INTRODUCTION

Hepatitis B virus (HBV) infection is an important health problem worldwide and HBV-infected patients can develop liver failure, liver cirrhosis, and hepatocellular carcinoma, resulting in an annual death toll of more than 1 million patients. In China, HBV is the major cause of liver cirrhosis, and approximately 3% of HBV-infected patients with compensated cirrhosis develop decompensated cirrhosis (DeCi) each year, with a 5-year survival rate of only 15%. Liver transplantation is an only reliable life-prolonging intervention for patients suffering from this condition. However, a shortage of donor livers and serious post-transplantation complications have limited its application. Therefore, identification of specific biomarkers that allow early assessment of prognosis of HBV-DeCi patients has gained importance in clinical practice.

It is well known that the systemic inflammatory status plays an important role in the pathogenesis of HBV infection. Several studies have demonstrated that inflammation is relatively common in patients with advanced cirrhosis and associated with poor outcomes. Monocyte-to-HDL-cholesterol (HDL-C) ratio (MHR) was a newly proposed inflammatory biomarker. Recently, MHR was reported to be closely associated with coronary heart disease, atrial fibrillation, hypertension, chronic kidney disease, and cerebrovascular accidents. However, no studies have investigated
the association between MHR and prognosis in HBV-DeCi patients. Therefore, we performed a retrospective study to determine the prognostic role of MHR in these patients.

2 | MATERIALS AND METHODS

2.1 | Patients

The study investigated 195 HBV-DeCi patients who underwent treatment in our hospital from July 2018 to March 2021. All patients had been positive for HBV surface antigen for >6 months. Eligibility criteria included age between 18 and 75 years. DeCi patients were defined by imaging appearances, laboratory tests, and clinical manifestations, with presence of ascites, variceal bleeding, hepatorenal syndrome, or hepatic encephalopathy. The exclusion criteria were as follows: (a) history of other liver diseases, such as autoimmune hepatitis; (b) co-infection with another hepatitis virus or HIV; (c) hepatocellular carcinoma; (d) hematological diseases; and (e) incomplete data. All participants received antiviral therapy from the start date (Lamivudine, Entecavir, or Tenofovir). The primary outcome was the 30-day survival status.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University College of Medicine.

2.2 | Data collection

Relevant demographic and clinical data were obtained from medical records. Routine biochemical tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, creatinine, total bilirubin, blood urea nitrogen, and HDL-C were measured in a Hitachi 7600 Analyzer. Routine blood tests including monocytes and hemoglobin were measured in a Sysmex XE-2100 Analyzer. Coagulation indices including international normalized ratio (INR) were measured in a Sysmex CA-7000 System Coagulation Analyzer. Baseline MHR was calculated as monocytes (×10^9/L) divided by HDL-C (mmol/L). Hepatic disease severity was evaluated by the Model for End-Stage Liver Disease (MELD) score as previously described.

2.3 | Statistical analysis

Statistical analyses were conducted using SPSS V. 21.0 or MedCalc V. 11.6 software. Two-sided *p* < 0.05 was considered to indicate statistical significance. Continuous variables were reported as median (interquartile range) and compared by the Mann-Whitney U test. Categorical variables were reported as number and compared by the *χ*^2^ test. Spearman’s correlation test was used for correlation analyses. To identify potential correlates of poor outcomes, univariate analyses were first performed in clinical variables. A multivariate regression was subsequently performed to include variables with *p* < 0.10 in the univariate analysis. Finally, a stepwise selection with the same set of variables was conducted using *p* < 0.05 as a criterion for inclusion. Logistic regression analyses were performed to identify significant predictors. Receiver operating characteristic (ROC) analysis was applied to assess the discriminatory potential of MHR and MELD score for predicting mortality.

3 | RESULTS

3.1 | Study population

A total of 145 HBV-DeCi patients were enrolled in the study after screening 195 patients (Figure 1). The main causes of hospitalization were variceal bleeding (17.9%), hepatorenal syndrome (11.1%), ascites
Median MHR was 0.68 (interquartile range, 0.40 to 1.35) at admission. The correlation analyses revealed that MHR was positively correlated with MELD score ($r = 0.333; p < 0.001$), serum ALT ($r = 0.181; p = 0.031$), and serum AST ($r = 0.282; p = 0.001$), and the negative correlation of HDL-C with serum AST ($r = -0.286; p = 0.001$) (Figure 2). No other correlations were observed.

### TABLE 1
Comparisons of baseline characteristics between the survivors and non-survivors

|                           | All patients ($n = 145$) | Non-survivors ($n = 20$) | Survivors ($n = 125$) | $p$   |
|---------------------------|--------------------------|--------------------------|-----------------------|-------|
| Gender (female/male)      | 29/116                   | 4/16                     | 25/100                | 0.763 |
| Age (years)               | 55.0 (47.0–63.0)         | 57.0 (50.0–62.0)         | 53.0 (46.0–63.0)      | 0.407 |
| Total protein (g/dl)      | 6.15 (5.67–6.68)         | 5.96 (5.20–6.82)         | 6.16 (5.77–6.67)      | 0.486 |
| Albumin (g/dl)            | 3.06 (2.64–3.45)         | 2.93 (2.64–3.25)         | 3.11 (2.65–3.46)      | 0.346 |
| ALT (U/L)                 | 29.0 (15.8–41.5)         | 40.0 (22.5–79.5)         | 28.0 (15.0–39.0)      | 0.043 |
| AST (U/L)                 | 43.0 (28.0–71.3)         | 56.0 (33.0–137.0)        | 41.0 (27.0–65.0)      | 0.046 |
| Serum creatinine (μmol/L) | 74.0 (61.0–87.0)         | 93.5 (64.5–127.0)        | 73.0 (60.8–84.0)      | 0.019 |
| Total bilirubin (μmol/L)  | 35.0 (17.8–83.3)         | 172.0 (66.5–249.0)       | 33.0 (16.8–61.3)      | <0.001|
| Blood urea nitrogen (μmol/L) | 5.7 (4.3–7.6) | 7.9 (5.7–14.0) | 5.6 (4.2–7.2) | 0.002 |
| INR                       | 1.32 (1.18–1.59)         | 1.69 (1.43–1.92)         | 1.30 (1.16–1.54)      | <0.001|
| Hemoglobin (g/L)          | 101.0 (83.8–116.3)       | 99.0 (79.0–109.5)        | 103.0 (84.0–118.0)    | 0.294 |
| Monocytes (x10^9/L)       | 0.50 (0.30–0.80)         | 0.75 (0.40–1.25)         | 0.50 (0.30–0.80)      | 0.024 |
| HDL-C (mmol/L)            | 0.73 (0.45–1.07)         | 0.41 (0.17–0.50)         | 0.78 (0.56–1.12)      | <0.001|
| MHR                       | 0.68 (0.40–1.35)         | 1.87 (0.92–4.14)         | 0.63 (0.37–1.21)      | <0.001|
| MELD score                | 11.1 (6.8–16.6)          | 20.7 (17.3–22.9)         | 10.1 (6.2–14.3)       | <0.001|

Note: Data are expressed as number or median (interquartile range).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; MHR, monocyte-to-HDL-cholesterol ratio.

### TABLE 2
Univariate and multivariate analyses of risk factors for mortality in HBV-DeCi patients

|                  | Univariate       | 95% CI      | $p$  | Multivariate   | Odds ratio | 95% CI      | $p$  |
|------------------|------------------|-------------|------|----------------|------------|-------------|------|
| Monocytes (x10^9/L) | 3.764            | 1.581–8.959 | 0.003|                |            |             |      |
| HDL-C (mmol/L)    | 0.019            | 0.003–0.148 | <0.001|                |            |             |      |
| ALT (U/L)         | 1.005            | 0.999–1.012 | 0.101|                |            |             |      |
| AST (U/L)         | 1.004            | 1.000–1.009 | 0.065|                |            |             |      |
| MHR               | 2.348            | 1.568–3.516 | <0.001| 1.826          | 1.157–2.881| 0.010       |
| MELD score        | 1.328            | 1.177–1.498 | <0.001| 1.274          | 1.125–1.442| <0.001      |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, Model for End-stage Liver Disease; MHR, monocyte-to-HDL-cholesterol ratio.
A total of 20 (13.8%) patients had died 30 days after admission. For further analyses, the patients were divided into survivors ($n = 125$) and non-survivors ($n = 20$). As shown in Table 1, significant differences were observed for creatinine, INR, MELD score, total bilirubin, monocytes, MHR, ALT, AST, blood urea nitrogen, and HDL-C between the two groups (all $p < 0.05$).

### 3.2 Factors associated with mortality

Clinical and laboratory data were investigated for prediction of mortality by univariate logistic regression analyses (Table 2). In the univariate analyses, monocytes, HDL-C, MHR, and MELD score were associated with mortality. A multivariate analysis further identified MHR and MELD score as independent predictors of mortality. Subsequently, ROC curve analyses were performed to evaluate the abilities of MHR and MELD score to predict mortality (Figure 3). The cutoff values were 18.2 for MELD score (sensitivity, 75.0%; specificity, 92.0%) and 0.73 for MHR (sensitivity, 90.0%; specificity, 62.4%). For prediction of mortality, the AUC of MHR was 0.825 and slightly lower than the AUC of MELD score (0.867; $Z = 0.574; p = 0.566$).

### 3.3 Comparisons of characteristics and baseline factors between patients with MHR >0.73 and ≤0.73

After stratification by the cutoff value (MHR ≤0.73 vs. MHR >0.73), the associations of MHR with clinical and laboratory characteristics were evaluated. Elevated MHR was significantly associated with increased mortality, AST, total bilirubin, monocytes, MELD score, and INR and decreased HDL-C (all $p < 0.05$) (Table 3).

### 4 DISCUSSION

To date, there have been no studies on the relationship between MHR and prognosis in HBV-DeCi patients. This study showed that

|                      | MHR ≤ 0.73, n = 80 | > 0.73, n = 65 | $p$   |
|----------------------|--------------------|---------------|-------|
| Gender (female/male) | 14/66              | 15/50         | 0.531 |
| Age (years)          | 52.5 (46.0–63.0)   | 56.0 (48.0–62.3) | 0.243 |
| Total protein (g/dL) | 6.10 (5.59–6.65)   | 6.24 (5.84–6.76) | 0.330 |
| Albumin (g/dL)       | 3.21 (2.64–3.53)   | 2.97 (2.68–3.22) | 0.079 |
| ALT (U/L)            | 26.6 (15.0–37.5)   | 37.0 (16.8–55.3) | 0.072 |
| AST (U/L)            | 36.0 (27.8–53.0)   | 53.0 (28.5–83.0) | 0.006 |
| Total bilirubin (µmol/L) | 27.0 (14.5–43.0) | 62.0 (25.0–142.3) | <0.001 |
| INR                  | 1.29 (1.14–1.51)   | 1.44 (1.25–1.75) | 0.001 |
| Serum creatinine (µmol/L) | 74.0 (61.5–85.0) | 75.0 (60.8–92.0) | 0.919 |
| Blood urea nitrogen (µmol/L) | 5.9 (4.4–7.6) | 5.6 (4.2–8.0) | 0.844 |
| Monocytes (x10⁹/L)   | 0.40 (0.30–0.50)   | 0.80 (0.50–1.10) | 0.001 |
| HDL-C (mmol/L)       | 1.00 (0.68–1.37)   | 0.49 (0.31–0.77) | <0.001 |
| MELD score           | 10.0 (6.3–12.6)    | 14.3 (6.9–19.8) | <0.001 |
| Hemoglobin(g/L)      | 101.5 (80.0–116.5) | 101.0 (86.0–116.5) | 0.709 |
| 30-day mortality (yes/no) | 2/78       | 18/47         | <0.001 |

Note: Data are expressed as number or median (interquartile range).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; MHR, monocyte-to-HDL-cholesterol ratio.
MHR was markedly higher in the non-survivors compared with the survivors and that MHR could predict poor 30-day outcomes in HBV-DeCi patients. During the last decade, the MELD score has been widely used to stratify the disease severity and assess the prognosis in liver diseases. In the present study, a multivariate analysis identified MHR and MELD score as independent predictors of mortality in HBV-DeCi patients, with both factors predicting mortality with similar power. Because MHR calculation involves only two common laboratory parameters, it is more easily acquired than the MELD score. Notably, previous studies identified some noninvasive factors that were associated with mortality in cirrhotic patients, such as neutrophil count-to-albumin ratio\(^\text{19}\) and INR-to-albumin ratio.\(^\text{20}\) Our findings complement these studies and demonstrate that MHR can be utilized as a predictive factor for adverse outcomes in HBV-DeCi patients.

The potential mechanism linking MHR and prognosis in HBV-DeCi patients should be considered. We found that monocytes were markedly higher in the non-survivors compared with the survivors. A previous study demonstrated that the inflammatory response triggers monocyte release into the peripheral blood and that monocytes secrete pro-inflammatory molecules that can accelerate the inflammatory reaction, leading to exacerbation of liver damage and poor outcomes. Meanwhile, liver cirrhosis affects the immune system, leading to an immunological imbalance. For example, advanced stages of cirrhosis are characterized by immunodeficiency.\(^\text{22,23}\) Monocytes are central mediators of the immune response with an essential role in the pathogenesis of liver cirrhosis, and monocyte-derived human leukocyte antigen-DR expression was significantly reduced in cirrhotic patients, reflecting the immune dysfunction in these patients.\(^\text{24,25}\) This monocyte-derived immune paresis may be the cause of the abnormal monocyte levels in HBV-DeCi patients. Moreover, HDL-C was significantly lower in the non-survivors compared with the survivors in the present study. Previous studies clarified that HDL-C generally acts as an anti-inflammatory lipoprotein\(^\text{26–28}\) and can bind and neutralize bacterial lipopolysaccharides to promote their excretion.\(^\text{29,30}\) Emerging data further suggest that inflammation remarkably modifies the composition and function of HDL-C, generating dysfunctional or even pro-inflammatory forms of HDL-C.\(^\text{31–35}\) Markus et al.\(^\text{36}\) reported that sera from cirrhotic patients had reduced levels of HDL-C and profoundly suppressed the activities of several enzymes involved in HDL-C maturation and metabolism. We found that the AST level was higher in the non-survivors compared with the survivors and that HDL-C was negatively correlated with AST, a widely used biomarker of liver injury. Because the liver is the main organ for cholesterol and apolipoprotein synthesis, it is possible that hepatic injury will directly affect the HDL-C level. In the present study, although monocytes and HDL-C were identified as risk factors for unfavorable outcomes in the univariate analyses, neither was identified as independent predictors for mortality in the multivariate analysis. This difference may have arisen because MHR is a ratio and is thus more stable than its individual parameters, which can be altered by several factors such as hydration or blood specimen handling. The present study further demonstrated positive correlations of MHR with MELD score, ALT, and AST, and that increasing MHR was correlated with increasing risk of death, suggesting that elevated MHR may be a predictor for liver injury severity and progression in HBV-DeCi patients. We suggest that increased hepatic necro-inflammatory activity as well as worsening liver function may be an explanation for the relationship between MHR and poor outcomes.

5 | CONCLUSIONS

In summary, MHR can provide a supplementary means to predict the prognosis for 30-day mortality in HBV-DeCi patients. The present findings provide risk stratification data and can be used to adjust treatment strategies in clinical practice. Our study is limited by its retrospective nature, small sample size, and was not carried out external validation cohort. Therefore, the findings require further validation in multicenter studies with larger sample numbers.

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CONFLICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data are available upon reasonable request.

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