted from their medical records. The biochemical parameters included total bilirubin, total protein, albumin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), CRP, and international normalized ratio (INR). Hematological parameters included leukocyte count,

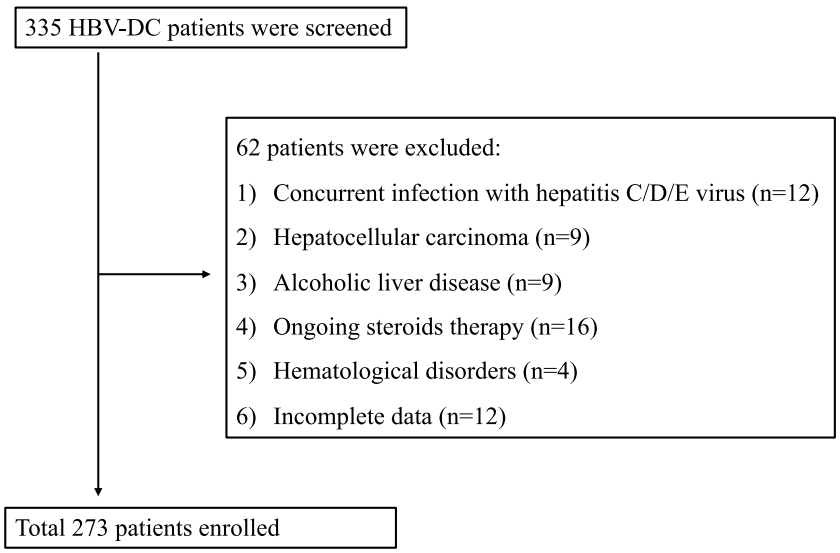


**Fig. 1.** Flow chart of the patients enrolled in the study.

leukocyte subpopulation counts, lymphocyte count, neutrophil count, monocyte count, RDW, MPV, platelet count, and hemoglobin. Biochemical parameters were measured using a Hitachi 7600 analyzer (Hitachi, Tokyo, Japan). Hematological parameters were measured using a Sysmex XE-2100 analyzer (Sysmex, Kobe, Japan). The INR was measured with a Sysmex CA1500 full-automatic analyzer (Sysmex Corp, Hyogo, Japan). The Model of End-stage Liver Disease (MELD) score was calculated to assess disease severity [15].

### 3.3. Calculation of the lymphocyte-based scores and MELD score

The scores were calculated using the baseline data at the time of admission as follows: CLR = CRP level/lymphocyte count; NLR = neutrophil count/lymphocyte count; MLR = monocyte count/lymphocyte count; MPVLR = MPV/lymphocyte count; RLR = RDW/lymphocyte count; MELD score = $3.8 \times \ln$ (total bilirubin) + $11.2 \times \ln$ (INR) + $9.6 \times \ln$ (creatinine) + 6.4.

### 3.4. Statistical analysis

Statistical analyses were conducted using SPSS ver. 19 or MedCalc ver. 19.7. Values of $P < 0.05$ were considered statistically significant. Continuous and categorical variables were expressed as median (interquartile range [IQR]) and number, respectively. The Mann–Whitney or chi-square test was used to compare the differences between two groups. Spearman's rank correlation was used to investigate the correlations of MELD score with CLR, NLR, MLR, MPVLR, and RLR. Univariate and multivariate analyses were performed to evaluate the associations of MELD score, CLR, MPVLR, RLR, NLR, and MLR with poor outcomes. Receiver operator characteristic (ROC) curve analyses were conducted to assess the predictive capabilities of the scores for poor outcomes. The obtained area under the ROC curve (AUC) values were used to estimate and compare the predictive values of the scores. The optimal cut-off values for each score were determined by the maximum Youden index, and the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

## 4. Results

### 4.1. Baseline characteristics

Based on the inclusion and exclusion criteria, we identified 273 HBV-DC patients who were eligible for the study. The most common complications were ascites in 209 patients (77%), followed by gastrointestinal bleeding in 84 patients (31%), hepatorenal syndrome in 40 patients (15%), and encephalopathy in 6 patients (2%). 75 patients (27%) had more than one feature of decompensation at the time of first presentation. The median values of CLR, MPVLR, RLR, NLR, and MLR at enrollment were 7.7 (IQR, 2.8–20.8), 11.9 (IQR, 8.0–16.4), 15.9 (IQR, 10.5–23.7), 2.9 (IQR, 1.8–5.1), and 0.6 (IQR, 0.5–0.9), respectively. In the correlation analyses, MELD score was not correlated with CLR, MPVLR, or RLR (all $P > 0.05$), but was positively correlated with NLR ($r = 0.364$, $P < 0.001$) and MLR ($r = 0.238$, $P < 0.001$).

The 30-day mortality was 20.9% (57/273). The causes of death were liver failure ($n = 15$), gastrointestinal bleeding ($n = 17$), encephalopathy ($n = 9$), hepatorenal syndrome ($n = 14$) and not known ($n = 2$). Based on their outcomes at 30 days, the patients were

**Table 1**
Comparisons of baseline clinical and laboratory parameters between the survivors and non-survivors.

| | All patients (n = 273) | non-survivors (n = 57) | survivors (n = 216) | *P* |
|---|---|---|---|---|
| Gender (female/male) | 49/224 | 13/44 | 36/180 | 0.378 |
| Age (years) | 51.0 (43.0–60.0) | 51.0 (42.8–57.0) | 51.0 (43.0–61.0) | 0.599 |
| Total protein (g/dL) | 5.94 (5.49–6.48) | 5.63 (5.25–6.27) | 6.00 (5.59–6.58) | 0.006 |
| Albumin (g/dL) | 3.12 (2.81–3.46) | 3.07 (2.76–3.48) | 3.13 (2.82–3.46) | 0.956 |
| ALT (U/L) | 62.0 (24.8–190.8) | 125.0 (48.0–245.3) | 48.0 (22.0–167.0) | 0.001 |
| AST (U/L) | 73.0 (38.0–140.5) | 104.0 (60.8–164.0) | 67.5 (35.0–121.0) | 0.004 |
| Serum creatinine (mmol/L) | 67.0 (57.0–82.0) | 63.0 (54.8–112.8) | 68.0 (57.0–81.0) | 0.776 |
| Total bilirubin (μmol/L) | 162.9 (30.8–333.2) | 326.9 (214.8–436.5) | 96.0 (24.0–287.6) | <0.001 |
| INR | 1.49 (1.25–1.89) | 1.99 (1.60–2.49) | 1.40 (1.22–1.74) | <0.001 |
| Lymphocytes ( $\times 10^9$/L) | 1.00 (0.70–1.50) | 0.94 (0.69–1.40) | 1.10 (0.70–1.60) | 0.077 |
| CLR | 7.7 (2.8–20.3) | 10.0 (3.3–29.3) | 7.0 (2.8–17.3) | 0.026 |
| MPVLR | 11.8 (8.0–16.4) | 12.7 (8.8–17.5) | 11.0 (7.8–16.3) | 0.094 |
| RLR | 15.9 (10.5–23.7) | 17.3 (15.6–26.5) | 14.9 (9.9–23.7) | 0.058 |
| NLR | 2.9 (1.8–5.1) | 6.2 (3.1–11.2) | 2.6 (1.6–3.9) | <0.001 |
| MLR | 0.61 (0.45–0.87) | 0.91 (0.63–1.24) | 0.57 (0.42–0.77) | <0.001 |
| Platelet ( $\times 10^9$/L) | 92.0 (61.8–132.5) | 90.0 (63.0–122.3) | 92.5 (60.0–136.0) | 0.877 |
| Hemoglobin (g/L) | 115.5 (94.0–128.0) | 120.0 (98.8–132.0) | 114.0 (93.3–128.0) | 0.192 |
| MELDs | 15.9 (10.0–21.1) | 22.4 (18.4–26.4) | 14.0 (8.1–19.3) | <0.001 |

Data are expressed as *n* or median (interquartile range).
Abbreviations: INR, international normalized ratio; CLR, C-reactive protein-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; MPVLR, mean platelet volume-to-lymphocyte ratio; RLR, red cell distribution width-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MELD score, Model for End-Stage Liver Disease score.

divided into survivors ($n = 216$) and non-survivors ($n = 57$). The baseline characteristics of the patients in the two groups are shown in Table 1. Obvious differences in ALT, AST, total bilirubin, total protein, INR, MELD score, CLR, NLR, and MLR were noted between the two groups (all $P < 0.05$).

### 4.2. Utility of lymphocyte-based scores for prediction of mortality in HBV-DC

Table 2 shows the correlations of the five lymphocyte-based scores and MELD score with mortality. In the univariate analyses, MELD score, CLR, NLR, and MLR were associated with mortality. In the multivariate analyses, NLR, MLR, and MELD score were identified as independent prognostic factors for mortality. The AUC values of the six scores for prediction of mortality are presented in Fig. 2. The AUC values for MELD score, NLR, and MLR were 0.813, 0.782, and 0.755, respectively, with no marked differences among the scores. The AUC values for MPVLR, RLR, and CLR were 0.572, 0.582, and 0.596, respectively, and also showed no marked differences. However, the AUC values for MELD score, NLR, and MLR were significantly higher than the values for MPVLR, RLR, and CLR (all $P < 0.05$).

Of the six scores evaluated in the study, NLR and MLR had the highest prognostic specificity for prediction of mortality (80.6 and 77.3, respectively), MELD score and CLR had the second-highest specificity (70.4 and 69.4, respectively), and MPVLR and RLR had the lowest specificity (23.6 and 31.9, respectively). Meanwhile, MLR and RLR had the highest prognostic sensitivity for prediction of mortality (93.0 and 87.7, respectively), MELD score, NLR, and MLR had the second-highest sensitivity (77.2, 64.9, and 63.2, respectively), and CLR had the lowest sensitivity (49.1). All six scores had excellent NPV (all >80%), indicating that they could be used to exclude mortality, while MELD score, NLR, and MLR had the best PPV among the scores (40.8%, 46.9%, and 42.8%, respectively), indicating that they could be used to predict worse prognosis (Table 3).

## 5. Discussion

Prognostic assessment in HBV-DC patients remains a challenging clinical issue. Therefore, identification of easily available and objective scores for predicting the prognosis of these patients is very important to decrease their high mortality. The present study focused on simultaneously determining the predictive values of five lymphocyte-based scores (NLR, CLR, MPVLR, RLR, and MLR) for prognosis in HBV-DC patients. Intriguingly, we found that the lymphocyte count was slightly lower in non-survivors compared with survivors in our cohort, and that the prognostic roles of CLR, NLR, MLR, MPVLR, and RLR were different. NLR and MLR were found to be superior to the other lymphocyte-based scores in prediction. The major findings of the research are summarized below.

First, inflammation is recognized as a key element for pathological progression of HBV-DC and is associated with adverse outcomes [16,17]. CRP is a universal inflammatory marker, and its plasma concentration increases rapidly in response to cell damage or tissue injury [18]. CLR is employed as a useful auxiliary prognostic indicator in several clinical situations [19–23]. Recently, Ye et al. [24] reported that high CLR was associated with mortality in HBV-DC. In this study, we observed higher CLR levels in non-survivors compared to survivors. However, it was not identified as an independent risk factor in the multivariate analysis and exhibited a failed predictive ability, as evidenced by an AUC of 0.596. We consider that the discrepancy may be related to the difference in severity of liver injury between the study cohorts. ALT and AST are well known to be reliable and sensitive biochemical markers of liver injury. The median serum ALT and AST levels in the present study were clearly higher than those in the previous study. Other reasons may be the differences in the sample sizes (134 in the previous study versus 273 in the present study) and mortality rates (12.7% in the previous study versus 21.3% in the present study).

Second, MPV and RDW are mathematically derived using a hematology analyzer, and are complete blood cell morphology-derived markers. We found that RLR and MLR had similar results for prediction of mortality in HBV-DC. Specifically, the two scores displayed no obviously difference between the non-survivors and survivors, and were not independent risk factors for mortality in the univariate and multivariate analyses. Moreover, the predictive abilities of the two scores were unsuccessful (both AUC<0.600) and were lower than those of the other three scores (NLR, MLR, and MELD score). These findings differ from those of Wu et al. [25] and Ding et al. [26], who found that MPVLR and RLR were associated with prognosis in HBV-DC patients, respectively. We consider that these discrepancies mainly arise because cell morphology is affected by multiple factors. For example, RDW reflects the heterogeneity of erythrocytes

**Table 2**
Logistic analysis of scores predicting mortality in HBV-DC patients.

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *P* | Odds ratio | 95% CI | *P* |
| MELD score | 1.206 | 1.139–1.277 | <0.001 | 1.179 | 1.107–1.256 | <0.001 |
| CLR | 1.014 | 1.002–1.026 | 0.030 | | | |
| MPVLR | 1.020 | 0.993–1.048 | 0.156 | | | |
| DLR | 1.015 | 0.997–1.034 | 1.103 | | | |
| NLR | 1.321 | 1.209–1.444 | <0.001 | 1.198 | 1.079–1.330 | 0.001 |
| MLR | 10.101 | 4.411–23.132 | <0.001 | 3.363 | 1.039–10.884 | 0.043 |

Abbreviations: CI, confidence interval; MELD score, Model for End-Stage Liver Disease score; CLR, C-reactive protein-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; MPVLR, mean platelet volume-to-lymphocyte ratio; RLR, Red cell distribution width-to-lymphocyte ratio; NLR, Neutrophil-to-lymphocyte ratio.

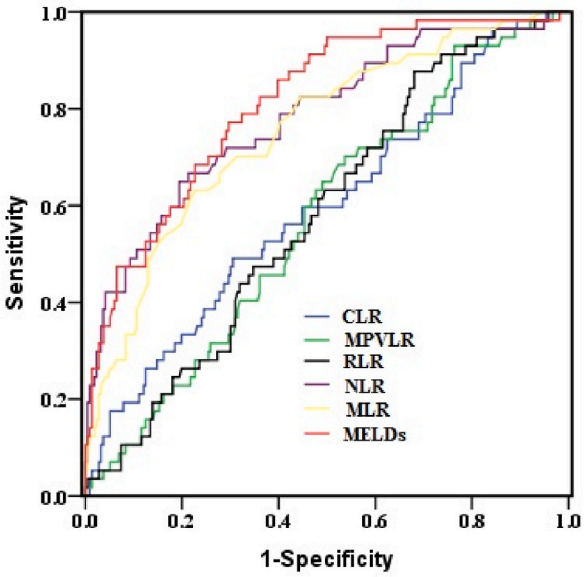


**Fig. 2.** ROC curve analyses for the five lymphocyte-based scores and MELD score for prediction of 30-day mortality in HBV-DC patients.

**Table 3**
Prognostic accuracies of different scores for predicting mortality in HBV-DC patients.

| | AUC | *P* | Cut-off value | Sensitivity | Specificity | NPV | PPV |
|---|---|---|---|---|---|---|---|
| MELD score | 0.813 [a] | <0.001 | 18.2 | 77.2 | 70.4 | 92.1 | 40.8 |
| CLR | 0.596 [b] | 0.026 | 12.2 | 49.1 | 69.4 | 83.8 | 29.8 |
| MPVLR | 0.572 [c] | 0.075 | 7.6 | 93.0 | 23.6 | 92.7 | 24.3 |
| RLR | 0.582 [d] | 0.039 | 10.9 | 87.7 | 31.9 | 90.8 | 25.4 |
| NLR | 0.782 [e] | <0.001 | 4.58 | 64.9 | 80.6 | 89.7 | 46.9 |
| MLR | 0.755 [f] | <0.001 | 0.81 | 63.2 | 77.3 | 89.1 | 42.8 |

Abbreviations: AUC, area under curve; CI, confidence interval; MELD score, Model for End-Stage Liver Disease score; CLR, C-reactive protein-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; MPVLR, mean platelet volume-to-lymphocyte ratio; RLR, Red cell distribution width-to-lymphocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value.
*Note:* a versus b: $p < 0.001$; a versus c: $p < 0.001$; a versus d: $p < 0.001$; a versus e: $p = 0.460$; a versus f: $p = 0.196$; b versus c: $p = 0.638$; b versus d: $p = 0.775$; b versus e: $p < 0.001$; b versus f: $p < 0.001$; c versus d: $p = 0.548$; c versus e: $p < 0.001$; c versus f: $p < 0.001$; d versus e: $p < 0.001$; d versus f: $p = 0.001$; e versus f: $p = 0.353$.

measured using a hematology analyzer. There are many factors that can cause changes in RDW, such as malnutrition, oxidative stress, and persistent inflammation [27]. Because the pathogenesis of liver cirrhosis is complex, various underlying complications in patients with liver diseases can have different effects on blood morphological parameters. Consequently, MPVLR or RLR may not effectively reflect the condition of the liver, the severity of the disease, or the prognosis of the patient. Therefore, the application of these two scores in clinical practice requires further research.

Third, NLR and MLR are blood cell-based inflammatory biomarkers that play important roles in various clinical conditions, including liver diseases. In the present study, MLR and NLR showed similar results for prediction of mortality in HBV-DC. The two scores were higher in non-survivors compared with survivors, and were positively correlated with MELD score, consistent with previous studies suggesting that these two scores may be closely associated with prognosis in HBV-DC [28–31]. Furthermore, our multivariate analyses identified MLR, NLR, and MELD score as independent predictive factors for worse prognosis, and these three scores had fair predictive values for poor prognosis in HBV-DC (all AUC>0.780) and superior predictive abilities compared with the other three scores (CLR, MPVLR, and RLR). Unlike MELD score, MLR and NLR involve only two common continuous parameters that are easily acquired in clinical practice and involve simple calculations. Inflammation is increasingly recognized as a key factor for pathological progression of HBV-DC, and is associated with changes in peripheral blood cell parameters. Compared with morphological indicators (MPV and RDW), blood cell parameters (neutrophil count and monocyte count) are more stable and effective for reflecting the inflammatory status in the body. Moreover, CRP is an acute-phase reactant that is non-specific for sex, age, obesity, insomnia, depression, smoking, and diabetes, which can all contribute to CRP elevation, meaning that CRP cannot effectively reflect the inflammatory status in the body. These factors may explain the superiority of NLR and MLR for predicting prognosis in HBV-DC patients, even though all of these indicators represent the body's inflammatory response and immune status.

## 6. Conclusions

In summary, the present study compared the prognostic values of five lymphocyte-based scores (NLR, CLR, MPVLR, RLR, and MLR) in HBV-DC patients. We found that NLR and MLR accurately predicted mortality, similar to MELD score, and had superior predictive values compared with CLR, MPVLR, and RLR. Our findings suggest that NLR and MLR provide a supplementary means to predict mortality in HBV-DC patients, and can be widely applied in clinical practice. The single-center and small-scale nature were the main limitations of the study. Currently, none of the scoring systems are perfect, and further studies are warranted to confirm the effectiveness of the scores.

## Author contribution statement

Chunyan He conceived and designed the experiments; Ting Mao and Bin Zhang performed the experiments; Ti Yang analyzed and interpreted the data, wrote the paper; Yinyan Qian and Chenchen Zhou contributed reagents, materials, analysis tools or data.

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## Data availability statement

The data that has been used is confidential.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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