Observational Study

Medicine®

OPEN

Red cell distribution width-to-lymphocyte ratio

A novel predictor for HBV-related liver cirrhosis

Xueyan Zhang, MD[a], Dawei Wang, BS[b], Zhongming Chen, BS[c], Naizhou Guo, BS[c], Wei Wang, BS[c], Cunquan Xiong, MD[a], Jun Liu, MD[d,*], Yinhong Yue, MD[e,*], Mingzhong Sun, BS[f,*]

Abstract

To evaluate the diagnostic power of red cell distribution width-to-lymphocyte ratio (RLR) for HBV-related liver cirrhosis via a retrospective cohort study.

Seven hundred fifty healthy controls, 327 chronic hepatitis B (CHB) patients, and 410 patients with HBV-related liver cirrhosis (HBV-LC) were enrolled in this study. RLR, lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW), AST to platelet ratio index (APRI), and fibrosis index based on the 4 factors (FIB-4) were compared between the 3 groups. The predictive powers of RLR and RDW for HBV-related liver cirrhosis and patient prognosis were evaluated using AUROC.

Patients with HBV-related liver cirrhosis had higher RLR, FIB-4, NLR, RDW, APRI, and lower LMR compared with the control and CHB groups. RLR in the HBV-LC group was significantly higher than both CHB and control groups (both $P < .05$). While RLR in the CHB group was also higher than the control group, the difference was not statistically significant ($P > .05$). The AUROC of RLR for predicting HBV-related liver cirrhosis was 0.87, and was superior to RDW (0.81), FIB-4 (0.79), and APRI (0.60). With an optimized cut-off value (10.87), RLR had the highest sensitivity (0.88) and specificity (0.72), and was superior to RDW (0.86, 0.64), FIB-4 (0.80, 0.65), and APRI (0.85, 0.48) as a biomarker. For all 3 groups, RLR was negatively correlated (all $P < .05$) with serum platelet (PLT) and was positively correlated (all $P < .05$) with FIB-4 and APRI. There was no significant statistical difference in RLR for patients in HBV-LC group who had different prognosis ($P > .05$).

The RLR, a routinely available, inexpensive, and easily calculated measure, can be used as a predictor of HBV-related liver cirrhosis, but not as a predictor of prognosis for patients with liver cirrhosis. Use of RLR may reduce the need for frequent liver biopsies in CHB patients.

Abbreviations: APRI = aspartate aminotransferase-to-platelet ratio index, CHB = chronic hepatitis B, FIB-4 = fibrosis index based on the 4 factors, HBV = hepatitis B virus, HBV-LC = HBV-related liver cirrhosis, INR = international normalized ratio, LMR = lymphocyte monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, RDW = red cell distribution width, RLR = red cell distribution width-to-lymphocyte ratio.

Keywords: chronic hepatitis B, HBV-related liver cirrhosis, novel predictor, red cell distribution width-to-lymphocyte ratio

Editor: Jen-Jung Pan.

XZ, DW, and ZC are equal contributors.

This research was supported by the Youth Medical Talent of Jiangsu Province (grant no. QNRC2016163) to JL.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Public Health, Jiangsu Vocational College of Medicine, [b] Department of Infectious Disease, The Second People's Hospital of Yancheng City, [c] Department of Laboratory Medicine, The First People's Hospital of Yancheng City, Yancheng, [d] Department of Laboratory Medicine, The Fifth Peoples Hospital of Wuxi, Wuxi, [e] Department of Urology Surgery, The First People's Hospital of Yancheng City, [f] Department of Laboratory Medicine, Affiliated Yancheng Hospital, School of Medicine, Southeast University, Yancheng, Jiangsu, China.

[*] Correspondence: Yinhong Yue, Department of Urology Surgery, The First People's Hospital of Yancheng City, Yancheng 224005, Jiangsu, China (e-mail: 2188347533@qq.com); Jun Liu, Department of Laboratory Medicine, The Fifth People's Hospital of Wuxi, Affiliated to Jiangnan University, Wuxi 214005, Jiangsu, China (e-mail: 15949255828@126.com); Mingzhong Sun, Department of Laboratory Medicine, Affiliated Yancheng Hospital, School of Medicine, Southeast University, Yancheng 224001, Jiangsu, China (e-mail: 15189300678@163.com).

How to cite this article: Zhang X, Wang D, Chen Z, Guo N, Wang W, Xiong C, Liu J, Yue Y, Sun M. Red cell distribution width-to-lymphocyte ratio: a novel predictor for HBV-related liver cirrhosis. Medicine 2020;99:23(e20600).

Received: 30 March 2019 / Received in final form: 2 May 2020 / Accepted: 6 May 2020

http://dx.doi.org/10.1097/MD.0000000000020600

1. Introduction

Globally, chronic hepatitis B virus (HBV) infection is still a challenging problem that can lead to chronic active hepatitis, liver cirrhosis, and hepatocellular carcinoma.[1,2] An accurate diagnosis of liver fibrosis in chronic hepatitis B (CHB) patients is not only crucial to determining if and when it is necessary to initiate antiviral therapy, but is also an essential factor for determining prognosis.[3,4]

Currently, taking liver biopsies are still the gold standard for diagnosis of cirrhosis. However, this method has several problems associated with it such as the invasive nature of the procedure, sampling error, disagreements in diagnosis between different pathologists, and complications caused by the use of a needle for biopsy.[5,6] However, CHB patients require regular monitoring of the amount of liver fibrosis to detect potential development of hepatocellular carcinoma and potential complications including death associated with CHB. As such, many studies focus on the use of noninvasive techniques for diagnosis of liver cirrhosis. There are 3 common noninvasive methods, each with its own pros and cons.[7] Imaging is widely used to evaluate liver fibrosis.[8] Generally, results obtained by imaging show significant correlation with that obtained by liver histology. However, some imaging methods require special instruments and specialists for interpretation. The second method is laboratory testing for hyaluronic acid, collagen, laminin, and YKL-40. However, these biochemical tests are not routinely available. Composite diagnostic panels are also being used and can be calculated from routine laboratory data. Such measures include aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (also known as AAR), and AST to platelet (PLT) ratio index (APRI).[9,10] Among the measures that are currently being used, fibrosis index based on 4 factors (FIB-4) and APRI are particularly useful for diagnosis of liver cirrhosis. Fukui et al comprehensively described diagnosis of liver cirrhosis by using a combination of measurements of blood markers and imaging modalities, but also asserted that ideally, a single noninvasive method for diagnosis should be developed.[11,12]

Some measures have recently been developed for indirectly diagnosing liver cirrhosis and assessing prognosis. Low lymphocyte-to-monocyte ratio (LMR) is an independent biomarker that predicts mortality in patients with hepatocellular carcinoma after curative resection.[13] Red cell distribution width (RDW) can also potentially be used to assess the severity of HBV-related liver disease.[14] Neutrophil-to-lymphocyte ratio (NLR) is predictive of early mortality in patients with HBV-related decompensated cirrhosis.[15] However, there are few studies on comparing the diagnostic value of using LMR, NLR, RDW, APRI, and FIB-4 for CHB-related liver cirrhosis. Inefficient immune clearance of HBV leads to CHB and increases the risk of liver cirrhosis.[16] Liver injury mediated by the immune system occurs during HBV infection,[17] and previous work by our group has shown that lymphocyte number is decreased during CHB and cirrhosis. Several studies have shown that RDW increases during liver cirrhosis.[14,18,19] We hypothesized that RDW-lymphocyte ratio (RLR), or a combination of these 2 parameters, might be a more powerful diagnostic tool than either parameter alone. Thus, the aims of this study were to evaluate and compare the use of RDW and RLR in the diagnosis of HBV-related liver cirrhosis.

2. Materials and methods

2.1. Subjects

We enrolled a total of 737 hepatitis B patients (M: 438, F: 299, aged 23–90 years) at the First People's Hospital of Yancheng City between January 2014 and July 2018 and conducted a retrospective study. All participants had their diagnoses confirmed by liver biopsy. Among them, 410 patients were diagnosed with HBV-related liver cirrhosis (HBV-LC) and 327 were diagnosed with chronic hepatitis B (CHB). An additional 30 HBV-LC patients and 30 CHB patients were enrolled to validate the diagnostic power of 2 parameters (RLR and RDW) in this study between August 2018 and February 2019. All patients enrolled in this study met the criteria for HBV-LC and CHB according to the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL).[20] The study exclusion criteria were: chronic liver disease of other etiology, coinfection with HCV or HEV; diagnosis of alcoholic or nonalcoholic fatty liver disease, thyroid disease, coronary heart disease treated with anticoagulants, coinfection with tuberculosis, hematological disease, renal and infectious diseases, patients with diabetes, hypertension, smoking etc. and patients with incomplete sets of data. Seven hundred fifty healthy individuals were enrolled as controls from the physical examination center of the same institution.

2.2. Ethics statement

This study was approved by the Ethics Committee of the First People's Hospital of Yancheng City in China [Identification No. HMU (Ethics): 20141203] and was performed in accordance with the principles of the Helsinki Declaration. Informed consent was obtained from all study subjects prior to commencement of the study.

2.3. Clinical information and laboratory examinations

Demographic and laboratory data of each subject were collected on study enrollment. This patient data included RDW, NLR, LMR, FIB-4, APRI, RLR, white blood cell counts (WBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, albumin, creatinine, prothrombin time, blood urea nitrogen, platelet counts (PLT), and international normalized ratio (INR). FIB-4 score is a grading standard for quantitative evaluation of liver reserve function. FIB-4 and APRI score for HBV-related liver diseases were calculated using the formulae below:

FIB-4 = age × (AST/platelets) × alanine aminotransferase (ALT)1/2;

APRI = [aspartate aminotransferase (AST)/(platelets × 40)] × 100.

2.4. Statistical analysis

Statistical analyses were performed using SPSS, version 19.0 (SPSS, Chicago, IL). Data are presented as the mean ± standard deviation when data was normally distributed or as medians and range if the distribution was skewed. The haematology and biochemistry data obtained from healthy participants (Control group), CHB group, and liver cirrhosis (HBV-LC) group were compared for statistical differences using one-way analysis of variance (ANOVA) for normally distributed data, and the

Table 1

Demographic and biochemical characteristics of the study participants.

Variable	1. Control	2. CHB	3. HBV-LC	*P*	3 vs 1	3 vs 2
Age, y	50.93 (29–77)	53.61 (29–90)	51.80 (23–82)	.026	0.200	0.236
Gender (M/F)	415/335	187/140	251/159	.801	0.729	0.507
ALT, U/L	17 (6–57)	65 (8–3167)	25 (5–626)	<.001	<0.001	<0.001
AST, U/L	20 (12–40)	59 (13–2679)	38 (14–740)	<.001	<0.001	0.017
ALB, g/L	40.98 (35.60–46.11)	32.60 (25.76–42.09)	31.90 (23.98–40.22)	<.001	<0.001	0.356
GGT, U/L	49.55 (37.21–62.12)	87.50 (52.10–152.00)	92.32 (55.87–165.77)	<.001	<0.001	0.798
Neutrophil ($\times 10^9$/L)	3.3 (1.7–6.6)	2.6 (0.8–10.1)	1.8 (0.4–16.9)	<.001	<0.001	<0.001
LYM ($\times 10^9$/L)	1.9 (0.7–3.9)	1.6 (0.5–3.2)	0.8 (0.2–3.4)	<.001	<0.001	<0.001
Monocyte ($\times 10^9$/L)	0.38 (0.16–1.25)	0.41 (0.11–1.32)	0.31 (0.03–2.24)	<.001	<0.001	<0.001
RDW, %	12.9 (11.8–19.4)	13.3 (11.6–21.1)	15.6 (12.4–26.1)	<.001	<0.001	<0.001
Platelet ($\times 10^9$/L)	218 (102–408)	157 (49–324)	57 (11–558)	<.001	<0.001	<0.001
TBIL, u mol/L	11.04 (3.05–19.06)	12.55 (3.22–20.31)	11.98 (3.14–18.12)	.812	0.945	0.906
UREA, mmol/L	4.21 (3.32–6.12)	4.45 (3.65–6.56)	4.76 (3.77–7.19)	.519	0.495	0.553
CR, u mol/L	72.32 (59.30–91.21)	74.08 (62.09–94.22)	75.99 (65.24–95.76)	.766	0.732	0.986
PT, s	11.95 (10.12–18.12)	13.10 (11.00–23.12)	13.56 (11.90–22.90)	.550	0.487	0.932
INR	1.49 (1.29–2.09)	1.51 (1.31–2.11)	1.51 (1.32–2.14)	.590	0.610	0.819
AFP, ng/mL	30.98 (6.79–65.21)	33.41 (7.00–85.00)	37.29 (9.40–91.12)	.521	0.588	0.815
CHE, (U/L	3103.12 (2759.16–3991.78)	2799.12 (2312.21–3224.19)	2718.19 (2421.15–3216.21)	.155	0.162	0.347
FER, ng/mL	2668.12 (1305.54–4772.12)	2809.81 (1355.49–4822.59)	2912.55 (1322.12–4817.52)	.951	0.461	0.992
NLR	1.68 (0.62–5.13)	1.64 (0.45–11.83)	2.26 (0.31–26.5)	<.001	<0.001	<0.001
LMR	5.26 (1.12–13.91)	3.78 (1.14–8.71)	2.73 (0.37–23.33)	<.001	<0.001	<0.001
FIB-4	1.14 (0.41–3.01)	2.25 (0.50–30.39)	7.01 (0.79–128.14)	<.001	<0.001	<0.001
APRI	0.23 (0.09–0.59)	0.97 (0.12–45.87)	1.70 (0.10–84.64)	<.001	<0.001	<0.001
RLR	6.90 (3.50–20.29)	8.60 (3.84–28.60)	21.28 (3.74–114.50)	<.001	<0.001	<0.001

3 vs 1 = HBV-LC vs Control, 3 vs 2, HBV-LC vs CHB, AFP = Alpha fetoprotein, ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHB = chronic HBV infection, CHE = cholinesterase, CR = creatinine, FER = Ferritin, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, INR = international normalized ratio, LMR = lymphocyte monocyte ratio, LYM = lymphocyte, NLR = neutrophil lymphocyte ratio, PT = prothrombin time, RDW = red cell distribution width, RLR = RDW lymphocyte ratio, TBIL = total bilirubin, UREA = urea nitrogen.

Kruskal–Wallis H test was used for non-normally distributed data. The level of significance was set at P value $< .05$. Receiver operator characteristic (ROC) curves and corresponding areas under the ROC curves (AUCs) were used to determine the discrimination threshold of each marker. The Youden index was used to determine appropriate cut-off points for an optimal combination of sensitivity and specificity. Binary logistic regression analyses were used to identify factors correlated with incidence of liver cirrhosis.

3. Results

3.1. Subject demographics and biochemical results

The demographics and biochemical test results of subjects are summarized in Table 1. Patients with HBV-LC had significant differences for ALT, AST, lymphocyte, neutrophil, RDW, RLR, PLT, ALB, NLR, LMR, FIB-4, and APRI when compared to healthy controls. We similarly found significant differences in these parameters between HBV-LC and CHB groups. Patients with HBV-LC had higher RLR, FIB-4, NLR, RDW, APRI, and lower LMR relative to control and CHB groups.

3.2. Performance of RLR as a diagnostic tool for HBV-related liver cirrhosis

First, we compared RDW and RLR between groups. We found that RDW was higher in the HBV-LC group compared to both CHB and control groups (both $P < .05$). Additionally, RDW was also higher in the CHB group compared to the control group ($P < .05$). There was a positive relationship between RDW and disease progression and severity (Fig. 1A). RLR was also higher in the HBV-LC group compared to both CHB and control groups (both $P < .05$). While observing a trend of higher RLR in the CHB group than the control group, the difference was not statistically significant ($P > .05$; Fig. 1B).

To evaluate the performance of RLR and RDW as diagnostic tools for HBV-related liver cirrhosis, a ROC analysis was performed for HBV-LC and CHB groups. The area under ROC of RLR for HBV-related liver cirrhosis was 0.87. This was superior to RDW (0.81), FIB-4 (0.79), and APRI (0.60). After optimization of cut-off values (10.87), we found that RLR had the highest sensitivity (0.88) and specificity (0.72), and was superior to RDW (0.86, 0.64), FIB-4 (0.80, 0.65), and APRI (0.85, 0.48) (Fig. 2).

Table 2 represents associations between RLR, RDW, and development of liver cirrhosis in HBV patients. The median value of RLR (14.40 ng/mL) was used to stratify study participants into "low" and "high" groups. Relative to patients with a low RLR, the crude odds ratio (OR) for risk of developing liver cirrhosis for HBV patients with a high RLR was 15.50 (95% CI: 8.66–27.75). The adjusted OR (AOR) for HBV patients with a high RLR was 6.60 (95% CI: 3.19–13.63, $P < .001$). A higher AOR was also observed for quartile analyses, clearly illustrating the positive relationship between increased RLR and development of liver cirrhosis in HBV patients. Compared to the group with the lowest RLR (Q1), the crude OR for risk of HBV-related liver cirrhosis was 4.46 (95% CI: 2.23–8.91), 19.83 (95% CI: 9.10– 43.24), and 114.75 (95% CI: 32.08–410.47) for Q2, Q3, and Q4 groups, respectively. We found that high RLR was associated with HBV-related liver cirrhosis ($P < .001$). Even after adjustment

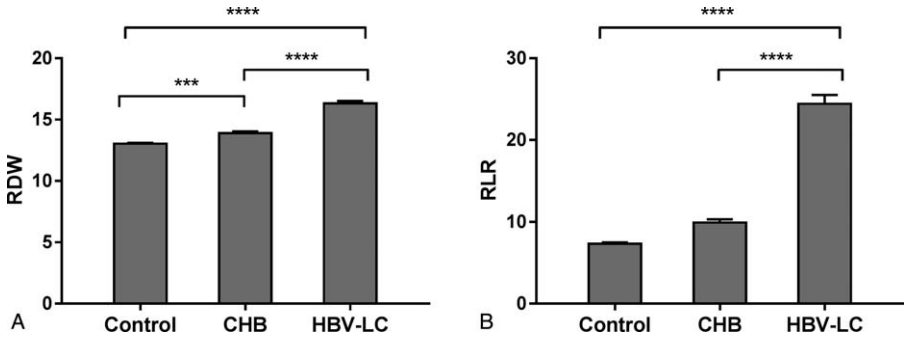

Figure 1. The levels of RDW and RLR in different disease states of hepatitis B virus infection. $^{***}P < .05$, $^{****}P < .01$. CHB = chronic hepatitis B, HBV-LC = HBV-related liver cirrhosis, RDW = red cell distribution width, RLR = RDW lymphocyte ratio.

for ALT, ALB, and TBIL, we observed that RDW, FIB-4, and APRI still showed a significant correlation ($P < .001$) with HBV-related liver cirrhosis (Fig. 3). As such, we concluded that RLR, RDW, FIB-4, and APRI were independent risk factors of HBV-related liver cirrhosis and may be used as predicting cirrhosis tools.

We then validated the diagnostic power of 2 parameters, RLR and RDW, with an additional 30 HBV-LC patients and 30 CHB patients who were enrolled later to this study between August 2018 and February 2019. Using the cut-off values of RLR (10.87) and RDW (13.90), the diagnostic capabilities of RLR and RDW for HBV-related liver cirrhosis were comparable to the use of liver biopsy with the original cohort (Table 3).

3.3. Correlation between RLR and other parameters of liver function

We then analyzed the correlation between RLR and other measures of liver function (Fig. 4). For all 3 groups, RLR showed a negative relationship with serum platelet (PLT) (all $P < .05$) and a positive association with FIB-4 and APRI (all $P < .05$). RLR showed a positive correlation with ALT in CHB group but this correlation did not reach the level of statistical significance ($P = .203$). RLR showed a negative correlation with ALT in the HBV-LC group ($P = .02$; Fig. 4). Correlations within each of the 3 groups are summarized in Figure 5. Our results suggest that RLR shows good agreement with PLT, FIB-4, and APRI measures in both CHB and HBV-LC groups.

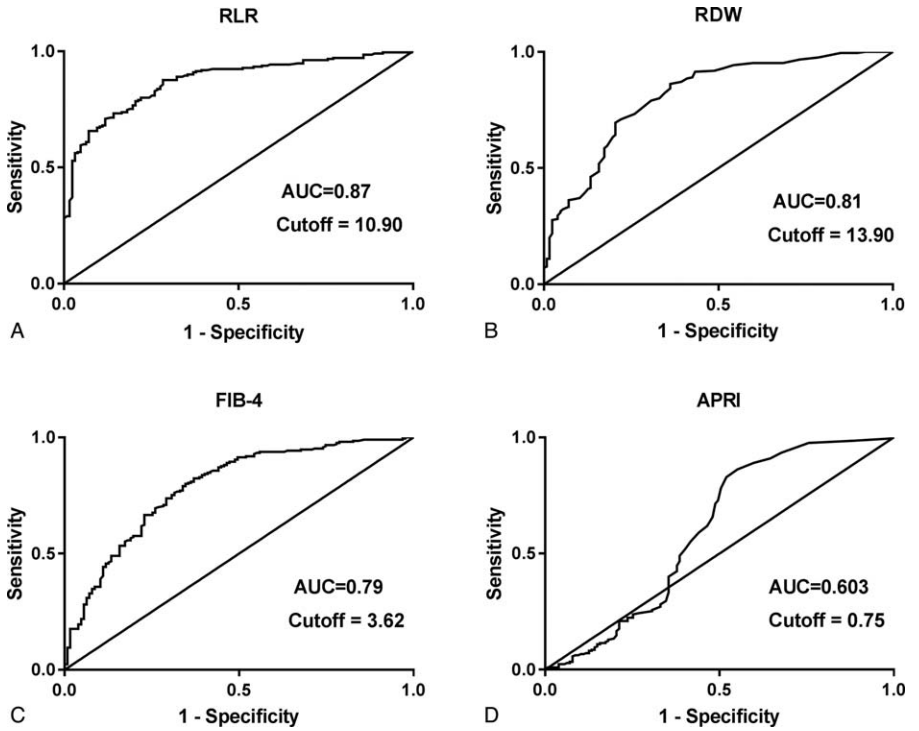

Figure 2. The predictive ability of RLR, RDW, FIB-4, and APRI for HBV-related liver cirrhosis between CHB group and HBV-LC group. APRI = aspartate aminotransferase-to-platelet ratio index, CHB = chronic hepatitis B, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, RDW = red cell distribution width, RLR = RDW lymphocyte ratio.

Table 2

Association analyses between RLR, RDW, FIB-4, APRI, and risk of HBV-related liver cirrhosis: OR (95% CI) using binary logistic regression.

		CHB	HBV-LC	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)*	*P* value*
RLR							
	Dichotomies [n (%)]						
	Low (<14.40)	209 (85.83)	159 (28.10)	1.00 (reference)		1.00 (reference)	
	High (≥14.40)	118 (14.17)	251 (71.90)	15.50 (8.66–27.75)	<.001	6.60 (3.19–13.63)	<.001
	Quartile [n (%)]						
	Q1 (<9.14)	118 (53.54)	66 (7.62)	1.00 (reference)		1.00 (reference)	
	Q2 (9.14–14.40)	91 (32.28)	93 (20.48)	4.46 (2.23–8.91)	<.001	3.52 (1.58–7.83)	.002
	Q3 (14.40–23.83)	65 (11.81)	120 (33.33)	19.83 (9.10–43.24)	<.001	10.88 (4.33–27.32)	<.001
	Q4 (>23.83)	53 (2.36)	131 (38.57)	114.75 (32.08–410.47)	<.001	31.35 (6.24–157.41)	<.001
RDW							
	Dichotomies [n (%)]						
	Low (<14.80)	201 (79.53)	168 (32.38)	1.00 (reference)		1.00 (reference)	
	High (≥14.80)	126 (20.47)	242 (67.62)	8.11 (4.83–13.63)	<.001	9.96 (4.73–20.95)	<.001
	Quartile [n (%)]						
	Q1 (<13.40)	115 (51.18)	67 (8.10)	1.00 (reference)		1.00 (reference)	
	Q2 (13.40–14.80)	86 (28.35)	101 (24.29)	5.42 (2.74–10.73)	<.001	3.73 (1.57–8.87)	.003
	Q3 (14.80–16.60)	67 (13.39)	116 (31.43)	14.84 (6.98–31.57)	<.001	13.47 (5.06–35.85)	<.001
	Q4 (>16.60)	59 (7.09)	126 (36.19)	32.29 (13.48–77.31)	<.001	28.71 (9.24–89.21)	<.001
FIB-4							
	Dichotomies [n (%)]						
	Low (<5.53)	198 (77.17)	170 (33.33)	1.00 (reference)		1.00 (reference)	
	High (≥5.53)	129 (22.83)	240 (66.67)	6.76 (4.08–11.19)	<.001	5.24 (2.30–11.95)	<.001
	Quartile [n (%)]						
	Q1 (<2.34)	114 (50.39)	70 (9.52)	1.00 (reference)		1.00 (reference)	
	Q2 (2.34–5.53)	84 (26.77)	100 (23.81)	4.71 (2.42–9.15)	<.001	3.68 (1.55–8.74)	.003
	Q3 (5.53–9.32)	68 (14.17)	117 (31.90)	11.91 (5.78–24.55)	<.001	11.25 (3.69–34.32)	<.001
	Q4 (>9.32)	61 (8.66)	123 (34.76)	21.24 (9.46–47.67)	<.001	24.24 (5.58–105.35)	<.001
APRI							
	Dichotomies [n (%)]						
	Low (<1.56)	174 (58.27)	194 (44.76)	1.00 (reference)		1.00 (reference)	
	High (≥1.56)	153 (41.73)	216 (55.24)	1.72 (1.10–2.69)	.017	3.85 (1.52–9.73)	.005
	Quartile [n (%)]						
	Q1 (<0.72)	105 (43.31)	79 (13.81)	1.00 (reference)		1.00 (reference)	
	Q2 (0.72–1.56)	69 (14.96)	115 (30.95)	6.49 (3.28–12.82)	<.001	5.74 (2.30–14.34)	<.001
	Q3 (1.56–3.16)	70 (15.75)	115 (30.95)	6.16 (3.14–12.09)	<.001	9.92 (3.07–32.10)	<.001
	Q4 (>3.16)	83 (25.98)	101 (24.29)	2.93 (1.57–5.49)	.001	82.59 (10.40–656.10)	<.001

CHB = chronic HBV infection, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, NLR = neutrophil lymphocyte ratio, RDW = red cell distribution width, RLR = RDW lymphocyte ratio.

* Adjustment for ALT and PLT.

3.4. Use of RLR to predict prognosis of patients with HBV-related liver cirrhosis

To evaluate the utility of RLR, RDW, FIB-4, and APRI in predicting prognosis of patients with HBV-related liver cirrhosis, we divided the liver cirrhosis patients into 2 groups with different treatment outcomes: recovery/improvement and treatment failure/death.

Table 4 shows associations between RLR, RDW, FIB-4, APRI, and prognosis of patients with HBV-related liver cirrhosis. As with before, using the median value of RLR (14.90), study participants were divided into "low" and "high" groups. Compared to patients with low RLR, the crude OR of prognosis for patients with liver cirrhosis with a high RLR was 15.48 (95% Cl: 8.27–27.57), and the AOR was 6.20 (95% Cl: 0.30–3.37, $P > .05$). Quartile analyses also showed higher AORs, illustrating the association between increased RLR and prognosis of patients with liver cirrhosis. Compared to the group with the lowest RLR (Q1), the crude OR was 4.64 (95% Cl: 2.31–8.97), 19.33 (95% Cl: 9.05–41.74), and 119.05 (95% Cl: 30.08–409.17) for Q2, Q3, and Q4 groups respectively. We found no significant correlation between RLR and prognosis for patients with liver cirrhosis ($P > .05$). As such, we concluded that RLR is not a useful predictor for prognosis of patients with liver failure. Similarly, we found no correlation for RDW, FIB-4, and APRI.

4. Discussion

The main findings of our study are as follows: HBV patients in both CHB and HBV-LC groups had higher RLR and RDW

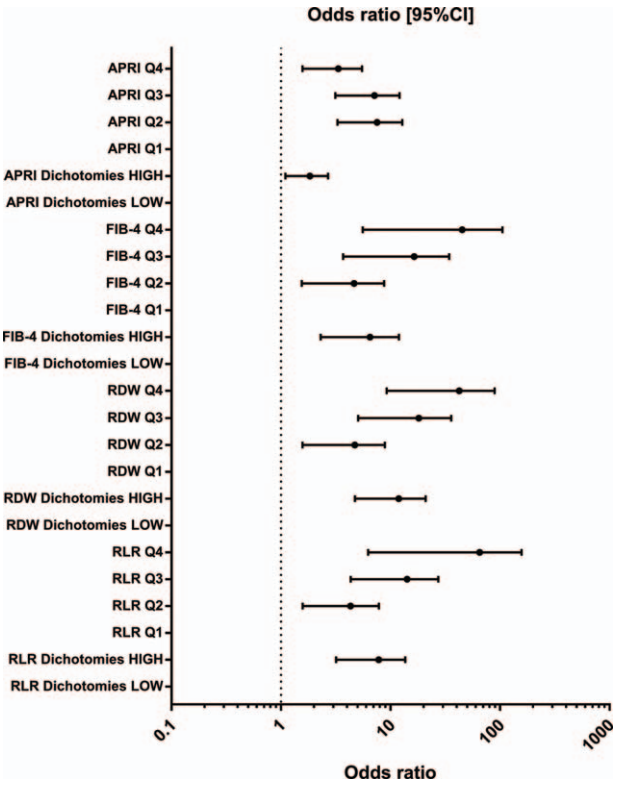

Figure 3. Association analyses between serum RLR, RDW, FIB-4, APRI, and risk of HBV-related liver cirrhosis. APRI = aspartate aminotransferase-to-platelet ratio index, FIB-4 = fibrosis index based on the 4 factors, RDW = red cell distribution width, RLR = RDW lymphocyte ratio.

relative to healthy controls. There were also significant differences observed between CHB and HBV-LC groups for both RLR and RDW. However, RLR has better sensitivity and specificity for diagnosis of HBV-related liver cirrhosis compared to RDW. As such, RLR can potentially be used as a diagnostic tool for liver cirrhosis. RLR correlates well with PLT, FIB-4, and APRI in both CHB and HBV-LC groups. However, we did not find any association between RLR and prognosis of patients with HBV-related liver cirrhosis. There was no significant difference observed for patients with different prognoses in the HBV-LC group; however, a larger study with more participants will be required to conclusively determine the absence or existence of any association.

HBV patients require long-term monitoring of the degree of liver fibrosis for treatment and prevention of complications.[21] The topic of using noninvasive techniques to diagnose liver cirrhosis has garnered a lot of interest and discussion. RDW is a reflection of the homeostastic state of erythrocytes. This study shows that RDW is higher in CHB patients compared to healthy controls. We also found further increases in RDW during cirrhosis. Although the exact mechanism that links RDW to cirrhosis remains to be elucidated, anemia is a common complication of cirrhosis. It has been proposed to result from portal hypertension in chronic liver diseases, which frequently causes enlargement of the spleen and subsequently reduces the numbers of red blood cells in circulation. Additionally, immune-mediated liver injury occurs during HBV infection, and decrease in lymphocyte promotes recurrent infection by HBV. Allen et al have shown that increased RDW may indicate inflammatory stress and impaired iron mobilization.[22] In fact, inflammation and iron overload play a key role in mediating the process related to liver fibrosis.[23] Furthermore, inflammatory cytokines may increase the heterogeneity of RBC maturation and injury, which is manifested as an increase in RDW.

On the other hand, lymphocytes were lower in CHB patients compared to healthy controls, with further decrease observed during cirrhosis. Hypersplenism in patients with cirrhosis leads to decreased WBC.[24] Lymphocytes play an important role in immune monitoring. The decrease of the number of lymphocytes may be related to apoptosis and dysfunction of immune cells, and the occurrence of advanced cirrhosis may be related to the gradual decrease of the number of lymphocytes.[25] Additionally, inefficient immune clearance of HBV leads to CHB and increases the risk for liver cirrhosis.[26] Immune-mediated liver injury occurred during HBV infection,[16,17] and decrease in lymphocyte number was promoted recurrent infection by HBV. The persistent presence of HBV and corresponding decrease in lymphocyte therefore contribute to progression of liver cirrhosis.'

In this retrospective study, we confirm that RLR, which combines 2 different parameters, is a more powerful diagnostic tool than the use of either parameter alone. In this study, RLR

Table 3

RLR and RDW were validated in clinical diagnosis of 30 HBV-LC patients and 30 CHB patients.

		HBV-LC patients	CHB patients	Sensitivity	Specificity
RLR	$>$ 10.87	26	8	0.87	0.73
	$\leq$ 10.87	4	22		
RDW	$>$ 13.90	26	11	0.87	0.63
	$\leq$ 13.90	4	19		
FIB-4	$>$ 3.62	25	10	0.83	0.67
	$\leq$ 3.62	5	20		
APRI	$>$ 0.75	25	15	0.83	0.50
	$\leq$ 0.75	5	15		
Total	–	30	30	–	–

APRI = aspartate aminotransferase-to-platelet ratio index, CHB = chronic HBV infection, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, RDW = red cell distribution width, RLR = RDW lymphocyte ratio.

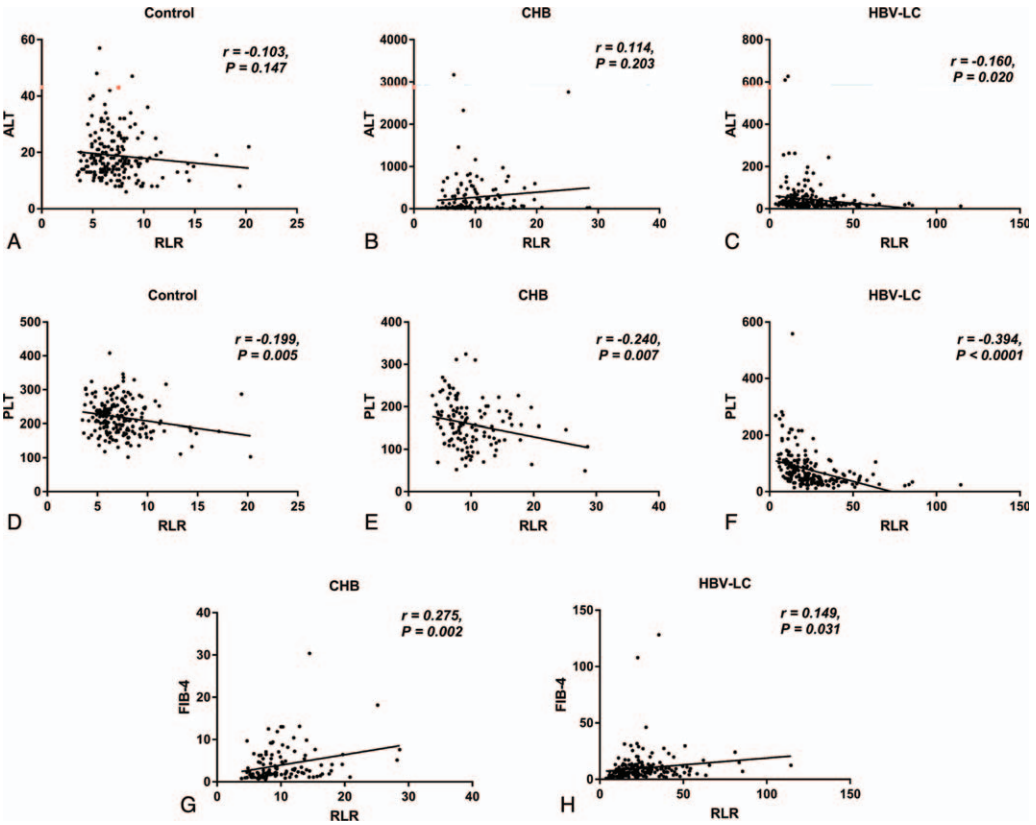

Figure 4. Correlations between ALT, PLT, FIB-4 score, APRI score, and RLR in patients with HBV-related liver diseases. RLR levels were negatively correlated with serum PLT and were positively correlated with FIB-4 and APRI in all 3 groups. RLR levels were positively correlated with serum ALT in CHB group but without statistically significant. RLR levels were negatively correlated with serum ALT in the HBV-LC group. ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, CHB = chronic hepatitis B, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, PLT = platelet, RLR = RDW lymphocyte ratio.

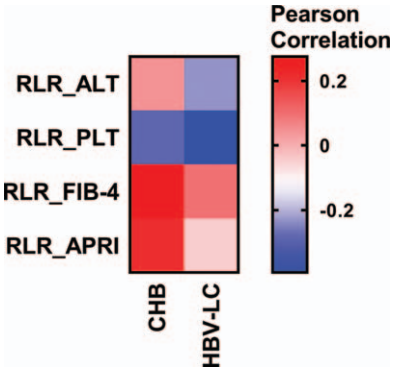

Figure 5. The heatmap for correlation between ALT, PLT, FIB-4 score, APRI score and RLR in patients with HBV-related liver diseases. The overall correlations in 3 groups suggested that serum RLR has a good correlation between PLT, FIB-4, and APRI in both CHB group and HBV-LC group. ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, CHB = chronic hepatitis B, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, PLT = platelet, RLR = RDW lymphocyte ratio.

was determined to be the most powerful tool for predicting HBV-related liver cirrhosis, and was superior to RDW, which has previously been described as a classic and powerful tool in other studies.[27] This is one of very few studies that aimed to assess the prediction performance of RLR relative to other measures for HBV-related cirrhosis. RDW has been described to be a better parameter than various indirect measures[28,29], however, we found that RLR outperforms RDW in this study.'

This study has several limitations. First of all, the diagnosis of cirrhosis was mainly made with imaging-based assessment of morphology. However, this shows good agreement with diagnosis by liver biopsy.[24] Secondly, the degree of liver fibrosis was not stratified in detail. Future studies shall focus on the relationship between RLR and each stage of liver fibrosis (with progression from significant fibrosis to cirrhosis). Thirdly, new markers such as transient elastography, fibrin, and the enhanced liver fibrosis test, were not compared with RLR in this study, and will be included in future work. Fourth, whether the RLR/RDW is associated with non-HBV-related chronic hepatitis was not examined in the present study.

In conclusion, this study has provided important insight into the use of noninvasive techniques for diagnosis of HBV-related

Table 4

Association analyses RLR, RDW, FIB-4, and APRI predicting prognosis of HBV-related liver cirrhosis: OR (95% CI) using binary logistic regression.

		Recovery/improvement	Treatment failure/death	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)*	*P* value*
RLR							
	Dichotomies [n (%)]						
	Low (<14.90)	57 (44.88)	139 (49.12)	1.00 (reference)		1.00 (reference)	
	High (≥14.90)	70 (55.12)	144 (50.88)	15.48 (8.27–27.57)	1.000	6.20 (3.19–12.28)	.997
	Quartile [n (%)]						
	Q1 (<9.59)	17 (13.39)	42 (14.84)	1.00 (reference)		1.00 (reference)	
	Q2 (9.59–14.90)	40 (31.50)	97 (34.28)	4.64 (2.31–8.97)	.690	3.52 (1.58–7.83)	.439
	Q3 (14.90–20.40)	37 (29.13)	87 (30.74)	19.33 (9.05–41.74)	.699	10.88 (4.33–27.32)	.563
	Q4 (>20.40)	33 (25.98)	57 (20.14)	119.05 (30.08–409.17)	1.000	31.35 (6.24–157.41)	.899
RDW							
	Dichotomies [n (%)]						
	Low (<15.00)	72 (56.69)	147 (51.94)	1.00 (reference)		1.00 (reference)	
	High (≥15.00)	55 (43.31)	136 (48.06)	8.09 (4.79–12.11)	.226	9.96 (4.73–20.95)	.120
	Quartile [n (%)]						
	Q1 (<13.50)	29 (22.83)	59 (20.85)	1.00 (reference)		1.00 (reference)	
	Q2 (13.50–15.00)	43 (33.86)	88 (31.09)	5.19 (2.69–9.99)	.819	3.73 (1.57–8.87)	.712
	Q3 (15.00–17.80)	33 (25.98)	82 (28.98)	13.84 (6.18–29.57)	.460	13.47 (5.06–35.85)	.320
	Q4 (>17.80)	22 (17.33)	54 (19.08)	30.19 (11.48–72.31)	.699	28.71 (9.24–89.21)	.564
FIB-4							
	Dichotomies [n (%)]						
	Low (<5.53)	66 (51.97)	150 (53.00)	1.00 (reference)		1.00 (reference)	
	High (≥5.53)	61 (48.03)	133 (47.00)	6.76 (4.08–11.19)	.599	5.23 (2.29–11.95)	.344
	Quartile [n (%)]						
	Q1 (<2.34)	46 (36.22)	103 (36.40)	1.00 (reference)		1.00 (reference)	
	Q2 (2.34–5.53)	20 (15.75)	47 (16.60)	4.61 (2.12–9.19)	.316	3.72 (1.28–8.64)	.201
	Q3 (5.53–9.32)	34 (26.77)	73 (25.80)	11.19 (5.55–20.55)	.432	11.19 (3.92–37.12)	.312
	Q4 (>9.32)	27 (21.26)	60 (21.20)	21.04 (9.16–45.21)	.599	22.29 (5.17–103.15)	.468
APRI							
	Dichotomies [n (%)]						
	Low (<1.58)	70 (55.12)	155 (54.77)	1.00 (reference)		1.00 (reference)	
	High (≥1.58)	57 (44.88)	128 (45.23)	7.16 (4.78–12.21)	.612	5.23 (2.29–11.95)	.398
	Quartile [n (%)]						
	Q1 (<0.74)	45 (35.43)	96 (33.92)	1.00 (reference)		1.00 (reference)	
	Q2 (0.74–1.58)	25 (19.69)	59 (20.85)	4.61 (2.12–9.19)	.341	3.99 (1.91–9.76)	.212
	Q3 (1.58–3.19)	32 (25.20)	73 (25.80)	10.19 (5.76–21.32)	.419	10.98 (4.91–35.31)	.398
	Q4 (>3.19)	25 (19.68)	55 (19.43)	22.42 (9.91–46.98)	.612	23.09 (5.22–99.75)	.479

CHB = chronic HBV infection, FIB-4 = fibrosis index based on the 4 factors, HBV-LC = HBV-related liver cirrhosis, NLR = neutrophil lymphocyte ratio, RDW = red cell distribution width, RLR = RDW lymphocyte ratio.

* Adjustment for ALT and PLT.

cirrhosis. RLR, which is an inexpensive method that combines 2 simple hematological parameters, has the greatest diagnostic and prediction power for liver fibrosis.

Author contributions

Conceptualization: Dawei Wang, yinhong Yue.
Data curation: Zhongming Chen, Naizhou Guo, Wei Wang, Cunquan Xiong, jun liu, yinhong Yue, Mingzhong Sun.
Formal analysis: Naizhou Guo.
Funding acquisition: jun liu.
Investigation: Wei Wang, yinhong Yue, Mingzhong Sun.
Methodology: Wei Wang, Mingzhong Sun.
Resources: Zhongming Chen.
Software: Cunquan Xiong.
Supervision: Zhongming Chen, Naizhou Guo, Cunquan Xiong.
Validation: Xueyan Zhang, jun liu, yinhong Yue.
Writing – original draft: Xueyan Zhang, Zhongming Chen, jun liu, Mingzhong Sun.
Writing – review & editing: Dawei Wang.

References

[1] Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med 2004;350:1118–29.
[2] Locarnini S, Hatzakis A, Chen D-S. Strategies to control hepatitis B: public policy, epidemiology, vaccine and drugs. J Hepatol 2015;62: S76–86.
[3] European Association For The Study Of The LiverEASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–85.

[4] Liaw Y-F, Sung JJY, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351: 1521–31.
[5] Friedman LS. Controversies in liver biopsy: who, where, when, how, why? Curr Gastroenterol Rep 2004;6:30–6.
[6] Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis. Hepatology 2003;38:1449–57.
[7] Fukui H, Ueno SH, Uto YH, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol 2016;51:629–50.
[8] Khallafi HQK. Imaging based methods of liver fibrosis assessment in viral hepatitis: a practical approach. Interdiscip Perspect Infect Dis 2015; 2015:1–0.
[9] Deng H, Qi X, Guo X. Diagnostic accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex scores in predicting the presence of esophageal varices in liver cirrhosis: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94:e1795.
[10] Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015;61:292–302.
[11] Petta S, Sebastiani G, Bugianesi E, et al. Noninvasive prediction of esophageal varices by stiffness and platelet in nonalcoholic fatty liver disease cirrhosis. J Hepatol 2018;69:878–85.
[12] Qiu L, Chen C, Li S-J, et al. Prognostic values of red blood cell distribution width, platelet count, and red cell distribution width-to-platelet ratio for severe burn injury. Sci Rep 2017;7:13720.
[13] Lin ZX, Ruan D-Y, Li Y, et al. Lymphocyte-to-monocyte ratio predicts survival of patients with hepatocellular carcinoma after curative resection. World J Gastroenterol 2015;21:10898–906.
[14] Huang R, Yang C, Wu K, et al. Red cell distribution width as a potential index to assess the severity of hepatitis B virus-related liver diseases. Hepatol Res 2014;44:E464–70.
[15] Zhang H, Sun Q, Mao W, et al. Neutrophil-to-lymphocyte ratio predicts early mortality in patients with HBV-related decompensated cirrhosis. Gastroenterol Res Pract 2016;2016:1–5.
[16] Cheng L-S, Liu Y, Jiang W. Restoring homeostasis of CD4, T cells in hepatitis-B-virus-related liver fibrosis. World J Gastroenterol 2015;21: 10721–31.
[17] Xu R, Zhang Z, Wang F-S. Liver fibrosis: mechanisms of immune-mediated liver injury. Cell Mol Immunol 2012;9:296–301.
[18] Chen B, Ye B, Zhang J, et al. RDW to platelet ratio: a novel noninvasive index for predicting hepatic fibrosis and cirrhosis in chronic hepatitis B. PLoS One 2013;8:e68780.
[19] Ding Y, Tao Z, Wang H, et al. Predictive value of the red blood cell distribution width-to-platelet ratio for hepatic fibrosis. Scand J Gastroenterol 2019;54:81–6.
[20] Wilkins T, Sams R, Carpenter M, et al. Hepatitis B: screening, prevention, diagnosis, and treatment. Am Fam Physician 2019;99: 314–23.
[21] Wu W, Yan H, Zhao H, et al. Characteristics of systemic inflammation in hepatitis B-precipitated ACLF: differentiate it from No-ACLF. Liver Int 2018;38:248–57.
[22] Allen LA, Felker GM, Mehra MR, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail 2010;16:230–8.
[23] Ramm GA, Ruddell RG. Iron homeostasis, hepatocellular injury, and fibrogenesis in hemochromatosis: the role of inflammation in a noninflammatory liver disease. Semin Liver Dis 2010;30:271–87.
[24] 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;15: 146.
[25] Meng J, Xu H, Liu X, et al. Increased red cell width distribution to lymphocyte ratio is a predictor of histologic severity in primary biliary cholangitis. Medicine (Baltimore) 2018;97:e13431.
[26] Hu YC, Liu H, Liu X-Y, et al. Value of gamma-glutamyltranspeptidase-to-platelet ratio in diagnosis of hepatic fibrosis in patients with chronic hepatitis B. World J Gastroenterol 2017;23:7425–32.
[27] Li Y, Chen Y, Zhao Y. The diagnostic value of the FIB-4 index for staging hepatitis B-related fibrosis: a meta-analysis. PLoS One 2014;9:e105728.
[28] Fan X, Deng H, Wang X, et al. Association of red blood cell distribution width with severity of hepatitis B virus-related liver diseases. Clin Chim Acta 2018;482:155–60.
[29] Zhang M, Zhu CS, Huang XA, et al. Value of red cell distribution width in assessing the severity of Hepatitis B virus-related decompensated cirrhosis. Clin Lab 2017;63:1467–74.