Received: 28 July 2020 | Revised: 11 August 2020 | Accepted: 13 August 2020

DOI: 10.1002/jcla.23556

RESEARCH ARTICLE

WILEY

Platelet-to-white blood cell ratio: A novel and promising prognostic marker for HBV-associated decompensated cirrhosis

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Abstract

Aim: The present study aimed to investigate associations of the platelet-to-white blood cell ratio (PWR)—a novel hematological indicator of inflammatory responses—with 30-day outcomes in patients with HBV-associated decompensated cirrhosis (HBV-DeCi).

Methods: We recruited 131 patients with HBV-DeCi for this retrospective study and extracted baseline clinical data and laboratory characteristics from medical records. Univariate and multivariate analyses were performed to determine major factors influencing 30-day mortality. Area under the receiver operating characteristic curve analyses was performed to compare the predictive values of prognostic markers.

Results: During the 30-day follow-up period, 15 patients died. The PWR was significantly different between nonsurvivors and survivors. Lower PWR was found to be associated with an increased risk of mortality, and PWR was found to be an independent predictor of mortality in patients with HBV-DeCi.

Conclusions: Our results demonstrate that low PWR may be a predictor of poor prognosis in patients with HBV-DeCi, and this factor may be a useful supplement to standard approaches to enable effective management of these patients.

KEYWORDS

decompensated cirrhosis, hepatitis B virus, mortality, platelet-to-white blood cell ratio

1 | INTRODUCTION

Hepatitis B virus (HBV) infection remains a major cause of liver cirrhosis in China.[1] Every year, approximately 3% of cases of compensated cirrhosis progress to decompensated cirrhosis, which is characterized by various complications and an estimated 5-year mortality rate of up to 85%.[2-4] The identification of accurate, objective, and user-friendly prognostic markers is essential to guide management strategies for patients with HBV-associated decompensated cirrhosis (HBV-DeCi).

There is increasing evidence that the hematological parameters, such as neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, red cell distribution width, and mean platelet volume, are reliable inflammatory markers and prognostic indices in a variety of medical conditions like cerebral hemorrhage,[5,6] major cardiac events,[7,8] brain infarct,[9,10] cancers,[11] sepsis, and infectious pathologies.[12] In recent years, a strong interest has been drawn to these indices, given that they may provide independent information on pathophysiology, risk stratification, and optimal management. Their low-cost and consequent wide and easy availability in daily clinical practice have made them very

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popular in the laboratory testing. Several studies have demonstrated the critical role of the inflammatory response in the pathogenesis of advanced cirrhosis and its association with worse outcomes.[13,14] Recently, hematological markers for the prognosis of different liver diseases have become an area of research focus. The neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, red cell distribution width, and mean platelet volume have been suggested to be inflammatory markers, and their prognostic value in the context of HBV-associated liver diseases has been verified.[15-17] There is increasing evidence that these hematological indicators play a crucial role in HBV-associated liver disease and thus are considered prognostic indicators for this condition.[18] The platelet-to-white blood cell ratio (PWR) is a recently identified hematological indicator of inflammation reported to have utility as a predictor of short-term postoperative outcomes in patients undergoing surgery for renal malignancy.[19] Chen *et al* found that the PWR can be used to predict outcomes in patients with ischemic stroke with intravenous thrombolysis.[20] Furthermore, PWR has been suggested to be a predictor of adverse outcomes in patients with HBV-associated liver failure.[21] However, the role of PWR in HBV-DeCi is unclear. Therefore, the present study aimed to investigate whether PWR is a predictive marker for mortality in patients with HBV-DeCi.

2 | MATERIALS AND METHODS

2.1 | Patients

We retrospectively recruited all patients diagnosed with HBV-DeCi who were treated at our hospital from May 2016 to June 2018. Liver decompensation was defined according to the presence of ascites, hepatic encephalopathy, and/or variceal bleeding at the time of enrollment.[14] Exclusion criteria were as follows: hematological diseases, malignancy, chronic liver disease (eg, viral infection other than HBV or drug-induced liver injury, autoimmune hepatitis, alcoholic liver disease), or undergoing immunosuppressive therapy in the 3 months before the study period. The 30-day survival rate was determined from the date of death, which was obtained from medical records.

The study and all its protocols were approved by the Ethical Committee of the Shengzhou People's Hospital.

2.2 | Data collection

Demographic and laboratory data of the patients were obtained by review of medical records. Recorded data included age; gender; complications; total protein; albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, blood urea nitrogen, and hemoglobin levels; international normalized ratio; white blood cell count (WBC); and platelet count (PLT). The PWR was defined as PLT divided by WBC. Liver function was evaluated at the time of admission using the Model for End-Stage Liver Disease (MELD) score, which was calculated as previously described.[22]

2.3 | Statistical analysis

All continuous data are expressed as mean and standard deviation, median, and interquartile range. Categorical data are presented as count. Differences between variables were analyzed using Student's *t* test, Mann-Whitney *U* tests, or chi-squared test as appropriate.

TABLE 1 Patient characteristics at baseline

	All patients (n = 131)	Surviving patients (n = 116)	Nonsurviving patients (n = 15)	*P*
Gender (female/male)	28/103	25/91	3/12	.844
Age (years)	52.8 ± 11.4	52.8 ± 12.3	52.3 ± 12.6	.865
Total protein (g/L)	61.3 ± 8.1	61.4 ± 7.9	60.3 ± 9.5	.609
Albumin (g/L)	30.2 ± 5.9	30.2 ± 6.0	30.0 ± 5.6	.920
Alanine aminotransferase (U/L)	33.0 (17.3-55.8)	33.0 (16.5-61.0)	37.0 (23.3-48.0)	.871
Aspartate aminotransferase (U/L)	49.0 (28.8-79.3)	49.0 (28.0-79.0)	49.0 (33.0-77.5)	.937
Serum creatinine (μmol/L)	73.0 (60.3-88.0)	73.0 (60.0-84.0)	100.0 (62.3-118.0)	.097
Total bilirubin (μmol/L)	58.0 (25.0-129.3)	45.0 (22.51-117.0)	90.0 (75.5-186.5)	.006
Blood urea nitrogen (μmol/L)	5.70 (4.30-7.88)	5.50 (4.20-7.40)	9.0 (7.15-13.0)	.002
INR	1.51 ± 0.41	1.46 ± 0.36	1.88 ± 0.58	<.001
WBC ($\times 10^9$/L)	4.4 (3.0-5.9)	4.2 (3.0-5.6)	5.1 (4.6-9.5)	.007
PLT ($\times 10^9$/L)	70.0 (44.5-109.8)	70.0 (44.0-111.0)	63.0 (55.5-79.5)	.553
PWR	16.0 (10.9-26.1)	16.9 (12.2-26.5)	10.9 (7.0-14.5)	.005
Hemoglobin (g/L)	104.0 (90.0-121.0)	105.5 (90.5-121.5)	93.0 (84.3-110.3)	.105
MELD score	13.7 (9.0-18.2)	12.6 (8.4-17.2)	20.0 (18.1-22.3)	<.001

Note: Data are expressed as number, mean ± standard deviation, or median (interquartile range).

Abbreviations: INR, international normalized ratio; MELD, Model for End-stage Liver Disease; PLT, platelet; PWR, platelet-to-white blood cell ratio; WBC, white blood cell.

Spearman's correlation test was used to evaluate the correlation between PWR and MELD score. Univariate and multivariate stepwise logistic regression analyses were carried out to identify independent indicators of mortality. After reciprocal transformation of the PWR (1/PWR), a receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) calculated to assess the prognostic value. All statistical analyses were performed using SPSS 20 (SPSS Inc) or MedCalc version 12.7 (Mariakerke, Belgium). Differences with *P* values of <.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

We recruited 169 patients as potentially eligible. Of these, 38 patients were excluded: five because of the presence of malignancy, three who had autoimmune liver disease, four with HIV infection, ten who had superinfection with hepatitis A or C virus, eight who had alcoholic liver disease, six who were undergoing immunomodulatory therapy, and two who had blood-system diseases. Finally, 131 patients were enrolled for analysis. Baseline characteristics are summarized in Table 1. Negative correlations were found between MELD score and PWR ($r = -0.277$, $P = .001$) (Figure 1).

At 30 days after admission, 15 patients (11.5%) had died. The demographic and laboratory data are compared between nonsurvivors and survivors in Table 2. Blood urea nitrogen and total bilirubin levels, INR, WBC, and MELD score were significant higher among nonsurvivors; however, the PWR was much lower among nonsurvivors than survivors. The PLT was slightly lower among nonsurvivors than survivors, although this difference was not statistically significant. Total protein, albumin, alanine aminotransferase, aspartate aminotransferase, creatinine, and hemoglobin levels; mean age; and gender ratio were not significantly different between the two groups.

3.2 | Factors associated with mortality

Following univariate analysis, MELD score, WBC, and PWR were entered into multivariate logistic regression (all $P < .01$). As shown in Table 2, multivariate analysis revealed MELD score and PWR to be independent predictors of poor outcomes after adjusting for influences of the above factors. The ROC curves of MELD score and PWR to predict mortality are illustrated in Figure 2. The cutoff value of the MELD score was found to be 17.4, which had a sensitivity of 93.3% and specificity of 75.9%. For PWR, the cutoff value was 14.2 with a sensitivity of 73.3% and specificity of 63.8%. The predictive powers of MELD score and PWR for mortality were not significantly different, as indicated by the similar AUC values (0.830 for MELD score *vs* 0.721 for PWR; Z = 1.468, *P* = .142).

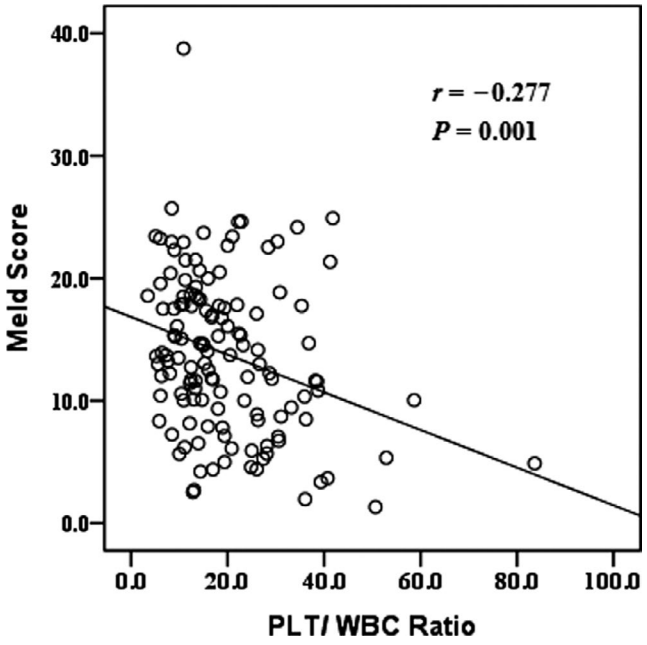

FIGURE 1 Scatter graphs illustrating the correlations between platelet-to-white blood cell ratio and Model for End-stage Liver Disease score in patients with hepatitis B virus-associated decompensated liver cirrhosis

3.3 | Baseline characteristics and factors related to platelet-to-white blood cell ratio

Participants were stratified into low- and high-PWR groups according to the cutoff value obtained by ROC analysis. Low PWR was found to be

TABLE 2 Logistic regression analysis to identify risk factors associated with mortality in patients with hepatitis B virus-associated decompensated liver cirrhosis

	Univariate			Multivariate		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Albumin (g/L)	0.995	0.909-1.090	.919			
MELD score	1.246	1.105-1.406	<.001	1.260	1.084-1.341	<.001
PWR	0.900	0.827	0.016	0.910	0.833-0.994	.037
WBC ($\times 10^9$/L)	1.253	1.067-1.472	.005			
PLT ($\times 10^9$/L)	0.997	0.988-1.006	.485			

Abbreviations: CI, confidence interval; MELD, Model for End-stage Liver Disease; PLT, platelet; PWR, platelet-to-white blood cell ratio; WBC, white blood cell.

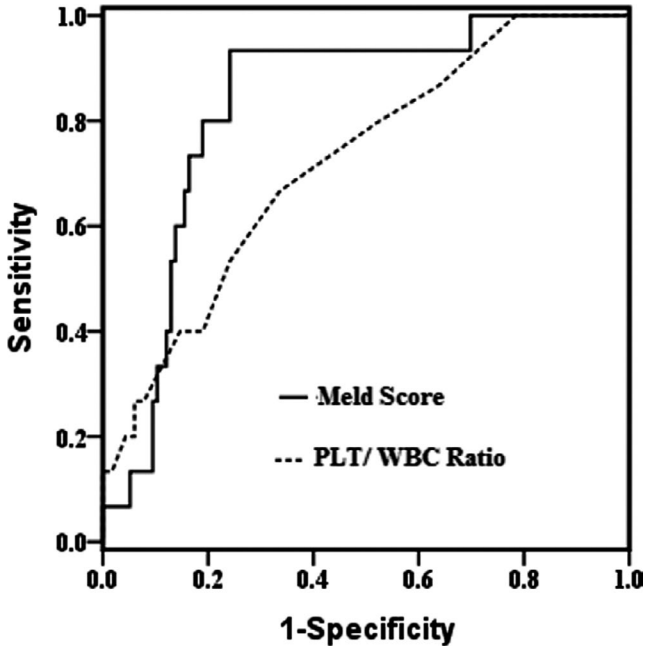

FIGURE 2 Receiver operating characteristic curves indicating the relative efficiencies of Model for End-stage Liver Disease score and platelet-to-white blood cell ratio for predicting 30-day mortality in patients with hepatitis B virus-associated decompensated liver cirrhosis

associated with higher WBC, INR, blood urea nitrogen, mortality rate, and MELD score but lower total protein and PLT (all $P < .05$) (Table 3).

4 | DISCUSSION

This study investigated the prognostic value of PWR for short-term mortality in patients with HBV-DeCi. Our results show that PWR is significantly correlated with MELD score, which indicates the severity of liver disease. Furthermore, we identified PWR as an independent predictor of mortality in patients with HBV-DeCi.

The MELD score is a validated prognostic modeling system that is used to predict 3-month mortality in patients with liver disease and widely used as a scoring system for organ allocation in liver transplantation.[22,23] However, approximately 15%-20% of candidates for liver transplantation are not well served by the MELD score because inflammation is not considered during calculation of the MELD score, although it can affect prognosis. Among our study population, nonsurviving participants had a lower PWR than surviving participants. In addition, PWR was found to be a surrogate predictor of 30-day mortality with predictive power similar to that of the MELD score. Calculation of the PWR requires assessment of two simple factors, which are more convenient than those used to

TABLE 3 Clinical data according to value of platelet-to-white blood cell ratio

	Low group (PWR ≤ 14.2, n = 53)	High group (PWR > 14.2, n = 78)	*P*
Gender (female/male)	11/42	17/61	.941
Age (years)	51.8 ± 11.7	53.5 ± 11.2	.394
Total protein (g/L)	59.2 ± 9.3	62.6 ± 6.9	.017
Albumin (g/L)	31.2 ± 3.5	30.9 ± 5.7	.114
Alanine aminotransferase (U/L)	35.0 (19.5-49.3)	30.5 (17.0-64.0)	.815
Aspartate aminotransferase (U/L)	50.5 (33.5-79.5)	49.0 (27.8-75.5)	.601
Total bilirubin (μmol/L)	74.0 (32.8-131.0)	42.0 (22.0-121.0)	.139
Blood urea nitrogen (μmol/L)	6.3 (4.6-10.1)	5.5 (4.2-7.2)	.036
INR	1.62 ± 0.45	1.44 ± 0.36	.012
Serum creatinine (μmol/L)	72.0 (58.8-88.5)	74.0 (62.0-88.0)	.718
WBC ($\times 10^9$/L)	4.70 (3.18-6.93)	4.05 (2.90-5.30)	.036
PLT ($\times 10^9$/L)	49.0 (28.0-62.3)	87.0 (66.0-134.0)	<.001
MELD score	15.2 (11.35-19.4)	12.1 (7.8-17.1)	.019
Hemoglobin (g/L)	102.0 (89.5-120.3)	104.5 (90.0-121.0)	.826
30-day mortality (yes/no)	11/42	4/74	.013

Note: Data are expressed as number, mean ± standard deviation, or median (interquartile range).
Abbreviations: PWR, platelet-to-white blood cell ratio; INR, international normalized ratio; WBC, white blood cell; PLT, platelet; MELD, Model for End-stage Liver Disease.

calculate the MELD score. Several hematological indices (including the mean platelet volume, red cell distribution width, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and so on) have been reported to be highly associated with prognosis in patients with HBV-DeCi.[24-28] Our study complements these previous studies by adding low PWR as a predictor of mortality in these patients.

The mechanistic relationship between PWR and prognosis in patients with HBV-DeCi remains to be elucidated. It is well known that inflammation plays a pivotal effect in the disease progression of HBV-DeCi. Among the study population of the present study, WBC was higher in nonsurvivors than survivors. High WBC suggests the presence of acute infection; hence, we can assume that elevated WBC reflects the severity of acute systemic inflammation following primary injury and influences the prognosis of patients with HBV-DeCi. In addition, our results indicate that the PLT is slightly higher in surviving patients with HBV-DeCi. Thrombocytopenia is common in patients with cirrhosis, and it has been recognized as a multifactorial phenomenon.[29,30] Accelerated platelet destruction or sequestration in enlarged spleen and suppressed thrombopoiesis because of reduced thrombopoietin production from diseased livers largely account for its pathophysiology.[31,32] Thrombopoietin is mainly produced in the liver and is an important regulator of platelet production,[33] and it has been reported to recover along with an increase in platelet count after liver transplantation [34]; therefore, we speculate that inadequate thrombopoietin production is due to impairment of liver cells, resulting in thrombocytopenia in patients with cirrhosis. Among the 131 patients in the present study, 96 (73.2%) had thrombocytopenia (PLT < 100×10^9/L). Xianghong et al reported PLT to be significantly correlated with survival among patients with cirrhosis[25,35]; however, neither WBC nor PLT alone was found to be predictors of mortality according to multivariate analysis in our study. There are two possible explanations for this result. First, either WBC or PLT is individual parameters and as such may be altered by several variables such as dehydration or blood specimen handling. The PWR, being a ratio, is more stable than individual blood parameters. Second, our study only included a limited number of patients. The present study reveals a significant negative correlation of PWR with MELD score and an association of lower PWR with higher in-hospital mortality, which suggests that lower PWR may be predictive of the severity and progression of liver injury among patients with HBV-DeCi. Therefore, we propose that low PWR might reflect the severity of liver injury and inflammation and may influence the prognosis of such patients. Further studies are needed to elucidate the underlying mechanism.

This study has some limitations that should be acknowledged. First, patients were retrospectively enrolled from a single center; therefore, selection bias may exist. Second, we did not assess whether PWR was correlated with other blood parameters (ie, mean platelet volume, red cell distribution width, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and so on) in patients with HBV-DeCi. Finally, inflammatory markers such as C-reactive protein and interleukin-6 were not analyzed. Evaluation of these markers may help to clarify the mechanism underlying our findings.

To the best of our knowledge, this is the first study to report the prognostic value of PWR in patients with HBV-DeCi. We conclude that PWR is an independent risk factor for mortality in such patients. This new score may provide valuable information to supplement conventional approaches of assessing disease condition. In patients with low PWR, more intensive medical therapy and control of mortality risk factors may be considered. Future studies are warranted to validate our findings.

ACKNOWLEDGMENTS

We would like to thank Amy Phillips, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

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How to cite this article: 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;34:e23556. https://doi.org/10.1002/jcla.23556