World Journal of Gastroenterology

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World J Gastroenterol 2023 June 21; 29(23): 3678-3687

DOI: 10.3748/wjg.v29.i23.3678

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Lymphocyte-to-white blood cell ratio is associated with outcome in patients with hepatitis B virus-related acute-on-chronic liver failure

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Desai GS, India; Kao JT, Taiwan; Papazafiropoulou A, Greece

Received: March 22, 2023
Peer-review started: March 22, 2023
First decision: April 14, 2023
Revised: April 28, 2023
Accepted: May 22, 2023
Article in press: June 21, 2023
Published online: June 21, 2023

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Abstract

BACKGROUND

The lymphocyte-to-white blood cell ratio (LWR) is a blood marker of the systemic inflammatory response. The prognostic value of LWR in patients with hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF) remains unclear.

AIM

To explore whether LWR could stratify the risk of poor outcomes in HBV-ACLF patients.

METHODS

This study was conducted by recruiting 330 patients with HBV-ACLF at the Department of Gastroenterology in a large tertiary hospital. Patients were divided into survivor and non-survivor groups according to their 28-d prognosis. The independent risk factors for 28-d mortality were calculated by univariate and multivariate Cox regression analyses. Patients were divided into low- and high-LWR groups according to the cutoff values. Kaplan-Meier analysis was performed according to the level of LWR.

RESULTS

During the 28-d follow-up time, 135 patients died, and the mortality rate was 40.90%. The LWR level in non-surviving patients was significantly decreased compared to that in surviving patients. A lower LWR level was an independent risk factor for poor 28-d outcomes (hazard ratio = 0.052, 95% confidence interval: 0.005-0.535). The LWR level was significantly negatively correlated with the Child-Turcotte-Pugh, model for end-stage liver disease, and Chinese Group on the Study of Severe Hepatitis B-ACLF II scores. In addition, the 28-d mortality was higher for patients with LWR < 0.11 than for those with LWR ≥ 0.11.

CONCLUSION
LWR may serve as a simple and useful tool for stratifying the risk of poor 28-d outcomes in HBV-ACLF patients.

Key Words: Lymphocyte-to-white blood cell ratio; Hepatitis B virus; Acute-on-chronic liver failure; Child-Turcotte-Pugh score; Model for end-stage liver disease score; Chinese Group on the Study of Severe Hepatitis B-Acute-on-chronic liver failure II score

Core Tip: This manuscript introduced a simple and effective inflammatory marker, the lymphocyte-to-white blood cell ratio (LWR). Our study found that a lower LWR level was associated with poor 28-d outcomes in hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF) patients. It may serve as a simple and useful tool for stratifying the risk of poor 28-d outcomes in HBV-ACLF patients, and it may be helpful in guiding a clinician to treatment allocation and assist in the prediction of prognosis.

Citation: Zhang Y, Chen P, Zhu X. Lymphocyte-to-white blood cell ratio is associated with outcome in patients with hepatitis B virus-related acute-on-chronic liver failure. *World J Gastroenterol* 2023; 29(23): 3678-3687
URL: https://www.wjgnet.com/1007-9327/full/v29/i23/3678.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i23.3678

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a life-threatening clinically complex syndrome characterized by high short-term mortality due to different combinations of multiorgan failures[1-3]. The main etiology of ACLF is hepatitis B virus (HBV) infection, with HBV-associated ACLF (HBV-ACLF) accounting for more than 70% of ACLF cases in most Asian countries[4]. The clinical characteristics of HBV-ACLF patients differ from those of alcoholic-related ACLF patients in Western countries, wherein coagulation and liver failure are the most common types of organ failure[5]. Early prediction of the prognosis of HBV-ACLF is important for clinical management and diminishing mortality. However, current score models are based on complicated assessments of organ failure. Therefore, it is necessary to identify an accurate and simple indicator to detect high-risk patients.

A growing body of research evidence suggests that HBV-ACLF is associated with systemic inflammation and immune paralysis[6,7]. In many recent studies, inflammation-related markers such as the platelet (PLT) to white blood cell ratio, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio have received increasing attention in clinical settings and are used in predicting the prognosis of HBV-ACLF[8-10]. The lymphocyte-to-white blood cell ratio (LWR) is a blood marker of the systemic inflammatory response. Studies have suggested that LWR has good prognostic value for patients with cancer, infective endocarditis and COVID-19[11-13]. However, the prognostic role of LWR in HBV-ACLF patients remains unclear. Therefore, our study aims to reveal whether LWR can risk-stratify poor prognosis in HBV-ACLF patients.

MATERIALS AND METHODS

Subjects

A total of 330 patients diagnosed with HBV-ACLF were retrospectively included from May 2014 to February 2021 at the Department of Gastroenterology, the First Affiliated Hospital of Nanchang University. The inclusion criteria were as follows: (1) Age ≥ 18 years; (2) Chronic liver disease due to HBV infection; and (3) HBV-ACLF diagnosed based on the diagnostic guidelines for liver failure established in 2019[14]. The exclusion criteria were as follows: (1) Coinfection with hepatitis A/C/D/E virus; (2) Other etiologies such as drugs, autoimmunity, alcohol, or toxins that may contribute to HBV-ACLF; (3) Complicated with hepatocellular carcinoma; (4) Human immunodeficiency virus infection; and (5) Loss to follow-up. The study was approved by the Institutional Review Board of the First Affiliated Hospital of Nanchang University.

Data collection

Demographic information and clinical data were comprehensively collected by searching medical

records. Laboratory blood tests were measured in the first 24-h period on admission. LWR was computed as the lymphocyte count (× 10^9/L) divided by the white blood cell count (× 10^9/L)[12]. The Child-Turcotte-Pugh (CTP), model for end-stage liver disease (MELD) and Chinese Group on the Study of Severe Hepatitis B-ACLF II (COSSHACLFII) scores were calculated as previously described[15-17]. All patients were followed from their diagnosis until either their death or the end of the 28-d follow-up period. The survival rates at 28 d were obtained from patients' medical records or by telephone calls with the patients or their kinsfolks.

Definitions

Chronic HBV infection was defined by the presence of hepatitis B surface antigen for > 6 mo[18]. HBV-ACLF was defined according to the Asian Pacific Association for the Study of the Liver criteria in 2019: (1) Serum bilirubin ≥ 5 mg/dL; (2) International normalized ratio (INR) ≥ 1.5 or prothrombin activity < 40%; (3) Complicated within 4 wk by clinical ascites and/or encephalopathy in patients with pre-existing chronic liver diseases (diagnosed or undiagnosed); and (4) High 28-d mortality[14].

Statistical analysis

Statistical analysis was performed using the SPSS 24.0 statistical package (SPSS Inc., Chicago, IL), R software version 4.1.0 (http://www.r-project.org/), and X-tile software (Version 3.6.1, Yale University, New Haven, CT, United States). Continuous variables were compared using the *t* test or the Mann-Whitney *U* test, whereas categorical variables were compared using the chi-square test or Fisher's exact test. Univariate analysis and multivariate Cox proportional hazards models were performed to identify whether LWR was related to poor outcomes. The optimal cutoff value of LWR was determined by using X-tile. The Kaplan-Meier survival curve was generated by the "survival" and "survminer" packages in R software. All statistical tests were two-sided with a statistical significance level set at *P* values < 0.05.

RESULTS

Baseline characteristics

The baseline characteristics of the patients are summarized in Table 1. A total of 330 patients with HBV-ACLF were recruited. In the cohort, the average age of patients was 49.68 ± 12.39 years, and approximately 83.9% of patients were male. The HBV-ACLF patients were divided into survivor and non-survivor groups according to the prognosis at 28 d. At follow-up, the age, prothrombin time (PT), INR, bilirubin, CTP score (CTPs), MELD score (MELDs), and COSSHACLFII score (COSSHACLFIIs) of the non-survivors were significantly higher than those of the survivors (*P* < 0.05). However, the PLT count and LWR level of the non-survivors were significantly lower than those of the survivors (*P* < 0.05). In addition, there were no significant differences in sex, costs, hemoglobin, albumin, creatinine, blood urea nitrogen (BUN), or serum Na between the non-survivor group and survivor group (*P* > 0.05).

Low LWR as an independent risk factor for mortality in patients with HBV-ACLF

The association between the LWR level and 28-d mortality is shown in Table 2. In univariate analysis, age, PLT, PT, hemoglobin, bilirubin, BUN, and LWR were significant factors for 28-d mortality (all *P* < 0.05). In multivariable analysis, the results showed that age, PT, bilirubin, and LWR were associated with short-term mortality [hazard ratio (HR) = 1.015, 95% confidence interval (CI): 1.001-1.030; HR = 1.028, 95%CI: 1.015-1.042; HR = 1.001, 95%CI: 1.000-1.003; HR = 0.052, 95%CI: 0.005-0.535, respectively].

Correlation between LWR levels and other score models

Next, we investigated the correlation between LWR levels and other score models, including CTPs, MELDs and COSSHACLFIIs. As shown in Figures 1A-C, LWR levels were significantly correlated with the CTPs, MELDs and COSSHACLFIIs (*r* = -0.29, *P* < 0.001; *r* = -0.31, *P* < 0.001; *r* = -0.49, *P* < 0.001, respectively).

Comparison of clinical data with different LWR levels

The median LMR of HBV-ACLF patients was 0.17 (0.11-0.23), and X-tile software was used to determine the optimal cutoff values for LWR for 28-d mortality. Consequently, the threshold of 0.11 enabled us to distinguish favorable and poor outcomes that were most significant in HBV-ACLF patients (Figure 2). HBV-ACLF patients were stratified into low LWR (LWR < 0.11) and high LWR (LWR ≥ 0.11) groups according to the cutoff values. As shown in Table 3, the patients in the group with LWR < 0.11 had an older age, lower PLT count, higher PT, higher INR, lower hemoglobin, lower albumin, higher creatinine, higher BUN, higher CTPs, higher MELDs, higher COSSHACLFIIs, and significantly shorter survival rate than those in the group with LWR ≥ 0.11.

Impact of LWR on the mortality of HBV-ACLF patients

As shown above, the patients with LWR < 0.11 had higher 28-d mortality than the high LWR group (*P* <

Table 1 Baseline characteristics of hepatitis B virus-acute on chronic liver failure patients

	All patients (*n* = 330)	Survivor patients (*n* = 195)	Non-survivor patients (*n* = 135)	*P* value
Age (yr)	49.68 ± 12.39	47.91 ± 12.12	52.23 ± 12.39	0.002
Male, *n* (%)	277 (83.9)	162 (83.1)	115 (85.2)	0.068
Costs (dollars)	10133.88 (5886.57-15955.07)	10734.72 (5958.59-16913.77)	9107.89 (5727.32-14945.14)	0.065
Ascites, *n* (%)				0.016
Mild	158 (47.9)	104 (53.3)	54 (40.0)	
Medium	102 (30.9)	59 (30.3)	43 (31.9)	
Severe	70 (21.2)	32 (16.4)	38 (28.1)	
PLT (10^9/L)	108.00 (72.75-144.25)	115.00 (82.00-148.00)	89.00 (57.00-138.00)	0.004
PT (s)	22.70 (19.30-29.25)	21.10 (18.90-25.20)	25.40 (21.80-32.80)	< 0.001
INR	2.01 (1.74-2.64)	1.88 (1.69-2.30)	2.4 (1.94-3.07)	< 0.001
Hemoglobin (g/L)	122.00 (102.00-136.00)	123.00 (107.00-137.00)	121.00 (94.00-135.00)	0.166
Bilirubin (μmol/L)	312.91 ± 135.85	299.15 ± 126.15	332.79 ± 146.96	0.027
Albumin (g/L)	31.40 (28.20-34.25)	31.50 (28.20-34.60)	31.10 (28.20-33.30)	0.151
Creatinine (μmol/L)	66.60 (57.08-84.73)	65.60 (57.00-81.00)	68.30 (57.50-91.90)	0.294
BUN (mmol/L)	4.00 (2.80-6.10)	4.00 (2.80-5.50)	4.10 (3.00-7.60)	0.074
Serum Na (mmol/L)	137.00 (133.30-139.10)	137.00 (133.20-139.00)	136.90 (133.30-139.10)	0.882
LWR	0.17 (0.11-0.23)	0.19 (0.12-0.25)	0.13 (0.08-0.20)	< 0.001
CTPs	11.00 (10.00-12.00)	11.00 (10.00-12.00)	12.00 (11.00-13.00)	< 0.001
MELDs	23.17 (20.03-27.27)	21.59 (18.86-25.46)	25.04 (21.78-29.10)	< 0.001
COSSHACLFIIs	7.18 (6.54-8.12)	6.80 (6.30-7.37)	7.95 (7.20-8.70)	< 0.001

PLT: Platelet; PT: Prothrombin time; INR: International normalized ratio; BUN: Blood urea nitrogen; LWR: Lymphocyte-to-white blood cell ratio; CTPs: Child-Turcotte-Pugh score; MELDs: Model for end-stage liver disease score; COSSHACLFIIs: Chinese group on the study of severe Hepatitis B-Acute-on-chronic liver failure II score.

0.05). To confirm the association of the LWR level and 28-d outcomes in detail, Kaplan-Meier analysis was performed to assess LWR in HBV-ACLF patients, and patients with low LWR levels had a worse outcome than those with high LWR levels (Figure 3).

DISCUSSION

In our study, we found that a low LWR level was an independent prognostic factor related to poor 28-d outcomes in patients with HBV-ACLF. Patients with LWR < 0.11 had higher 28-d mortality than those with high LWR levels.

Systemic inflammation plays an important role in the development of HBV-ACLF[19]. The activation of inflammatory cytokines causes organ hypoperfusion and systemic circulatory dysfunction, which increase the activation of coagulation, tissue microthrombosis, and the development of organ failure [20]. Many studies have indicated that the inflammatory response can be reflected by inflammatory markers such as lymphocytes, white blood cells, PLTs, and neutrophils[21,22]. The combination of these inflammatory markers, such as the neutrophil-lymphocyte ratio (NLR), platelet-to-white blood cell ratio (PWR), and LWR, has been confirmed as a prognostic marker in a variety of liver diseases. Bernsmeier *et al*[23] reported that the NLR was an independent risk factor in patients with acute decompensation (AD) cirrhosis. Kim *et al*[22] included 1670 AD patients from a prospective cohort and found that patients with a PWR ≤ 12.1 had a higher 28-d mortality than those with a PWR > 12.1, and a lower PWR level was a prognostic factor for 28-d adverse outcomes. Overall, these inflammation-based markers could be useful for stratifying the severity of liver disease.

Our study found that LWR levels were significantly decreased in non-survivor HBV-ACLF patients, and low LWR levels were an independent risk factor for 28-d mortality in HBV-ACLF patients. The decreased LWR levels may reflect an enhanced inflammatory response and/or impaired immune

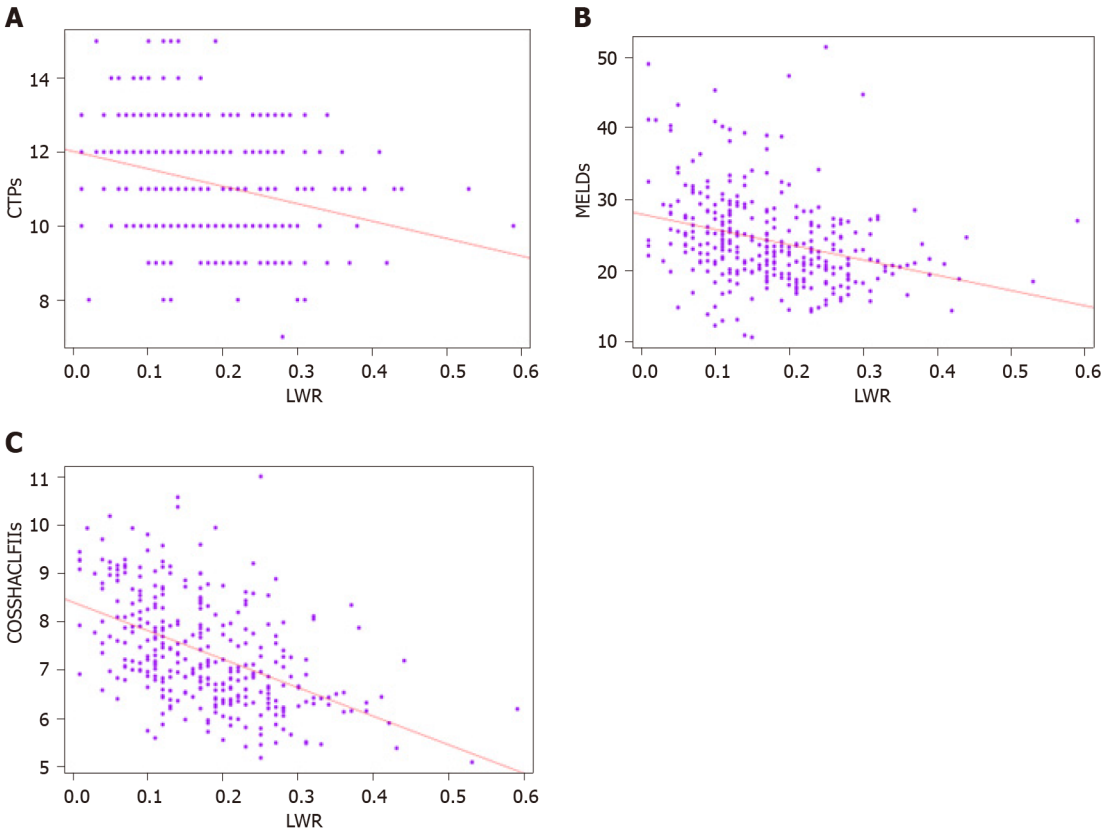

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Figure 1 Scatter plot illustrating the correlation. A: Scatter plot illustrating the correlation between lymphocyte-to-white blood cell ratio (LWR) and Child-Turcotte-Pugh scores; B: Scatter plot illustrating the correlation between LWR and model for end-stage liver disease scores; C: Scatter plot illustrating the correlation between LWR and Chinese group on the study of severe Hepatitis B-Acute-on-chronic liver failure II scores. CTPs: Child-Turcotte-Pugh score; MELDs: Model for end-stage liver disease score; COSSHACLFIIs: Chinese group on the study of severe Hepatitis B-Acute-on-chronic liver failure II score; LWR: Lymphocyte-to-white blood cell ratio.

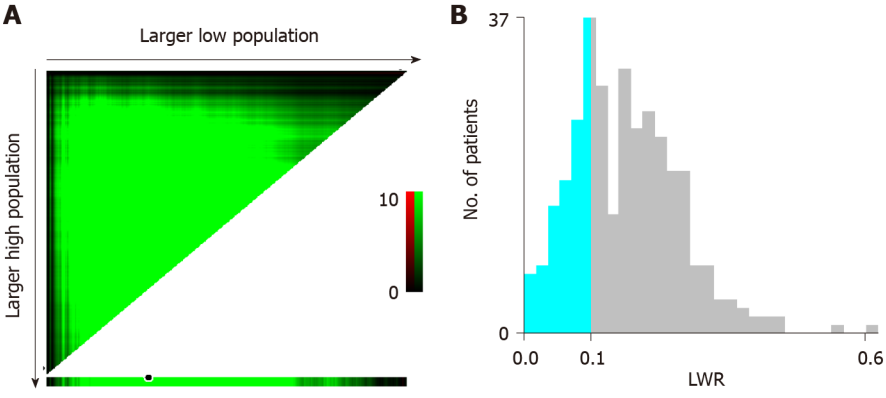

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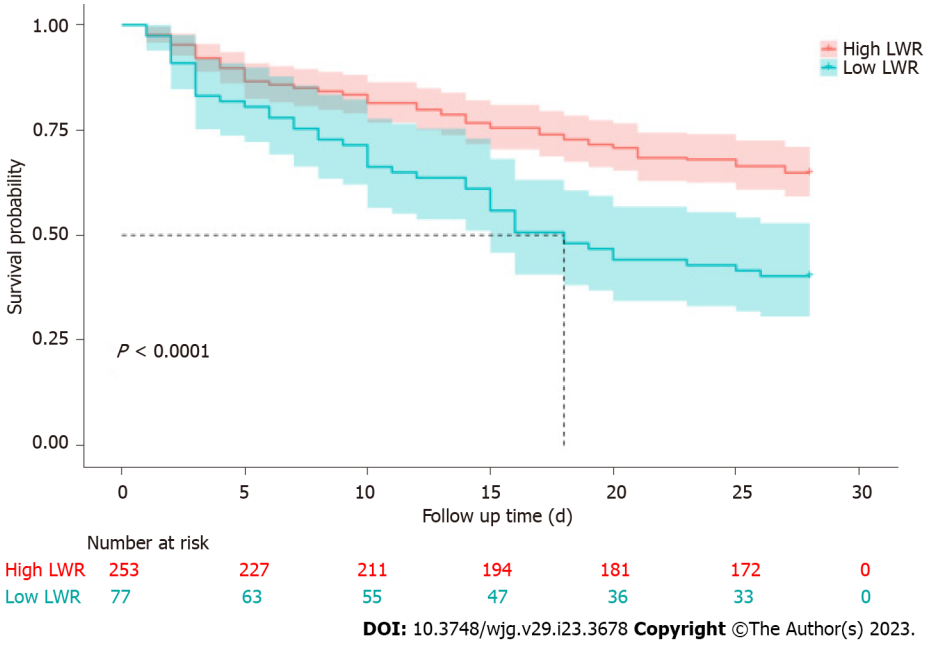
Figure 2 Analysis of lymphocyte-to-white blood cell ratio by using X-tile. A: The data on the horizontal ordinate increase from the left to the right, defined as the larger low population. The data on the vertical ordinate decrease from the top to the bottom, defined as the larger high population; B: The prognostic significance of lymphocyte-to-white blood cell ratio for hepatitis B virus-acute on chronic liver failure patients was determined by using a statistical algorithm in X-tile to calculate the most efficient cutoff point. LWR: Lymphocyte-to-white blood cell ratio.

response, which may explain the results. A previous study confirmed that lymphocytes play a critical role in the body's immune defense functions, immune response, and immune surveillance[12]. The elevated white blood cell count showed severe systemic inflammation, which was related to the prognosis of HBV-ACLF patients[24]. In addition, a recent study indicated that a low LWR level was an independent factor for poor outcomes in patients with decompensated liver cirrhosis, and the cut off value of LWR for 1 mo was 0.163. Patients with LWR < 0.163 had higher mortality than patients with LWR > 0.163[25]. Similar to this study, our research found that the cutoff value of LWR was 0.11, and

Table 2 Univariate and multivariate Cox regression analyses in hepatitis B virus-acute on chronic liver failure patients (*n* = 330)

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.021 (1.007-1.035)	0.002	1.015 (1.001-1.030)	0.037
Male sex	1.202 (0.747-1.932)	0.448		
PLT (10^9/L)	0.997 (0.994-0.999)	0.046		
PT (s)	1.020 (1.011-1.030)	< 0.001	1.028 (1.015-1.042)	< 0.001
INR	1.042 (0.993-1.094)	0.093		
Hemoglobin (g/L)	0.993 (0.987-0.999)	0.027		
Bilirubin (μmol/L)	1.001 (1.000-1.003)	0.025	1.001 (1.000-1.003)	0.041
Albumin (g/L)	0.968 (0.933-1.005)	0.091		
Creatinine (μmol/L)	1.001 (1.000-1.001)	0.179		
BUN (mmol/L)	1.036 (1.014-1.058)	0.001		
Serum Na (mmol/L)	1.001 (0.999-1.003)	0.249		
LWR	0.011 (0.001-0.088)	< 0.001	0.052 (0.005-0.535)	0.013

In univariate analysis, $P < 0.1$ were subjected to multivariate analysis and was indicated in bold; in multivariate analysis, $P < 0.05$ was considered significant and was indicated in bold. CI: Confidence interval; HR: Hazard ratio; PLT: Platelet; PT: Prothrombin time; INR: International normalized ratio; BUN: Blood urea nitrogen; LWR: Lymphocyte-to-white blood cell ratio.



DOI: 10.3748/wjg.v29.i23.3678

Figure 3 Kaplan-Meier analysis of 28-d overall survival. The mortality rate was higher in patients with lymphocyte-to-white blood cell ratio (LWR) < 0.11 than in patients with LWR ≥ 0.11. LWR: Lymphocyte-to-white blood cell ratio.

patients with LWR < 0.11 had higher mortality than patients with LWR ≥ 0.11, and the results showed a significant negative correlation between LWR and CTPs, MELDs and COSSHACLFIIs. There are several limitations in our study. First, this is a single-center and retrospective study, which may cause selection biases. Second, lymphocytes and white blood cells were not tested dynamically during follow-up.

CONCLUSION

In conclusion, LWR is easily accessible and conveniently calculated, and it might be a good marker for

Table 3 Clinical characteristics between low and high lymphocyte-to-white blood cell ratio groups in hepatitis B virus-acute on chronic liver failure patients

	Low LWR level (*n* = 77)	High LWR level (*n* = 253)	*P* value
Age (yr)	52.99 ± 12.57	48.67 ± 12.19	0.007
Male, *n* (%)	59 (76.6)	218 (86.2)	0.046
Costs (dollars)	7625.18 (3899.37-12070.55)	10984.59 (6639.92-16693.10)	< 0.001
Ascites, *n* (%)			0.007
Mild	25 (32.5)	133 (52.6)	
Medium	29 (37.7)	73 (28.9)	
Severe	23 (29.9)	47 (18.6)	
PLT (10^9/L)	86.00 (55.50-138.50)	110.00 (79.50-145.50)	0.039
PT (s)	23.20 (19.70-33.50)	22.40 (19.20-28.00)	0.016
INR	2.13 (1.76-3.11)	1.99 (1.73-2.54)	0.018
Hemoglobin (g/L)	109.00 (89.50-125.50)	125.00 (108.00-139.00)	< 0.001
Bilirubin (μmol/L)	331.52 ± 153.46	307.25 ± 129.82	0.170
Albumin (g/L)	30.10 (26.30-32.50)	31.80 (28.85-34.55)	< 0.001
Creatinine (μmol/L)	82.40 (58.40-126.10)	64.80 (56.85-77.95)	< 0.001
BUN (mmol/L)	7.00 (4.00-11.10)	3.70 (2.70-5.20)	< 0.001
Serum Na (mmol/L)	135.30 (131.50-139.05)	137.20 (133.90-139.10)	0.086
CTPs	12.00 (11.00-13.00)	11.00 (10.00-12.00)	< 0.001
MELDs	25.79 (22.52-30.91)	22.44 (19.55-26.13)	< 0.001
COSSHACLFIIs	8.11 (7.26-9.06)	6.94 (6.40-7.79)	< 0.001
28-d mortality, *n* (%)	46 (59.7)	89 (35.2)	< 0.001

PLT: Platelet; PT: Prothrombin time; INR: International normalized ratio; BUN: Blood urea nitrogen; LWR: Lymphocyte-to-white blood cell ratio; CTPs: Child-Turcotte-Pugh score; MELDs: Model for end-stage liver disease score; COSSHACLFIIs: Chinese group on the study of severe Hepatitis B-Acute-on-chronic liver failure II score.

identifying the risk of poor outcomes in HBV-ACLF patients. Therefore, our findings can help clinicians intervene in high-risk patients as early as possible.

ARTICLE HIGHLIGHTS

Research background

The lymphocyte-to-white blood cell ratio (LWR) is a blood marker that reflects the systemic inflammatory response. The prognostic value of the LWR remains unclear in hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF) patients.

Research motivation

It is necessary to find an easy and effective marker that can reflect the prognosis in HBV-ACLF patients, so we explored whether LWR can risk-stratify poor prognosis in HBV-ACLF patients.

Research objectives

This study aimed to investigate whether LWR could be an easy and useful marker that can identify the risk of poor outcomes in HBV-ACLF patients.

Research methods

A total of 330 HBV-ACLF patients were included in this study, and patients were divided into survivor and non-survivor groups according to 28-d outcome. Univariate and multivariate Cox regression analyses were performed to select independent risk factors for 28-d mortality. The correlation test was

performed to evaluate the correlation between LWR and Child-Turcotte-Pugh score (CTPs), model for end-stage liver disease score (MELDs), and Chinese Group on the Study of Severe Hepatitis B-ACLF II score (COSSHACLFIIs). The cutoff value of LWR was calculated by X-tile software, and Kaplan-Meier analysis was performed to assess the association of the LWR level and 28-d outcomes in HBV-ACLF patients.

Research results

Low LWR was an independent risk factor for 28-d mortality in patients with HBV-ACLF (hazard ratio = 0.052, 95% confidence interval: 0.005-0.535), and LWR levels were significantly negatively correlated with CTPs, MELDs and COSSHACLFIIs. Moreover, the patients with low LWR levels had a higher 28-d mortality than those with high LWR levels.

Research conclusions

LWR is a simple, useful, and effective marker that could stratify the risk of 28-d adverse outcomes in HBV-ACLF patients.

Research perspectives

Further large-sample and multicenter prospective studies should be conducted to verify and confirm the prognostic value of the LWR.

FOOTNOTES

Author contributions: Zhang Y and Chen P contributed equally to this study, and they wrote the original draft; Zhang Y designed this study; Chen P analyzed the data; Zhu X critically revised the manuscript; and all authors have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 81960120 and 81660110; the Postgraduate Innovation Special Foundation of Jiangxi Province, No. YC2022-B052; and "Gan-Po Talent 555" Project of Jiangxi Province, No. GCZ (2012)-1.

Institutional review board statement: The study was reviewed and approved by the First Affiliated Hospital of Nanchang University Institutional Review Board (Approval No. IIT2021009).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Data can be acquired from the corresponding author.

Country/Territory of origin: China

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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