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ORIGINAL ARTICLE

Peripheral Blood Lymphocyte-to-Monocyte Ratio Predicts Mortality in Patients with HBV-Related Decompensated Cirrhosis

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SUMMARY

Background: **Recent reports suggest that the lymphocyte-to-monocyte ratio (LMR) is a potential biomarker for predicting clinical outcomes. In the present study, LMR in patients with hepatitis B virus-related decompensated cirrhosis (HBV-DeCi) was investigated to evaluate whether LMR may have utility as a new predictive marker for mortality in HBV-DeCi patients.**

Methods: **This was a retrospective cohort study that included 135 patients with HBV-DeCi. Logistic regression analysis and receiver operating characteristic curve were employed to assess the independent predictors for 1-month mortality rate of patients with HBV-DeCi.**

Results: **A significantly lower LMR was detected in non-surviving patients than in surviving patients, and a lower LMR was associated with increased 1-month mortality. Multivariate analysis suggested that both LMR and the model for end-stage liver disease were independent predictors of 1-month mortality in patients with HBV-DeCi (both $p < 0.001$).**

Conclusions: **Our results suggest that a low LMR can be considered a new independent biomarker for predicting 30-day mortality in patients with HBV-DeCi.**

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KEY WORDS

lymphocyte-to-monocyte ratio, hepatitis B virus, decompensated cirrhosis

LIST OF ABBREVIATIONS

ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
AUC - Area under the curve
DeCi - Decompensated cirrhosis
HBV - Hepatitis B virus
HE - Hepatic encephalopathy
HRS - Hepatorenal syndrome
INR - International normalized ratio
LMR - Lymphocyte-to-monocyte ratio
MELD score - Model for End-stage liver disease score
SBP - Spontaneous bacterial peritonitis
ROC - Receiver operating characteristic

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INTRODUCTION

Liver cirrhosis is a growing global problem, with increased worldwide morbidity and mortality in recent decades [1]. Hepatitis B virus (HBV) is an important cause of liver cirrhosis in China. Approximately 2 - 5% of these patients with compensated cirrhosis develop decompensated cirrhosis (DeCi) each year [2], and the prognosis of decompensated cirrhosis is quite poor. Specifically, the 5-year survival rate of patients with decompensated cirrhosis is only 14%, while that of patients with compensatory cirrhosis is 84% [3]. Currently, the most effective therapy for DeCi is liver transplantation. However, the shortage of donor organs, the serious post-transplantation complications, and the considerable cost have limited its clinical application. Therefore, it is crucial to determine predictors of early mortality. This will help improve clinical management to mitigate the high rate of mortality.

Peripheral blood lymphocyte-to-monocyte ratio (LMR), as a novel inflammatory biomarker, has been recently investigated and confirmed to be a predictor of clinical outcomes in lymphoma [4,5], colon cancer [6], non-small cell lung cancer [7], nasopharyngeal carcinoma [8], breast cancer, and gastric cancer [9,10]. Zhang et al. indicated that a low LMR can be considered an independent biomarker for predicting mortality in patients with liver cirrhosis [11]. In a very recent study conducted in 2017, Zhu et al. demonstrated that reduced LMR is associated with the short-term outcomes in patients with HBV-related acute-on-chronic liver failure [12]. To the best of our knowledge, data on LMR in HBV-related decompensated cirrhosis (HBV-DeCi) patients have not been reported. We hypothesized that LMR is potentially associated with clinical outcomes in HBV-DeCi patients and hence investigated LMR as a predictor for 1-month mortality in a cohort of HBV-DeCi patients.

MATERIALS AND METHODS

Patients

The study was conducted as a retrospective follow-up of a cohort of 135 consecutive in-patients with HBV-DeCi from July 2015 to January 2017 in our hospital. Patients had to be HBsAg positive, previously diagnosed with HBV-related compensated cirrhosis, and presenting clinical manifestations of decompensated liver disease for the first time. There were no age or gender based exclusions. None of the patients had previous liver or other organ transplantation. Only patients with complete follow-up data and required clinical information were included. DeCi was defined as in previous studies according to the presence of ascites, hepatic encephalopathy (HE) and/or variceal bleeding at the time of the study. Patients were excluded if they (1) had acute hepatitis; (2) were concomitantly infected with hepatitis A virus, hepatitis C virus, hepatitis D virus, or human immunodeficiency virus, or had concurrent autoimmune or other liver diseases; had a (3) malignancy or (4) hematologic disorder; (5) were taking antibiotics or had undergone anti-inflammatory or immunosuppressive therapy in the preceding 2 weeks. In our study, 100 patients were receiving antiviral therapy, 55 had started antiviral therapy before admission, and 45 had started after admission. Only 35 patients did not receive any antiviral therapy throughout the clinical course for economic reasons. For each patient, demographic and clinical data (i.e., age, gender, and complications related to liver disease, such as ascites, HE, spontaneous bacterial peritonitis (SBP), HRS, and clinical course in the hospital) were obtained at baseline from medical records and were recorded in a specific liver disease proforma. The laboratory parameters included measurement of total protein, serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, and international normalized ratio (INR), hemoglobin, leukocyte counts and differential counts, and platelet count were recorded. The peripheral LMR was calculated as the ratio of the absolute peripheral lymphocyte count to monocyte count. In addition, the model for end-stage liver disease (MELD) score and serological indexes (HBsAg, HBeAg, anti-HBc, and HBV DNA status) were detected at baseline. All patients were followed for at least 2 months in order to identify short-term survival status.

This study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region.

MELD score

Liver disease severity was evaluated via MELD score, which uses the patient's serum total bilirubin and creatinine levels and the INR for prothrombin time to predict survival. The MELD score was calculated with the following equation: MELD score = 3.78 x ln (total bilirubin, mg/dL) + 11.2 x ln (INR) + 9.57 x ln (creatinine, mg/dL) + 6.4 [13].

Statistical analysis

All continuous variables were expressed as mean ± standard deviation (mean ± SD) and the median with interquartile ranges (IQR), and categorical data were expressed as percentages. The differences between non-surviving patients versus surviving patients with DeCi were assessed using an independent sample *t*-test, the Mann-Whitney *U* test or the χ^2 test, as appropriate. Spearman's correlation test was used in correlation analyses. The diagnostic accuracy of prognostic variables was examined using receiver operating characteristic (ROC) curves. Logistic regression analysis was employed to demonstrate the independent predictors for 1-month mortality rate of patients with HBV-DeCi. Areas under the curve (AUC) analyses were performed using MedCalc statistical software version 15.2.1 (MedCalc, Ostend, Belgium). Other analyses were performed using

Table 1. Baseline demographic and clinical characteristics of study participants.

	HBV-DeCi patients (n = 135)
Gender (male/female)	106/29
Age (years)	52.8 ± 11.3
Total protein (g/L)	60.9 ± 8.3
Albumin (g/L)	30.1 ± 6.0
ALT (U/L)	33.0 (17.3 - 59.0)
AST (U/L)	49.0 (28.8 - 80.0)
Total bilirubin (μmol/L)	58.0 (25.3 - 123.3)
INR	1.51 ± 0.41
Platelets (x 10^9/L)	70.0 (46.8 - 110.0)
Hemoglobin (g/L)	103.0 (89.3 - 120.8)
MELD score	13.7 (9.0 - 18.2)
HBsAg positive	135
HBeAg positive	100
HBcAb IgM positive	0
HBV DNA positive	135
HE (n)	3
HRS (n)	18
Ascites (n)	98
Variceal bleeding (n)	30
SBP (n)	38
Leukocyte counts (x 10^9/L)	4.40 (3.03 - 6.00)
Lymphocyte (x 10^9/L)	1.00 (0.70 - 1.40)
Monocytes (x 10^9/L)	0.50 (0.40 - 0.80)
LMR	1.75 (1.20 - 2.45)

Data are expressed as n, mean ± SD, or median (IQR).
Abbreviations: ALT - alanine aminotransferase, AST - aspartate aminotransferase, INR - international normalized ratio, MELD score - Model for End-Stage Liver Disease score, HE - hepatic encephalopathy, HRS - hepatorenal syndrome, SBP - spontaneous bacterial peritonitis, LMR - lymphocyte-to-monocyte ratio.

SPSS software version 19.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, and a value of $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 135 HBV-DeCi patients were included in the present retrospective study.

The baseline characteristics of all participants are listed in Table 1. Mean age of patients on admission was 52.8 years (range, 19 - 76 years; SD, 11.3 years) and 106 (78.5%) of the patients were males. There was no correlation between LMR and MELD score ($r = -0.052$; $p = 0.654$).

Comparison of LMR levels between non-surviving and surviving patients with HBV-DeCi

HBV-DeCi patients were divided into non-surviving (n = 17) and surviving groups (n = 118). The clinical and laboratory characteristics of these patients are listed in Table 2. The non-surviving patients had a higher MELD score, leukocyte counts, monocytes, total bilirubin, creatinine, and INR compared with those in surviving patients. However, a much lower LMR appeared in the non-surviving group compared with that in the surviving patients. The lymphocyte count of the non-surviving group was slightly lower than those of the surviving group, but the difference did not reach statistical significance. These data suggested that the lower LMR in the non-surviving group could be attributed primarily to the increased number of monocytes and secondarily due to decreased lymphocytes. No significant differences in total protein, albumin, ALT, AST, platelet count, hemoglobin, gender, or age were detected.

Relative risk factors for 30-day mortality

The patients were followed up for a median of 21 days (IQR: 14 - 69 days). During the follow-up, 17 patients died within 30 days due to upper gastrointestinal bleeding (n = 5), HE (n = 3), hepatic failure (n = 3), and HRS (n = 6). Univariate logistic regression analysis showed that high leukocyte counts, high MELD score, and low LMR were independent risk factors for 30-day mortality in HBV-DeCi patients. Multivariate logistic regression analysis identified both MELD score and the LMR as related to this mortality (Table 3). ROC curves were established to evaluate the relative efficiencies of the LMR and MELD score for predicting the 30-day mortality (Figure 1). The LMR was converted to 1/LMR by inverse transformation. The AUROCs of 1/LMR and the MELD score were 0.799 (95% CI 0.721 to 0.803; $p < 0.001$) and 0.830 (95% CI 0.756 to 0.889; $p < 0.001$), respectively. The optimal cut-point for baseline MELD score in predicting death was 16.1, with sensitivity of 94.1% and specificity of 72.0%. LMR had a cutoff value of 1.7 with sensitivity of 94.1% and specificity of 59.3%. When LMR and the MELD score were combined, the AUC was 0.925 (95% CI 0.878 to 0.971; $p < 0.001$), higher than the AUC of the MELD score ($p = 0.01$), and the specificity (83.9%) or the sensitivity (94.1%) was improved.

DISCUSSION

In the present retrospective study of HBV-DeCi, we found that the LMR was significantly lower in non-surviving patients than that in surviving patients. More importantly, low LMR was an independent predictive factor of mortality. These results provide the evidence for an association between LMR and mortality in HBV-

Table 2. The clinical characteristics and differences in variables between non-surviving and surviving patients with HBV-DeCi.

	Non-surviving patients (n = 17)	Surviving patients (n = 118)	p
Age (years)	52.7 ± 11.9	52.8 ± 11.3	0.709
Gender (male/female)	14/3	92/26	0.681
Total protein (g/L)	59.3 ± 10.5	61.2 ± 8.0	0.384
Albumin (g/L)	29.2 ± 5.9	30.3 ± 6.0	0.500
ALT (U/L)	37.0 (22.3 - 48.0)	33.0 (17.0 - 63.0)	0.939
AST (U/L)	49.0 (31.0 - 77.0)	49.0 (28.5 - 83.0)	0.866
Total bilirubin (µmol/L)	83.0 (72.3 - 161.5)	43.5 (23.0 - 117.0)	0.011
Creatinine (mmol/L)	104.0 (62.8 - 121.0)	73.0 (60.0 - 84.0)	0.025
INR	1.85 ± 0.55	1.46 ± 0.36	0.009
MELD score	20.0 (17.8 - 21.9)	12.4 (8.4 - 17.1)	< 0.001
Platelets (x 10^9/L)	63.0 (58.5 - 100.0)	70.0 (44.0 - 110.0)	0.969
Hemoglobin (g/L)	93.0 (82.0 - 109.3)	104.5 (90.0 - 121.0)	0.887
Leukocyte counts (x 10^9/L)	6.90 (4.65 - 11.60)	4.25 (3.00 - 5.70)	0.002
Lymphocyte (x 10^9/L)	0.80 (0.60 - 1.15)	1.00 (0.70 - 1.40)	0.288
Monocytes (x 10^9/L)	0.70 (0.58 - 1.53)	0.50 (0.30 - 0.80)	0.014
LMR	1.17 (0.80 - 1.44)	2.00 (1.33 - 2.50)	< 0.001

Data are expressed as n, mean ± SD, or median (IQR).
Abbreviations: ALT - alanine aminotransferase, AST - aspartate aminotransferase, INR - international normalized ratio, MELD score - Model for End-Stage Liver Disease score, LMR - lymphocyte-to-monocyte ratio.

Table 3. Risk factors associated with 1-month mortality, as analyzed by Cox proportional hazards analysis.

	Univariate		p	Multivariate		p
	Odds ratio	95% CI		Odds ratio	95% CI	
LMR	0.183	0.065 - 0.516	0.001	0.108	0.027 - 0.435	0.002
MELD score	1.250	1.113 - 1.403	0.001	1.340	1.140 - 1.576	0.001
Age (years)	1.000	0.956 - 1.046	0.987			
Total protein (g/L)	0.973	0.916 - 1.034	0.381			
ALT (U/L)	0.995	1.984 - 1.006	0.339			
Leukocyte counts (x 10^9/L)	1.150	1.052 - 1.257	0.002	1.148	0.979 - 1.346	0.090
Monocytes (x 10^9/L)	0.923	0.916 - 1.034	0.381			

Abbreviations: LMR - lymphocyte-to-monocyte ratio, MELD score - model for end-stage liver disease score, ALT - alanine aminotransferase.

DeCi patients. The MELD score has been widely used as a scoring system for organ allocation in liver transplantation and is the current standard prognostic tool for assessing the 3- to 6-month survival in patients with liver failure [13]. Although waiting list mortality has decreased since MELD implementation, former studies revealed that mortality might not be predicted appropriately by MELD score in patients suffering from frequent complications of cirrhosis. This is because complications (i.e., HE, HRS, and upper gastrointestinal bleeding) that can affect the prognosis of patients were not taken into consideration in the MELD score [14-17]. In the current study, we found no correlation between MELD score and LMR. This result differs from the data from Zhang's group [11]. They found that LMR in the liver cirrhosis group negatively correlated with the MELD score ($r = -0.241$; $p < 0.05$). This difference may largely reflect differences in stages of liver diseases of patients recruited between studies. In the Zhang study, only 23% of patients had decompensated cirrhosis;

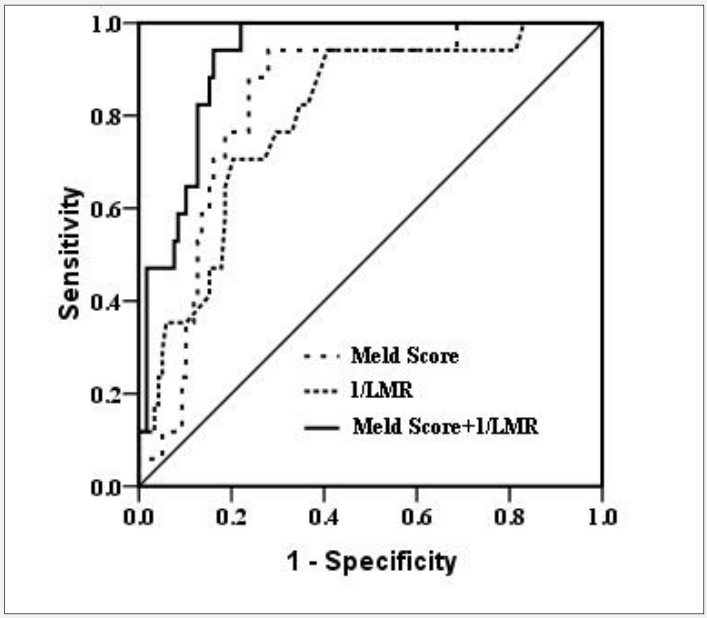

Figure 1. Receiver operating characteristic curve indicating relative efficiencies for prediction of 1-month mortality by 1/LMR (▪▪▪▪), MELD score (▪ ▪ ▪), and their combination (▬▬) at admission. Data are plotted to generate the receiver operating characteristic curve.

however, all patients in our study had DeCi. Our result suggests that LMR may rescue some patients who are not prioritized by MELD. In our cohort, the predictive power of LMR was lower than that of the MELD score, but the difference did not reach statistical significance (0.799 ± 0.053 vs. 0.830 ± 0.044, p = 0.679). However, the LMR involves only two markers, which makes it simpler and easier to calculate than the MELD score. A combination of LMR and MELD score could increase prediction efficiency to 93%.

There are at least two possible explanations as to why LMR is an independent predictor of mortality in patients with HBV-DeCi during follow-up in our study. First, we noted that there were marked increases in the leukocyte counts and monocyte counts in the non-survival group compared with those in the survival group. Previous studies have reported that systemic inflammation occurs frequently in patients with advanced cirrhosis and may be associated with poor outcomes [18,19]. In liver cirrhosis, intestinal bacterial overgrowth and translocation of bacterial products are widespread [20, 21], both of which contribute to the increased accumulation of endotoxin in the liver and peripheral blood. Endotoxin can trigger monocyte release from the bone marrow to the peripheral blood and differentiation of blood monocytes into tissue macrophages [22]. Furthermore, monocytes can secrete various pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor-α into the serum. This release is proportional to liver disease severity. In our study, there were 98 patients with ascites, of whom 38 had SBP. Therefore, the higher monocyte count may, in part, be a response to the hepatic inflammation. As a consequence, a high absolute monocyte count may indicate poor prognosis. Second, our result showed that lymphocytes in the non-survival group showed a trend towards lower levels as compared with the survival group, without reaching statistical significance. Such a decline might be attributed to lymphocytopenia. According to previous research, lymphopenia is associated with patient frailty leading to poor outcome [23-26]. Recently, it was reported that pre-transplant absolute lymphocyte count was one of the prognostic factors in liver transplant recipients [27,28]. Lymphopenia was a marker of malnutrition and poor response of immunity in patients with chronic liver disease [26,29]. Our findings indicate that the lower LMR mainly resulted from increased monocyte counts and decreased lymphocyte counts. Therefore, high monocyte counts together with low lymphocyte counts may reflect the severity and progresssion of liver injury in patients with HBV-DeCi.

CONCLUSION

The results from the present study show that LMR can function as an additional marker for predicting 1-month mortality in patients with HBV-DeCi. LMR is readily obtained by an easily available, low cost test, and it can be objectively evaluated. However, findings of the current study should be interpreted within its possible limitations. First, due to the retrospective design of the study and the small sample size, selection bias was inevitable, which might have influenced the survival analysis. Second, LMR was not dynamically observed, and thus, whether LMR declined stepwise when patient's condition progressively deteriorated remains unclear. Finally, inflammatory biomarkers (e.g., CRP, serum IgM concentration) might have been helpful in establishing a mechanism for the observed results. Therefore, the underlying mechanism enabling the LMR to indicate possible outcomes in HBV-DeCi patients has only been partially investigated in the present study. Our findings need to be verified in large multi-center and prospective studies.

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Declaration of Interest:
The author has no commercial or other association that might pose a conflict of interest.

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