Clin. Lab. 2021;67:XXX-XXX


## ORIGINAL ARTICLE

# Peripheral Blood Cell Ratios as Prognostic Predictors of Mortality in Patients with Hepatitis B Virus-Related Decompensated Cirrhosis

XiaoTing Qi [1], ChangMin Wang [1], XinJie Shan [2]

[1] *Department of Clinical Laboratory, The People's Hospital of Xinjiang Uygur Autonomous Region, Tianshan District, Uygur, China*
[2] *Department of Clinical Laboratory, Children's Hospital of Xinjiang Uygur Autonomous Region, Uygur, Xinjiang, China*

### SUMMARY

***Background:*** **We sought to determine the correlations between peripheral blood cell ratios (neutrophil-to-lymphocyte ratio (NLR), mean platelet volume-to-lymphocyte ratio (MPVLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-neutrophil ratio (PNR), and platelet-to-white blood cell ratio (PWR)) and short-term prognosis in patients with hepatitis B virus (HBV)-associated decompensated cirrhosis (HBV-DeCi).**
***Methods:*** **A total of 144 HBV-DeCi patients were enrolled. Demographic characteristics and laboratory data for the patients were acquired from their medical records. Multivariate regression analysis was applied to determine risk factors for unfavorable outcomes. The predictive performance of different ratios was examined by receiver operating characteristic curve analysis. Liver function was assessed by the Model for End-Stage Liver Disease (MELD) score.**
***Results:*** **Twenty-one HBV-DeCi patients (14.6%) had died at 30 days. Survival was associated with lower NLR, MLR, MPVLR, and MELD score and higher PWR and PNR than non-survival. Multivariate analyses identified NLR and MELD score as independent prognostic predictors. The ability of NLR to predict mortality was higher than that of MLR, PNR, MPVLR, and PWR, but slightly lower than that of MELD score.**
***Conclusions:*** **The present results suggest that peripheral blood cell ratios can be useful for predicting mortality in HBV-DeCi patients. These ratios should be considered together with other measures for evaluation of prognosis in HBV-DeCi patients and are conducive to clinical practice.**
**(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2021.210238)**

**Correspondence:**
XinJie Shan
Department of Clinical Laboratory
Children's Hospital of Xinjiang Uygur Autonomous
Altay Road No. 393
Uygur
Xinjiang
830014 China
Phone/Fax: +86 991-3056220
Email: xjxinjie100@yeah.net

Manuscript accepted May 3, 2021

### KEY WORDS

peripheral blood cell ratios, prognostic factors, decompensated cirrhosis, mortality

### LIST OF ABBREVIATIONS

AUCs - Area under the curve
CI - Confidence interval
DeCi - Decompensated cirrhosis
HBV - Hepatitis B virus
MELD score - Model for End-stage liver disease score
MLR - Monocyte-to-lymphocyte ratio
MPVLR - Mean platelet volume-to-lymphocyte ratio
NLR - Neutrophil-to-lymphocyte ratio
PNR - Platelet-to-neutrophil ratio
PWR - Platelet-to-white blood cell ratio

ROC - Receiver operating characteristic
SIRS - Systemic inflammatory response syndrome
WBC - White blood cell

## INTRODUCTION

In China, hepatitis B virus (HBV) is the major cause of liver cirrhosis [1]. Decompensated cirrhosis (DeCi) is a terminal liver disease, accompanied by various complications responsible for death. The estimated 5-year survival rate is only 15% [2-4]. Consequently, there is an urgent need to determine simple, effective, and accurate noninvasive markers that can predict the prognosis of HBV-DeCi patients.

Systemic inflammatory response syndrome (SIRS) is very common in patients with complicated liver cirrhosis. There is accumulating evidence for a correlation between the systemic inflammatory response and DeCi development and progression [5,6]. The inflammatory response is reflected by the levels of white blood cells (WBCs), neutrophils, lymphocytes, and platelets. Thus, a series of combinations of these factors, such as neutrophil-to-lymphocyte ratio (NLR), mean platelet volume-to-lymphocyte ratio (MPVLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-white blood cell ratio (PWR), and platelet-to-neutrophil ratio (PNR) may be potential prognostic markers for DeCi patients. Indeed, several reports have shown that these blood cell ratios are useful predictors of clinical outcomes in liver diseases [7-10]. However, few studies have examined these ratios for prediction of prognosis in HBV-DeCi patients. In the present study, we aimed to compare the predictive significance and capacity of NLR, MLR, PWR, PNR, and MPVLR in HBV-DeCi patients to guide clinical practice.

## MATERIALS AND METHODS

### Patients

We retrospectively enrolled HBV-DeCi patients in our hospital between March 2014 and May 2018. DeCi patients were defined by clinical, biochemical, and imaging data, with presence of ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy, or any combination of these [11]. Patients who met our inclusion and exclusion criteria were selected. The inclusion criteria were: (1) HBsAg positivity for at least 6 months; (2) age of 18 - 70 years. The exclusion criteria were: (1) co-infection with HAV, HCV, HDV, HEV, or HIV; (2) presence of malignant tumors; (3) co-existence of other causes of liver disease such as autoimmune hepatitis, alcoholic liver disease, and drug-induced liver injury; (4) complication with cardiac diseases or hematologic disorders. In our cohort, 128 patients were receiving antiviral therapy (Lamivudine, Entecavir or Tenofovir); 84 of them started antiviral therapy before admission and 44 started after admission. Only 16 patients did not receive any antiviral therapy throughout the clinical course for economic or other reasons. The primary outcome was 30-day survival. Date of death was obtained from the medical records.

The study and all its protocols were approved by the Ethical Committee of People's Hospital of Xinjiang Uygur Autonomous Region.

### Clinical data collection

Clinical data for the patients were acquired from their medical records. Hematological parameters including white blood cell counts and the relevant subpopulations (i.e., lymphocyte, neutrophil, and monocyte counts), platelet counts. MPV and hemoglobin levels were analyzed using an automated analyzer (Sysmex XN-9000, Japan). NLR was calculated as the absolute value for the ratio of neutrophils to lymphocytes. MLR was calculated as the absolute value for the ratio of monocytes to lymphocytes. PWR was calculated as the absolute value for the ratio of platelets to white blood cells. PNR was calculated as the absolute value for the ratio of platelets to neutrophils. MPVLR was calculated as mean platelet volume divided by lymphocytes. Liver function at baseline was evaluated by the Model for End-Stage Liver Disease (MELD) score, which was calculated as previously described [11].

### Statistical analysis

Statistical analyses were conducted with SPSS 20.0 software (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA) and MedCalc 15.6 software (MedCalc, Ostend, Belgium). Baseline and clinical characteristics were presented as median (quartile) or number. Differences in variables were analyzed by Student's *t*-test or Mann-Whitney U test. Correlations between two variables were assessed by Spearman's rank correlation test. After adjustment for confounders in univariate analyses, the associations between probable predictors and 30-day mortality were determined by stepwise multivariate regression analysis. Receiver operating characteristic (ROC) curve analyses were performed to compare the performances of MELD score, NLR, MLR, PWR, PNR, and MPVLR for predicting adverse outcomes in HBV-DeCi patients, and the areas under the ROC curves (AUCs) were calculated. Statistical significance was defined at $p < 0.05$.

## RESULTS

### Patient characteristics

The flowchart for inclusion of the enrolled patients is shown in Figure 1. Overall, 51 patients were excluded and 144 patients were finally included. The symptoms of the decompensation events responsible for hospitalization were ascites (n = 101, 70.1%), gastrointestinal bleeding (n = 28, 19.4%), hepatorenal syndrome (n = 15, 10.4%), and hepatic encephalopathy (n = 3, 2.1%). MELD score was positively correlated with NLR (*r* =

**Table 1. Comparisons of baseline characteristics between survivors and non-survivors.**

| | All patients (n = 144) | Non-surviving patients (n = 21) | Surviving patients (n = 123) | p |
|---|---|---|---|---|
| Gender (female/male) | 29/115 | 6/15 | 23/100 | 0.454 |
| Age (years) | 54.0 (46.5 - 62.0) | 57.0 (48.3 - 65.3) | 53.0 (46.3 - 62.0) | 0.504 |
| Total protein (g/L) | 61.20 (56.42 - 67.00) | 56.40 (55.28 - 66.40) | 61.50 (67.63 - 66.98) | 0.055 |
| Albumin (g/L) | 30.60 (26.40 - 34.68) | 29.60 (26.40 - 31.73) | 31.10 (26.43 - 34.88) | 0.185 |
| Alanine aminotransferase (U/L) | 32.5 (17.3 - 55.0) | 41.0 (20.8 - 68.5) | 31.00 (17.25 - 50.25) | 0.350 |
| Aspartate aminotransferase (U/L) | 46.0 (28.0 - 76.8) | 56.0 (31.3 - 146.8) | 46.0 (28.0 - 73.3) | 0.274 |
| Serum creatinine (mmol/L) | 74.0 (60.5 - 87.5) | 111.0 (65.3 - 134.5) | 73.0 (60.0 - 83.8) | < 0.001 |
| Total bilirubin (µmol/L) | 41.0 (19.0 - 103.0) | 90.0 (64.8 - 269.0) | 35.0 (17.0 - 89.0) | < 0.001 |
| Blood urea nitrogen (µmol/L) | 5.60 (4.20 - 7.50) | 8.75 (7.05 - 15.30) | 5.20 (4.10 - 6.90) | < 0.001 |
| International normalized ratio | 1.34 (1.19 - 1.62) | 1.66 (1.39 - 1.95) | 1.31 (1.16 - 1.54) | < 0.001 |
| NLR | 2.18 (1.40 - 3.76) | 6.64 (2.72 - 10.29) | 2.00 (1.27 - 3.07) | < 0.001 |
| MLR | 0.56 (0.37 - 0.83) | 0.71 (0.58 - 1.00) | 0.53 (0.34 - 0.75) | 0.010 |
| PWR | 18.29 (12.19 - 26.74) | 12.35 (7.68 - 15.42) | 20.00 (13.26 - 27.26) | 0.002 |
| PNR | 33.84 (19.00 - 52.68) | 16.74 (9.14-25.23) | 36.25 (21.31-54.75) | < 0.001 |
| MPVLR | 11.57 (8.11 - 17.80) | 17.7 (9.5 - 24.1) | 10.8 (8.1 - 16.2) | 0.024 |
| MELD score | 11.56 (6.74 - 17.36) | 20.33 (17.50 - 22.77) | 10.44 (6.04 - 14.70) | < 0.001 |
| Platelet count (x $10^9$/L) | 74.5 (48.5 - 121.5) | 63.0 (54.8 - 100.0) | 78.0 (46.5 - 121.8) | 0.632 |
| Hemoglobin (g/L) | 109.0 (91.0 - 121.5) | 100.0 (86.8 - 114.8) | 110.0 (92.3 - 122.0) | 0.151 |
| HBV-DNA ($Log_{10}$ IU/mL) | 4.6 (3.5 - 7.6) | 3.9 (3.1 - 5.6) | 5.5 (4.1 - 8.0) | 0.323 |
| HBeAg-positive (yes/no) | 51/93 | 6/15 | 45/78 | 0.644 |

**Data are expressed as n, or median (quartile).**
**Abbreviations: NLR - neutrophil-to-lymphocyte ratio, MLR - monocyte-to-lymphocyte ratio, PWR - platelet-to-white blood cell ratio, PNR - platelet-to-neutrophil ratio, MPVLR - mean platelet volume-to-lymphocyte ratio, MELD score - Model for End-Stage Liver Disease score.**

**Table 2. Results of multivariate analyses to identify independent factors associated with adverse outcomes in HBV-DeCi patients.**

| | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | p | Odds ratio | 95% CI | p |
| MELD score | 1.288 | 1.157 - 1.433 | < 0.001 | 1.313 | 1.151 - 1.498 | < 0.001 |
| NLR | 1.456 | 1.238 - 1.734 | < 0.001 | 1.514 | 1.212 - 1.891 | < 0.001 |
| MPVLR | 1.067 | 1.019 - 1.118 | 0.006 | | | |
| MLR | 3.937 | 1.338 - 11.585 | 0.013 | | | |
| PNR | 0.944 | 0.911 - 0.978 | 0.002 | | | |
| PWR | 0.930 | 0.877 - 0.986 | 0.016 | | | |

**Abbreviations: CI - confidence interval, MELD - Model for End-Stage Liver Disease, NLR - neutrophil-to-lymphocyte ratio, MPVLR - mean platelet volume-to-lymphocyte ratio - MLR, monocyte-to-lymphocyte ratio, PWR - platelet-to-white blood cell ratio, PNR - platelet-to-neutrophil ratio.**

0.309, $p < 0.001$) and inversely correlated with PWR and PNR ($r = -0.477$, $p < 0.001$ and $r = -0.489$, $p < 0.001$, respectively). MLR and MPVLR were not correlated with MELD score ($r = 0.024$, $p = 0.779$ and $r = 0.066$, $p = 0.429$, respectively). Twenty-one patients had died at 30 days after admission, giving a 30-day

**Table 3. Predictive powers of various scores for 30-day mortality.**

| | AUC | 95% CI | p | Cutoff value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| **MELD score** | **0.873 ± 0.035** | **0.808 - 0.923** | **< 0.001** | **15.8** | **85.71** | **80.49** |
| **NLR** | **0.840 ± 0.047** | **0.770 - 0.896** | **< 0.001** | **3.78** | **71.43** | **84.55** |
| **MPVLR** | **0.654 ± 0.075** | **0.570 - 0.731** | **0.041** | **15.00** | **66.67** | **69.11** |
| **MLR** | **0.676 ± 0.064** | **0.593 - 0.752** | **0.006** | **0.59** | **76.19** | **60.98** |
| **PNR** | **0.766 ± 0.061** | **0.688 - 0.833** | **< 0.001** | **25.42** | **80.95** | **67.48** |
| **PWR** | **0.711 ± 0.070** | **0.630 - 0.783** | **0.002** | **15.92** | **80.95** | **62.60** |

**Abbreviations: AUC - area under curve, CI - confidence interval, MELD - Model for End-Stage Liver Disease, NLR - neutrophil-to-lymphocyte ratio, MPVLR - mean platelet volume-to-lymphocyte ratio, MLR - monocyte-to-lymphocyte ratio, PWR - platelet-to-white blood cell ratio, PNR - platelet-to-neutrophil ratio.**

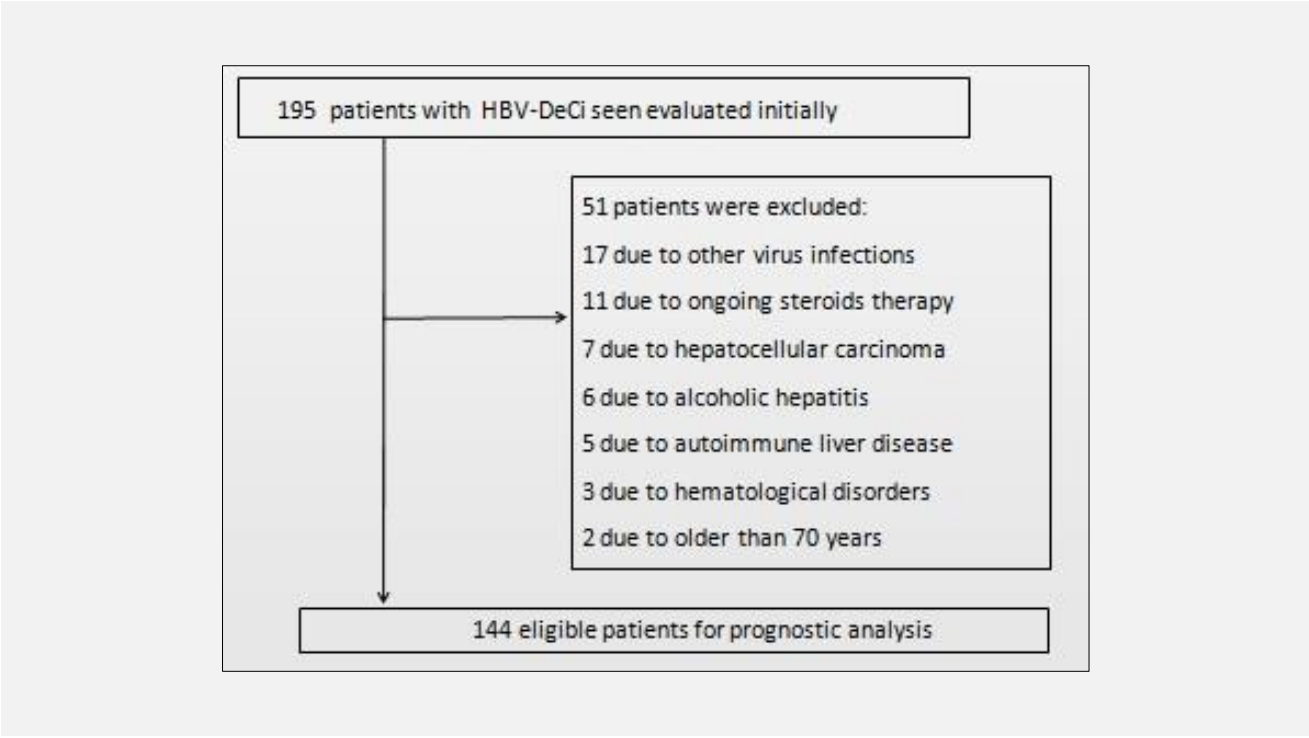


**Figure 1. Flowchart for inclusion of the enrolled patients.**

mortality rate of 14.6%. The causes of death were upper gastrointestinal bleeding (n = 8), hepatic encephalopathy (n = 3), hepatic failure (n = 4), hepatorenal syndrome (n = 5), and uncertain (n = 1). The patients were further subdivided into non-surviving and surviving groups. The clinical and laboratory data for the patients in these groups are shown in Table 1. Significant differences in total bilirubin, creatinine, international normalized ratio, all five blood cell ratios, blood urea nitrogen, and MELD score were found between the two groups (all $p < 0.05$).

**Factors associated with mortality**

Univariate and multivariate analyses were carried out to identify independent prognostic risk factors in HBV-DeCi patients. As shown in Table 2, all five blood cell ratios and MELD scores were significantly associated with mortality according to the univariate analyses. After adjustment for confounding factors, multivariate analyses demonstrated that only NLR and MELD score were independent predictive factors for poor outcomes. The ROC curves for the predictive values of the markers for mortality are presented in Figure 2. The AUC for

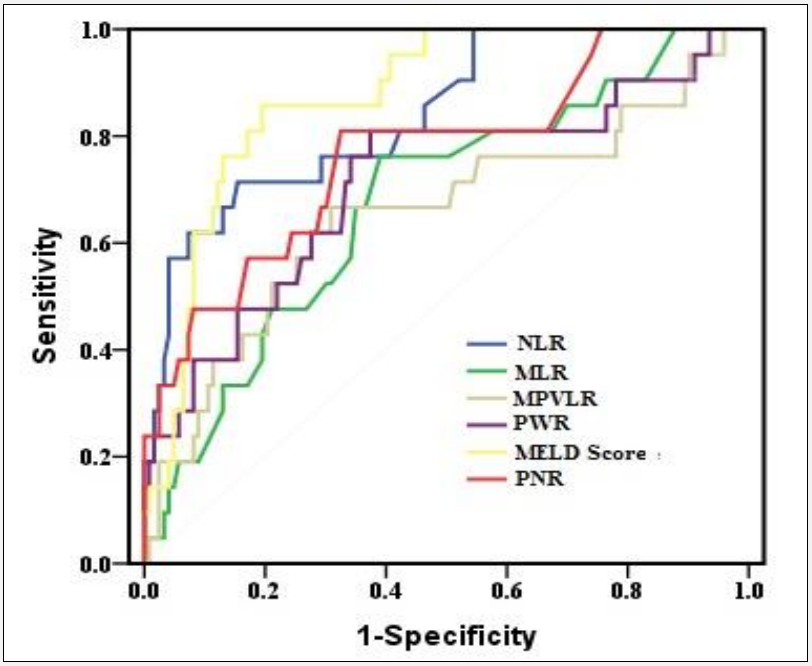


**Figure 2. Receiver operating characteristic curves of MELD score and all five peripheral blood cell ratios for prediction of 30-day mortality in HBV-DeCi patients.**

NLR to predict mortality was 0.840, which was higher than that for MLR (0.676), PWR (0.711), MPVLR (0.654), and PNR (0.766), but slightly lower than that for MELD score (0.873) (Table 3). When NLR and MELD score were combined, the AUC was 0.931, which was higher than that for MELD score or NLR alone (both $p < 0.05$).

## DISCUSSION

Identification of effective and accurate noninvasive biomarkers for predicting the prognosis of HBV-DeCi patients has remained a hot topic in this research field. Current research has mainly focused on investigating the predictive value of peripheral blood cell ratios for the prognosis of these patients. To our knowledge, this is the first study to compare the five blood cell ratios for mortality evaluation in HBV-DeCi patients. In the present study, 14.6% of patients died within 30 days, consistent with the findings in previous studies wherein approximately 11.0% of patients with DeCi died within 28 days [12-14]. We found that MELD score, NLR, PNR, and PWR displayed excellent predictive significance and capacity for 30-day unfavorable outcomes in HBV-DeCi patients (all AUC > 0.700). Although lacking significance, the predictive capacity of NLR and MELD score appeared superior to that of MLR, PNR, MPVLR, and PWR. Multivariate analyses further confirmed that NLR and MELD score were independent prognostic predictors. Moreover, the combination of NLR and MELD score was a more accurate prognostic indicator for predicting mortality in HBV-DeCi patients than either marker alone.

WBCs and their subtypes (lymphocytes, monocytes, neutrophils) have different prognostic roles in HBV-DeCi patients. On the one hand, SIRS occurs frequently in patients with advanced cirrhosis [5,6]. Bacterial infections are the most common causes of high WBCs, and thus high WBCs are suggestive for the presence of infection. On the other hand, cirrhotic patients usually have low WBCs due to hypersplenism. The distribution of WBCs was classified as low ($\leq 4.0 \times 10^9$/L, n = 66, 45.8%), normal ($4.0 - 10.0 \times 10^9$/L, n = 70, 48.6%), and high ($\geq 10.0 \times 10^9$/L, n = 8, 5.6%) in the present study cohort. In our study, univariate and multivariate analyses revealed that WBCs failed to predict 30-day mortality (data not shown). A previous study demonstrated that lymphocytes and neutrophils played key roles in the pathogeneses of different diseases and immune defense mechanisms [15]. Peripheral neutrophils are recognized as markers of acute and chronic inflammation [16], while lymphocyte levels reflect the outcome of controlled immune responses [17]. The combination of

neutrophils and lymphocytes is considered an important and useful index that can reflect the balance between inflammation and immune reactions. In the present study, elevated NLR was identified as a risk factor for unfavorable prognosis in HBV-DeCi patients, consistent with previous research [20–23]. Furthermore, NLR was positively correlated with MELD score and its ability to predict mortality was better than that of the other four ratios.

Monocytes are central mediators of immune responses and have an important and complex function in the pathogenesis of liver cirrhosis. On the one hand, the inflammatory response triggers the release of monocytes into the peripheral blood [24]. The released monocytes then secrete proinflammatory cytokines like interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor-α exacerbating liver damage. On the other hand, studies have shown that expression of monocyte-derived human leukocyte antigen-DR is reduced in cirrhotic patients [25, 26], usually in association with immune dissonance and high bacterial complication. The reduction is proportional to the severity of liver cirrhosis [26,27]. Therefore, DeCi patients with poor prognosis may have a high monocyte count, but low monocyte function. This monocyte-derived immune paresis may be the cause of the alterations in monocyte count and MLR in HBV-DeCi patients. However, the underlying reasons remain to be elucidated in future studies.

At present, platelets are generally accepted to play a key role in the development of liver diseases [28]. Platelet count was reported to be associated with liver fibrosis [29,30]. Thrombocytopenia is a common hematologic abnormality in patients with liver diseases, and is considered to be caused by multiple factors [31,32]. We found a significant negative correlation of PWR with MELD score and an association between low PWR and high in-hospital mortality, suggesting that low PWR may be a predictive factor for severity and progression of liver injury among patients with HBV-DeCi. Similar to PWR, the AUC of PNR for prediction of mortality was slightly higher than that of PWR in the present study. It is possible that neutrophil counts are a better indicator of the inflammatory state of the disease than WBCs. However, the underlying mechanisms require further elucidation.

MPVLR is considered a novel inflammatory index [33]. We did not find that MPVLR was an independent predictor of mortality in our multivariate analyses, and its predictive ability was inferior to that of the other four ratios. These findings differ from those of Wu et al. [10], who indicated that MPVLR had an association with prognosis in patients with cirrhosis. It is possible that the increase in MPVLR is related to the complex pathogenesis of HBV-DeCi.

In summary, we evaluated five peripheral blood cell ratios (NLR, MLR, PWR, PNR, and MPVLR) for prediction of mortality in HBV-DeCi patients. Our study indicated that all five ratios were useful for predicting mortality in HBV-DeCi patients, although the MELD score remained the best predictor of prognosis in these patients. Because the peripheral blood cell ratios are simple, noninvasive, and convenient biomarkers of liver disease, they can provide valuable information to complement conventional measures for assessing the disease condition in HBV-DeCi patients, and can assist clinicians in achieving early assessment of prognosis and implementation of appropriate interventions in these patients. However, because this was a retrospective study, further prospective clinical trials are warranted to validate the present findings.

**Declaration of Interest:**

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

**References:**


1. Xiao J, Wang F, Wong NK, et al. Global liver disease burdens and research trends: Analysis from a Chinese perspective. J Hepatol 2019 Jul; 71(1):212-21 (PMID: 30871980).

2. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014 May 17;383(9930):1749-61 (PMID: 24480518).

3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018 Aug;69(2):406-60 (PMID: 29653741).

4. D'Amico G. The clinical course of cirrhosis. Population based studies and the need of personalized medicine. J Hepatol 2014 Feb;60(2):241-2 (PMID: 24211741).

5. Behroozian R, Bayazidchi M, Rasooli J. Systemic inflammatory response syndrome and MELD score in hospital outcome of patients with liver cirrhosis. Middle East J Dig Dis 2012 Jul; 4(3): 168-72 (PMID: 24829652).

6. Abdel-Khalek EE, El-Fakhry A, Helaly M, Hamed M, Elbaz O. Systemic inflammatory response syndrome in patients with liver cirrhosis. Arab J Gastroenterol 2011 Dec;12(4):173-7 (PMID: 22305496).

7. Cai YJ, Dong JJ, Dong JZ, et al. A nomogram for predicting prognostic value of inflammatory response biomarkers in decompensated cirrhotic patients without acute-on-chronic liver failure. Aliment Pharmacol Ther 2017 Jun;45(11):1413-26 (PMID: 28345155).

8. Zhang J, Qiu Y, He X, Mao W, Han Z. Platelet-to-white blood cell ratio: A novel and promising prognostic marker for HBV-associated decompensated cirrhosis. J Clin Lab Anal 2020 Dec;34(12):e23556 (PMID: 32893950).

9. XK Li , JP Wu , WL Mao. Evaluation of the neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and red cell distribution width for the prediction of prognosis of patients with hepatitis B virus-related decompensated cirrhosis. J Clin Lab Anal 2020 Nov; 34(11):e23478 (PMID: 32666632).

10. Wu J, Mao W, Li X. Mean Platelet Volume/Lymphocyte Ratio as a Prognostic Indicator for HBV-Related Decompensated Cirrhosis. Gastroenterol Res Pract 2020 Jul 2;2020:4107219 (PMID: 32714387).

11. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Hepatology 1988 May-Jun; 8(3):493-6 (PMID: 3371868).

12. Cheng XP, Zhao J, Chen Y, et al. Comparison of the ability of the PDD-ICG clearance test, CTP, MELD, and MELD-Na to predict short-term and medium-term mortality in patients with decompensated hepatitis B cirrhosis. Eur J Gastroenterol Hepatol 2016 Apr;28(4):444-8 (PMID: 26649802).

13. Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Medicine (Baltimore) 2016 Feb;95(8):e2877 (PMID: 26937922).

14. Xavier SA, Vilas-Boas R, Boal Carvalho P, Magalhães JT, Marinho CM, Cotter JB. Assessment of prognostic performance of Albumin-Bilirubin, Child-Pugh, and Model for End-stage Liver Disease scores in patients with liver cirrhosis complicated with acute upper gastrointestinal bleeding. Eur J Gastroenterol Hepatol 2018 Jun; 30(6):652-8 (PMID: 29438135).

15. Wang W, Wang Y, Qu C, et al. The RNA genome of hepatitis E virus robustly triggers an antiviral interferon response. Hepatology 2018 Jun;67(6):2096-112 (PMID: 29194722).

16. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol 2013 Mar;13(3): 159-75 (PMID: 23435331).

17. Kwon JH, Jang JW, Kim YW, et al. The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis. BMC Gastroenterol 2015 Oct 23;15:146 (PMID: 26498833).

18. Nagai S, Abouljoud MS, Kazimi M, Brown KA, Moonka D, Yoshida A. Peritransplant lymphopenia is a novel prognostic factor in recurrence of hepatocellular carcinoma after liver transplantation. Transplantation 2014 Mar 27;97(6):694-701 (PMID: 24637 868).

19. Fernández-Ruiz M, López-Medrano F, Romo EM, et al. Pretransplant lymphocyte count predicts the incidence of infection during the first two years after liver transplantation. Liver Transpl 2009 Oct;15(10):1209-16 (PMID: 19790140).

20. Halazun KJ, Aldoori A, Malik HZ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol 2008 Jan;34(1):55-60(PMID: 17448623).

21. Alkhouri N, Morris-Stiff G, Campbell C, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2012 Feb;32(2):297-302 (PMID: 22097893).

22. Muller I, Munder M, Kropf P, Hansch GM. Polymorphonuclear neutrophils and T lymphocytes: strange bedfellows or brothers in arms? Trends Immunol 2009 Nov;30(11):522-30 (PMID: 19775 938).

23. Biyik M, Ucar R, Solak Y, et al. Blood neutrophil-to-lymphocyte ratio independently predicts survival in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2013 Apr;25(4):435-41 (PMID: 23249602).

24. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol 2011 Oct 10;11(11):762-74 (PMID: 21984070).

25. Lin CY, Tsai IF, Ho YP, et al. Endotoxemia contributes to the immune paralysis in patients with cirrhosis. J Hepatol 2007 May; 46(5):816-26 (PMID: 17328986).

26. Berry PA, Antoniades CG, Carey I, et al. Severity of the compensatory anti-inflammatory response determined by monocyte HLA-DR expression may assist outcome prediction in cirrhosis. Intensive Care Med 2011 Mar;37(3):453-60 (PMID: 21161643).

27. Berres ML, Schnyder B, Yagmur E, et al. Longitudinal monocyte human leukocyte antigen-DR expression is a prognostic marker in critically ill patients with decompensated liver cirrhosis. Liver Int 2009 Apr;29(4):536-43 (PMID: 18795898).

28. Nilles KM, Flamm SL. Thrombocytopenia in Chronic Liver Disease: New Management Strategies. Clin Liver Dis 2020 Aug; 24 (3):437-51 (PMID: 32620282).

29. Nwokediuko SC, Ibegbulam O. Quantitative Platelet Abnormalities in Patients With Hepatitis B Virus-Related Liver Disease. Gastroenterology Res 2009 Dec;2(6):344-9 (PMID: 27990204).

30. Bashour FN, Teran JC, Mullen KD. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. Am J Gastroenterol 2000 Oct;95(10):2936-9 (PMID: 11051371).

31. Dou J, Lou Y, Wu J, Lu Y, Jin Y. Thrombocytopenia in patients with hepatitis B virus-related chronic hepatitis: Evaluation of the immature platelet fraction. Platelets 2014;25(6):399-404 (PMID: 24047408).

32. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of “hypersplenic” thrombocytopenia. J Clin Invest 1966 May;45(5):645-57 (PMID: 5327481).

33. Hudzik B, Szkodziński J, Lekston A, Gierlotka M, Poloński L, Gąsior M. Mean platelet volume-to-lymphocyte ratio: a novel marker of poor short- and long-term prognosis in patients with diabetes mellitus and acute myocardial infarction. J Diabetes Complications 2016 Aug;30(6):1097-102 (PMID: 27138871).