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ORIGINAL ARTICLE

Mean Platelet Volume/Platelet Count Ratio as a Predictor of 3-Month Mortality in HBV-Related Decompensated Cirrhosis Patients

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SUMMARY

Background: **Hepatitis B virus (HBV)-associated decompensated cirrhosis (HBV-DeCi) has a high mortality rate if liver transplantation is not performed. The study aimed to evaluate the association between the mean platelet volume to platelet count ratio (MPR) and outcomes of HBV-DeCi patients.**
Methods: **This was a retrospective study of 109 patients newly diagnosed with HBV-DeCi. Univariate and multivariate regression models were used to determine risk factors for 90-day mortality.**
Results: **The MPR was observed to be higher in nonsurvivors than in survivors. Multivariate analysis suggested that the model for end-stage liver disease score and MPR were independent predictors in HBV-DeCi patients.**
Conclusions: **This study demonstrated that the MPR can serve as a potential predictor of 3-month mortality in HBV-DeCi patients.**
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KEY WORDS

mean platelet volume (MPV), platelet (PLT), mean platelet volume to platelet count ratio (MPR), Hepatitis B virus, decompensated cirrhosis

LIST OF ABBREVIATIONS

ALT - alanine aminotransferase
AST - aspartate aminotransferase
AUCs - areas under the curve
CTP score - Child-Turcotte-Pugh score
DeCi - decompensated cirrhosis
HBV - Hepatitis B virus
HE - hepatic encephalopathy
INR - international normalized ratio
LC - liver cirrhosis
MELD score - model for end-stage liver disease score
MPV - mean platelet volume
MPR - mean platelet volume to platelet count ratio
PLT - platelet

ROC - receiver operating characteristic
SBP - spontaneous bacterial peritonitis

INTRODUCTION

Chronic hepatitis B virus (HBV) infection remains a serious health problem [1]. In China, the incidence of liver cirrhosis (LC) in chronic HBV patients ranges from 8% to 20% within a 5-year period, and approximately 3% of untreated patients advance into decompensated cirrhosis (DeCi) each year [2]. DeCi is characterized by ascites, gastrointestinal hemorrhage or hepatic encephalopathy (HE) [3]. Within the 5-year period, mortality is estimated to be as high as 85% if liver transplantation is not performed [4]. Although many prognostic prediction models of HBV-DeCi have been proposed, an accurate, objective, low-cost marker for HBV-DeCi prognosis is urgently needed.

Mean platelet volume (MPV) is a precise measure of platelet size and reflects platelet activation and function [5,6]. MPV has been found to be associated with poor outcomes in different clinical situations. For example, previous studies have identified that an increased MPV is related to coronary artery disease and that MPV has been suggested to be an independent risk factor for stroke and myocardial infarction [7-9]. Recently, the relationship between MPV and liver disease has attracted the attention of clinicians. Several studies have demonstrated that HBV-associated LC and fibrosis are related to MPV [10-13]. In addition, an elevated MPV is associated with poor outcomes in patients with HBV- associated acute-on-chronic liver failure or HBV-DeCi [14, 15]. It is known that platelet counts (PLTs) are reduced in various liver diseases, such as LC and hepatosplenomegaly. Some studies have illustrated an inverse relationship between MPV and PLTs in critically ill patients [16,17]. Emerging evidence suggests that the combination of PLTs and MPV may be more clinically significant than PLTs or MPV alone [16,18-20]. The MPV to platelet count ratio (MPR) is a novel biomarker, and it has been revealed that an elevated MPR is a better independent indicator of long-term cardiovascular mortality in non-ST patients than MPV or PLTs alone [21]. Additionally, MPR is a promising predictor of an unfavorable outcome in patients with severe sepsis [22]. Moreover, a study reported that a high MPR was associated with a high risk of HCC, and compared with MPV alone, the MPR exhibited superior diagnostic performance [23]. Another study reported by Iida et al. showed that the MPR may be an independent predictor of LC [24]. However, to date, few studies have assessed the relationship between the MPR and prognosis of HBV-DeCi. Therefore, we aimed to investigate whether the MPR can be used as a potential predictor of 3-month mortality in HBV-DeCi patients.

MATERIALS AND METHODS

Patients

This retrospective study enrolled 160 newly diagnosed HBV-DeCi patients from our hospital between June 2016 and March 2019. DeCi was defined as the development of clinical ascites, gastrointestinal bleeding, and HE [3]. Of these patients, 51 were excluded because they had alcoholic liver disease (n = 11), autoimmune hepatitis (n = 3), drug-induced liver injury (n = 4), other viral infection (hepatitis A, C, or E virus or HIV infection) (n = 9), HCC (n = 3), drug use history (aspirin, clopidogrel, or steroids) (n = 4), cardiac disease (n = 5), heart failure (n = 3), hematological disease (n = 2) or had received anti-viral or immunomodulatory therapy in the past 3 months (n = 3) or a blood transfusion in the last 3 months (n = 4). Ultimately, 109 patients were included in this study. All patients were followed for 3 months or longer to assess 3-month mortality.

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

Data collection

Laboratory parameters, including total protein, serum albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and creatinine levels; international normalized ratios (INRs); MPVs; and PLT counts, were obtained from medical records. The normal adult reference ranges of MPV and the PLTs in our laboratory were 7.4 - 12.0 fL and 101 - 300 x 10^9/L, respectively. The MPR was calculated by dividing the patient MPV by the PLTs. Demographic and clinical data including age, gender, and complications related to liver disease, such as ascites, HE, and spontaneous bacterial peritonitis (SBP), were retrieved from medical records. In addition, prognostic scores (including Child-Turcotte-Pugh [CTP] and model for end-stage liver disease [MELD] scores) were subsequently calculated using the parameters obtained at baseline. The MELD score was calculated using the following formula: MELD score = 3.78 ln (total bilirubin, mg/dL) + 11.2 ln (INR) + 9.57 ln (creatinine, mg/dL) + 6.4 [25]. The CTP score was calculated with five variables including the total bilirubin level, albumin level, INR, ascites status, and degree of HE [26].

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation or median (interquartile range), while categorical variables were expressed as a percentage. Comparisons of demographic and clinical features were performed using a sample *t*-test, the Mann-Whitney *U* test or the Chi-square test, as appropriate. Spearman's correlation test was used in correlation analyses. Univariate and multivariate stepwise logistic regression models were used to evaluate independent clinical parameters predicting mortality. Receiver operating characteristic (ROC) curve analysis was performed to iden-

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

	HBV-DeCi patients (n = 109)
Gender (male/female)	89/20
Age (years)	53.2 ± 11.7
Total protein (g/L)	60.5 ± 7.6
Albumin (g/L)	29.6 ± 5.1
ALT (U/L)	33.0 (18.0 - 55.5)
AST (U/L)	50.0 (31.5 - 75.5)
Total bilirubin (μmol/L)	55.0 (22.5 - 152.5)
INR	1.53 ± 0.42
Creatinine (mmol/L)	75.0 (61.5 - 91.0)
HE (n)	3
Ascites (n)	77
SBP (n)	40
Gastrointestinal bleeding (n)	26
MPV (fL)	16.2 (14.2 - 19.4)
PLTs (x 10^9/L)	72.0 (37.8 - 121.0)
MPR	0.240 (0.135 - 0.440)
MELD score	14.1 (8.1 - 18.4)
CTP score	8.0 (7.0 - 10.0)

Data are expressed as n, mean ± SD, or median (interquartile range).
Abbreviations: ALT - alanine aminotransferase, AST - aspartate aminotransferase, INR - international normalized ratio, HE - hepatic encephalopathy, SBP - spontaneous bacterial peritonitis, MPV - mean platelet volume, PLTs - platelet counts, MPR - mean platelet volume to platelet count ratio, MELD score - model for end-stage liver disease score, CTP score - Child-Turcotte-Pugh score.

tify the sensitivity and specificity of parameters according to the corresponding cutoff point. The area under the receiver operating characteristic curve (AUC) was calculated to estimate and compare the predictive values of different prognostic variables. The data were analyzed using SPSS19.0 (Chicago, IL, USA) and Medcalc 10.0 software (Ostend, Belgium). Statistical significance was defined as $p < 0.05$.

RESULTS

Baseline characteristics

One hundred nine HBV-DeCi patients were included in this retrospective study.

The baseline characteristics of the study patients are listed in Table 1. The mean age of all patients was 53.2 ± 11.7 years, and 89 (81.7%) of the patients were male. The most common complication was ascites (n = 77, 70.6%), followed by gastrointestinal bleeding (n = 26, 23.9%), and HE was found in 3 (2.8%) of the patients. In addition, 77 patients (70.6%) had a PLTs < 100 x 10^9/L, whereas 39 (8.3%) had a PLTs < 50 x 10^9/L. The median MPR was 0.240 (IQR range: 0.135 - 0.440) in our patients at admission. Positive correlations were found between the MPR and MELD score ($r = 0.239$, $p = 0.012$) or CTP score ($r = 0.166$, $p < 0.001$). Nevertheless, we did not find any correlation between the MPR and age ($p = 0.099$). There was also no correlation between the MPV and PLTs ($p = 0.231$). In addition, the MPR was not different between men and women in our study ($p = 0.872$).

Comparison of the MPR between survivors and nonsurvivors

The 3-month mortality of the HBV-DeCi patients was 40.4% (44/109). After a 3-month follow-up, the HBV-DeCi patients were then subdivided into survivors and nonsurvivors. The clinical and laboratory parameters of the patients are shown in Table 2. The mean age, total protein level, albumin level, ALT level, AST level, creatinine level, and gender distribution were not different between the two groups (all $p < 0.05$). Conversely, the MPR was significantly elevated in the nonsurvivors compared to the survivors (median 0.35, IQR 0.18 - 0.58 vs. 0.17, 0.11 - 0.34, respectively; $p = 0.001$). Similarly, the patients who did not survive had higher MELD scores, CTP scores, MPVs, INRs, and TBil levels and lower PLTs than those who survived (all $p < 0.01$).

MPR was associated with a poor outcome in HBV-DeCi patients

By univariate analysis, MPV, PLTs, MPR, and MELD and CTP scores were independent risk factors for 3-month mortality (all $p < 0.05$). After multivariate analysis, the MELD score and MPR remained independently predictive of mortality (both $p < 0.05$). These findings were shown in Table 3. The prognostic value of MPR and MELD score in predicting 3-month outcomes was further assessed using AUROC analysis. The MELD score had a cutoff point for the prediction of death by the baseline MELD score of 17.76, with 47.70% sensitivity and 84.62% specificity. The MPR had a cutoff point of 0.390, with 43.22% sensitivity and 83.15% specificity. The AUC values for predicting mortality were 0.713 ± 0.050 for the MELD score (95% confidence interval (CI): 0.619 - 0.796, $p < 0.001$) and 0.703 ± 0.050 for the MPR (95% CI: 0.608 - 0.787, $p < 0.001$). In the present study, the powers of the MPR and MELD score for predicting death were not significantly different ($p = 0.877$). When the MPR and MELD score were combined, the AUC for predicting mortality was 0.756 ± 0.047 (95% CI: 0.664 - 0.833, $p < 0.001$), which was slightly higher than the individual AUCs of the MELD score and MPR, and the specificity (76.92%) and sensitivity (63.64%) were also improved (Figure 1).

Table 2. Clinical characteristics and differences in variables between nonsurviving and surviving patients with HBV-DeCi.

	Nonsurviving patients (n = 44)	Surviving patients (n = 65)	p
Age (years)	54.6 ± 10.5	52.2 ± 12.4	0.301
Gender (male/female)	36/8	53/12	0.830
Total protein (g/L)	59.4 ± 6.8	61.2 ± 8.0	0.223
Albumin (g/L)	28.7 ± 4.3	30.2 ± 5.6	0.137
ALT (U/L)	37.0 (17.0 - 66.0)	32.0 (19.5 - 48.0)	0.711
AST (U/L)	54.5 (34.5 - 113.8)	48.0 (29.0 - 72.0)	0.073
Total bilirubin (μmol/L)	101.0 (41.5 - 209.8)	37.0 (20.0 - 99.5)	0.002
Creatinine (mmol/L)	74.5 (63.8 - 99.3)	75.0 (59.0 - 84.0)	0.327
INR	1.68 ± 0.44	1.45 ± 0.38	0.007
MELD score	17.4 (12.0 - 21.5)	11.7 (7.1 - 16.7)	< 0.001
CTP score	10.0 (7.3 - 11.0)	8.0 (7.0 - 10.0)	0.015
MPV (fL)	18.1 (15.1 - 20.7)	15.2 (13.1 - 17.8)	0.001
PLTs (x 10^9/L)	51.0 (31.5.1 - 92.3)	81.0 (48.0 - 151.0)	0.007
MPR	0.35 (0.18 - 0.58)	0.17 (0.11 - 0.34)	0.001

Data are expressed as n, mean ± SD, or median (interquartile range).
Abbreviations: ALT - alanine aminotransferase, AST - aspartate aminotransferase, INR - international normalized ratio, MELD score - model for end-stage liver disease score, CTP score - Child-Turcotte-Pugh score, MPV - mean platelet volume, PLTs - platelet counts and MPR, mean platelet volume to platelet count ratio.

Table 3. Cox proportional hazards analysis of predictors of death.

	Univariate			Multivariate		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
MPV (fL)	1.168	1.050 - 1.298	0.003			
PLT (x 10^9/L)	0.991	0.984 - 0.998	0.004			
MPR	20.485	2.937 - 143.366	0.001	15.248	2.049 - 113.449	0.008
Age (years)	1.018	0.984 - 1.053	0.295			
Albumin (g/L)	0.944	0.874 - 1.019	0.133			
CTP score	1.293	1.047 - 1.597	0.017			
MELD score	1.294	1.056 - 1.208	< 0.001	1.124	1.048 - 1.205	0.001

Abbreviations: MPV - mean platelet volume, PLT - platelet count, MPR - mean platelet volume to platelet count ratio, CTP score - Child-Turcotte-Pugh score, MELD score - model for end-stage liver disease score, HR - hazard ratios, CI - confidence interval.

DISCUSSION

To date, the identification of simple and accurate markers for the prognosis of HBV-DeCi remains an area of intense interest. Our study is the first to investigate the relationship between the MPR and outcomes in HBV-DeCi patients. In the current study, we indicated a significant elevation in the MPR in nonsurvivors compared to survivors. Spearman's analysis showed that the MPR was positively correlated with MELD and CTP scores. These findings illustrated that an elevated MPR may be associated with pathogenesis in HBV-DeCi. Furthermore, we mainly focused on investigating the predicative value of the MPR in the prognosis of HBV-DeCi. Univariate and multivariate regression analyses identified that the MPR could serve as a surrogate predictor of 3-month mortality. In fact, the MPR had a predictive efficacy similar to that of the MELD score. Moreover, the MPR requires only two simple factors, which are objective and more easily acquired than the factors used to calculate MELD scores. Finally, combining the MPR with the MELD score further improved the ability to

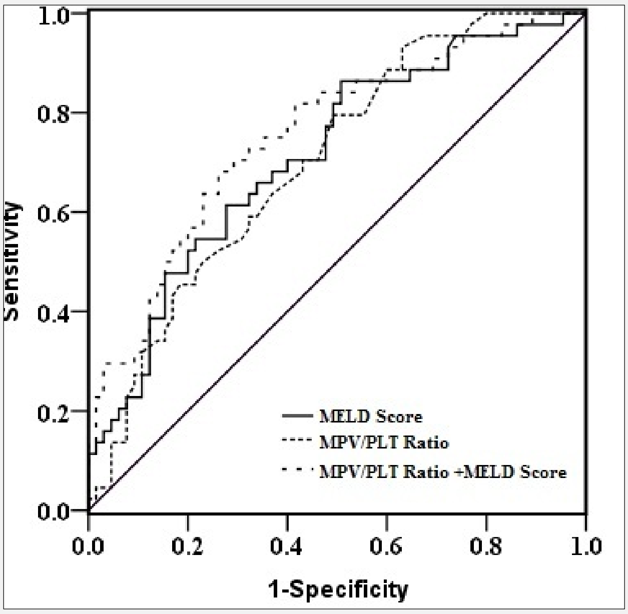

Figure 1. Receiver operating characteristic curves of the MPV/PLT ratio (▪▪▪▪), the MELD score (▬▬), and their combination (▪ ▪ ') at admission for the prediction of 3-month mortality in HBV-DeCi patients.

predict mortality. Previous studies have reported that the ferritin level [27], C-reactive protein level [28], total bilirubin level [29], platelet counts [30], and age [31] are associated with poor outcomes in cirrhosis patients. This study supplements previous research and suggests that a high MPR can also be used to predict prognosis in HBV-DeCi patients.

The mechanisms underlying the correlation between the MPR and the prognosis of HBV-DeCi remain unclear, but there are more studies on the MPV and PLTs separately than on the MPR. In the current study, patients with poor outcomes displayed higher MPVs and lower PLTs than those who had favorable outcomes. Thrombocytopenia is a common hematological complication in LC patients, and it is mainly a result of portal hypertension and platelet sequestration in the enlarged spleen [32,33]. In our cohort, 77 patients had thrombocytopenia (PLTs < 100 x 10^9/L), of whom 39 exhibited severe thrombocytopenia (PLTs < 50 x 10^9/L). Previous studies have reported that systemic inflammation occurs frequently in patients with advanced LC and may be associated with worse outcomes [34,35]. A study reported by Survak et al. showed that MPV is a novel indicator of systemic inflammation in LC patients with ascitic fluid infection [36]. In our study, there were 77 patients with ascites, of whom 40 had SBP. Therefore, we believe that an increase in inflammatory processes may occur in patients with HBV-DeCi. An elevated MPV is an indicator of increases in size and reactivity in platelets resulting from increased platelet turnover; it may be used as an indicator of inflammatory disease and is related to disease severity [37]. Previous studies have shown that MPV and the PLTs are usually inversely related. However, there was no correlation between MPV and the PLTs in our patients. These controversial results may be partly explained by the small sample size in our study or the different pathophysiological mechanisms underlying diseases. In the current study, MPV and the PLTs were prognostic factors for mortality in univariate analyses. However, neither MPV nor the PLTs alone could predict mortality in a multivariate analysis. The main reason may be that the MPR, as a ratio, is more stable than its individual parameters, as the MPR integrates the morphology and quantity of PLTs and has a better predictive value than either parameter alone. Therefore, we concluded that the MPR could increase the discriminatory power in the prediction of disease severity and was a more reliable and precise marker than MPV or the PLT count alone. Our findings indicated that increased MPRs mainly resulted from an increased MPV value and decreased PLTs. Therefore, a high MPV together with low PLTs may reflect the severity and progression of liver injury in patients with HBV-DeCi. Thus, we believe that the MPR could be helpful in the assessment of the prognosis of patients with HBV-DeCi. More research is needed to further investi-

gate the underlying mechanism.
This study has potential limitations. First, our study is a retrospective study, which may have led to a selection bias, and the sample size was not sufficient. In addition, we failed to evaluate some inflammatory markers, such as C-reactive protein or IL-6, which might be helpful in establishing the mechanism underlying these findings. Finally, there is a lack of validation of the mortality predictors. Thus, these findings need to be confirmed in large, multicenter, prospective studies.

CONCLUSION

This study is the first to illustrate that the MPR is an additional marker for 90-day mortality in HBV-DeCi patients. The MPR is readily available and inexpensive and can be objectively evaluated. The use of the MPR should be considered in conjunction with other measures for the evaluation of short-term prognosis and for clinical decision-making in HBV-DeCi patients. A prospective clinical trial is necessary to validate the current results.

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

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