Clinical Biochemistry 63 (2019) 24–31

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

RDW, NLR and RLR in predicting liver failure and prognosis in patients with hepatitis E virus infection

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ARTICLE INFO

Keywords:
Hepatitis E
Liver failure
Red cell distribution width
Neutrophil-lymphocyte ratio
RDW-Lymphocyte Ratio

ABSTRACT

Background & aims: Hepatitis E virus (HEV) infection contributes to substantial proportion of acute liver injury. This study aims to evaluate the ability of red cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR) and RDW to lymphocyte ratio (RLR) in predicating the development of liver failure following HEV infection and the prognosis.

Methods: 93 healthy controls, 152 current/recent HEV infected patients without liver failure (HEV-non-LF) and 62 HEV patients who developed liver failure (HEV-LF) were enrolled in the study. The clinical and laboratory characteristics on admission, including RDW, neutrophil, lymphocyte, were recorded. Additional 24 HEV-LF patients and 24 HEV-non-LF patients were enrolled to validate the diagnostic efficacy of the three parameters.

Results: RDW, NLR and RLR were higher in HEV patients developing liver failure, compared with HEV-non-LF patients. Positive associations of increased RDW, RLR, NLR and incidence of liver failure were found. The AUC of RLR for predicting HEV-related liver failure was 0.74, superior to NLR and RDW. The sensitivity and specificity of RLR for predicting HEV-related liver failure were 0.74 and 0.65 respectively, superior to NLR (0.66, 0.70) and RDW (0.58, 0.67). However, no correlation between any of the three parameters and prognosis of HEV-LF was found. In addition, the three parameters were correlated with ALB, TBIL and Child-Pugh score in HEV-non-LF subjects, other than in HEV-LF patients.

Conclusion: RDW, NLR and RLR are capable to predicate the development of liver failure in HEV patients, among which RLR showed the best sensitivity and specificity. These routinely available parameters shall be considered as new preliminarily diagnostic markers for fulminant hepatic damage in HEV patients.

1. Introduction

Hepatitis E virus (HEV) infection is one of the most common causes of acute viral hepatitis. Although it is self-limiting, fulminant hepatitis leading to acute or acute-on-chronic liver failure (ALF/ACLF) has been frequently reported in endemic areas [1]. About 20%–40% of acute HEV patients in developing countries may progress to ALF, and this percentage is increased in pregnant women infected with genotype 1 HEV with high mortality [2]. Sporadic acute hepatitis E accounts for 4% of acute or subacute liver failure with poor prognosis. In addition, HEV patients with chronic liver disease have high risk to develop ACLF, leading to high mortality ranging from 0% to 67% with a median of 34% [3]. Thus, it is essential to evaluate the short-term prognosis of ACLF.

Red blood cell distribution width (RDW) and neutrophil to lymphocyte ratio (NLR) are routinely tested biochemical parameters. RDW is usually used to explore the etiology of anemia, especially for differential diagnosis of iron deficiency-related anemia [4,5]. In recent years, studies have reported that RDW could be used for predicting the risk, prognosis or severity of several other diseases irrelevant to anemia, such as cardiovascular diseases, hepatitis B virus (HBV)-related liver diseases, autoimmune diseases or stroke [6,7]. NLR is defined as the ratio of neutrophils percentage to lymphocytes percentage, which is generally used to predict early mortality in patients with HBV related decompensated cirrhosis [8]. Decreased lymphocyte counts in CHB and cirrhosis and increased RDW in liver cirrhosis have been reported in several studies [5]. RDW-lymphocytes ratio (RLR), the combination of the two parameters, is more powerful than one parameter alone in

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https://doi.org/10.1016/j.clinbiochem.2018.11.012
Received 21 August 2018; Received in revised form 24 October 2018; Accepted 28 November 2018
Available online 28 November 2018

diagnosis of liver cirrhosis. In addition, RDW, NLR and RLR have also been reported as prognostic factors for patients with acute cerebral infarction [9,10].

Recently, NLR has been reported for predicting ACLF mortality, but need further authentication in clinical practice [11]. In this study, we evaluated the role of RDW, NLR, RLR in predicating the development and prognosis of liver failure in patients with HEV infection.

2. Materials and methods

2.1. Patients

152 subjects diagnosed of acute HEV infection with positive anti-HEV IgM without developing liver failure (HEV-non-LF) in the First People's Hospital of Yancheng City between January 2013 and June 2017 and 62 HEV infection patients who were complicating with non-chronic liver failure (HEV-LF) (acute liver failure, subacute liver failure and acute-on-chronic liver failure) from Beijing 302 Hospital between September in 2015 to Septembei in 2017 were enrolled in our study. In addition, 93 healthy individuals absence of HEV infection or other diseases were also included, serving as controls. All the enrolled liver failure patients met the criteria from the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) as follows:

The onset of illness is urgent. The performances during 2–26 weeks were as follows: [1] The patient's physique is extremely weak, and there are obvious gastrointestinal symptoms; [2] The jaundice increased rapidly and serum bilirubin level was 10 times higher than normal; [3] With or without hepatic encephalopathy; [4] Bleeding tendency, PTA ≤ 40% (or INR = 1.5), without other reason [12].

The exclusion criteria were as follows: [1] Patients who received drugs that may induce severe liver damage in 3 months before admission; [2] Patients with liver cancer; [3] Patients with blood disease; [4] Patients who accepted liver transplantation.

This study was approved by the Ethics Committee of the First People's Hospital of Yancheng City and Beijing 302 Hospital, and was performed in accordance with the Helsinki Declaration. Informed consent was obtained from all the subjects.

2.2. Clinical information and laboratory examinations

The clinical and laboratory characteristics on admission, including RDW, neutrophil, lymphocyte, white blood cell counts, liver enzymes, serum bilirubin, albumin, creatinine, prothrombin time, ascites, blood urea nitrogen, platelet counts, and International Normalized Ratio (INR) were recorded.

Child-Pugh score is a grading standard for quantitative evaluation of liver reserve function. Child-Pugh scores for HEV-related liver diseases were calculated as: [1] Bilirubin: < 34 umol/L, 1 point, 34–51 umol/L, 2 points, > 51 umol/L, 3 points; [2] Albumin: > 35 g/L, 1 point; 28–35 g/L, 2 points; < 28 g/L, 3 points; [3] Ascites: No, 1 point; easy to control, 2 points; difficult to control, 3 points; [4] Hepatic encephalopathy: No, 1 point, light (grade 1–2), 2 points, weight (coma 3–4), and 3 points; [5] Prothrombin time: lengthening 1–3 s, 1 point; 4–6 s, 2 points; > 6 s, 3 points; [6] The scores of each patient were added as follows: A: 5–6 points; B grade 7–9; C grade 10–15.

2.3. Definition of liver failure treatment outcomes

Treatment outcomes of liver failure were classified as follows: a) recovery: Clinical symptoms disappear, no jaundice, liver size and liver function recover to normal level, and PTA or INR returns to normal level; b) improvement: Disease manifestations relieve, encephalopathy disappears, total bilirubin (TBIL) level reduces over 1/3%, and PTA level increases compared to that of before treatment; c) treatment failure: No response or clinical features were not improved to above mentioned indexes; d) death.

2.4. Statistical analysis

Statistical analyses were performed using graphpad prism 7 (La Jolla, CA 92037 USA). Data are presented as the mean ± standard deviation when data was normally distributed or as medians and range if the distribution was skewed. The comparisons between groups were tested using Analysis of Variance (ANOVA). Correlation analysis between variable was conducted using Pearson correlation coefficient analysis. $P < .05$ was considered statistically significant. Receiver operator characteristic (ROC) curves were plotted, and areas under the ROC curves (AUCs) were calculated to evaluate the discrimination threshold of each marker. The appropriate cut-off points for the optimal combination of sensitivity and specificity were determined by the Youden index. General linear regression was used to study correlations between RDW, NLR and RLR levels and other liver function parameters. Binary logistic regression analyses were used to determine factors associated with the incidence of liver failure. We performed binary logistic regression analyses to calculate the adjusted odds ratio (AOR) and 95% confidence interval (CI) values based on maximum likelihood estimation of RDW, NLR and RLR.

3. Results

3.1. Patient characteristics

Demographic and biochemical characteristics of enrolled healthy subjects, HEV-non-LF patients and HEV-LF patients were summarized in Table 1. No significant difference was found regard to age and gender between the three groups. However, the average level of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total billirubin (TBIL), prothrombin time (PT) and white blood cell (WBC) were gradually increased in control group, HEV-non-LF group and HEV-LF group. While the level of platelet (PLT) was gradually decreased in the three groups.

Table 1
Demographic and biochemical characteristics of the study participants.

Variable	1. Healthy controls (n = 93)	2. HEV- non-LF (n = 152)	3. HEV-LF (n = 62)
Age (years)	51.52 (30–78)	51.25 (28–75)	51.75 (24–78)
Gender (M/F)	59/34	98/54	41/21
ALT (U/L)	19.92 ± 8.92	129.32 ± 8.21[a]	459.12 ± 7.91[a,b]
AST (U/L)	17.16 ± 4.12	108.02 ± 4.25[a]	225.32 ± 4.68[a,b]
TBIL (μmol/L)	8.34 ± 3.21	35.99 ± 4.01[a]	69.19 ± 3.99[a,b]
ALB (g/L)	49.56 ± 4.19	39.02 ± 3.51[a]	34.21 ± 4.16[a,b]
CRE (μmol/L)	67.26 ± 43.12	65.02 ± 14.14	69.12 ± 15.79
BUN (mmol/L)	5.16 ± 2.16	5.21 ± 1.29	5.32 ± 1.99
PT (S)	11.81 ± 1.12	14.12 ± 3.41[a]	27.62 ± 7.83[a,b]
WBC ($\times 10^9$/L)	5.11 ± 2.12	12.92 ± 3.75[a]	15.52 ± 4.01[a,b]
PLT ($\times 10^9$/L)	202.16 ± 25.29	140.0 ± 14.77[a]	78.25 ± 16.78[a,b]

Data are expressed as the means ± standard deviation or n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, serum albumin concentration.
TBIL, total billirubin; PLT, platelet counts; BUN, blood urea nitrogen; CRE,creatinine; PT, prothrombin time; WBC: white blood cell.
[a] $P < 0.05$ when compared with healthy controls.
[b] $P < 0.05$ when compared with HEV-non-LF.

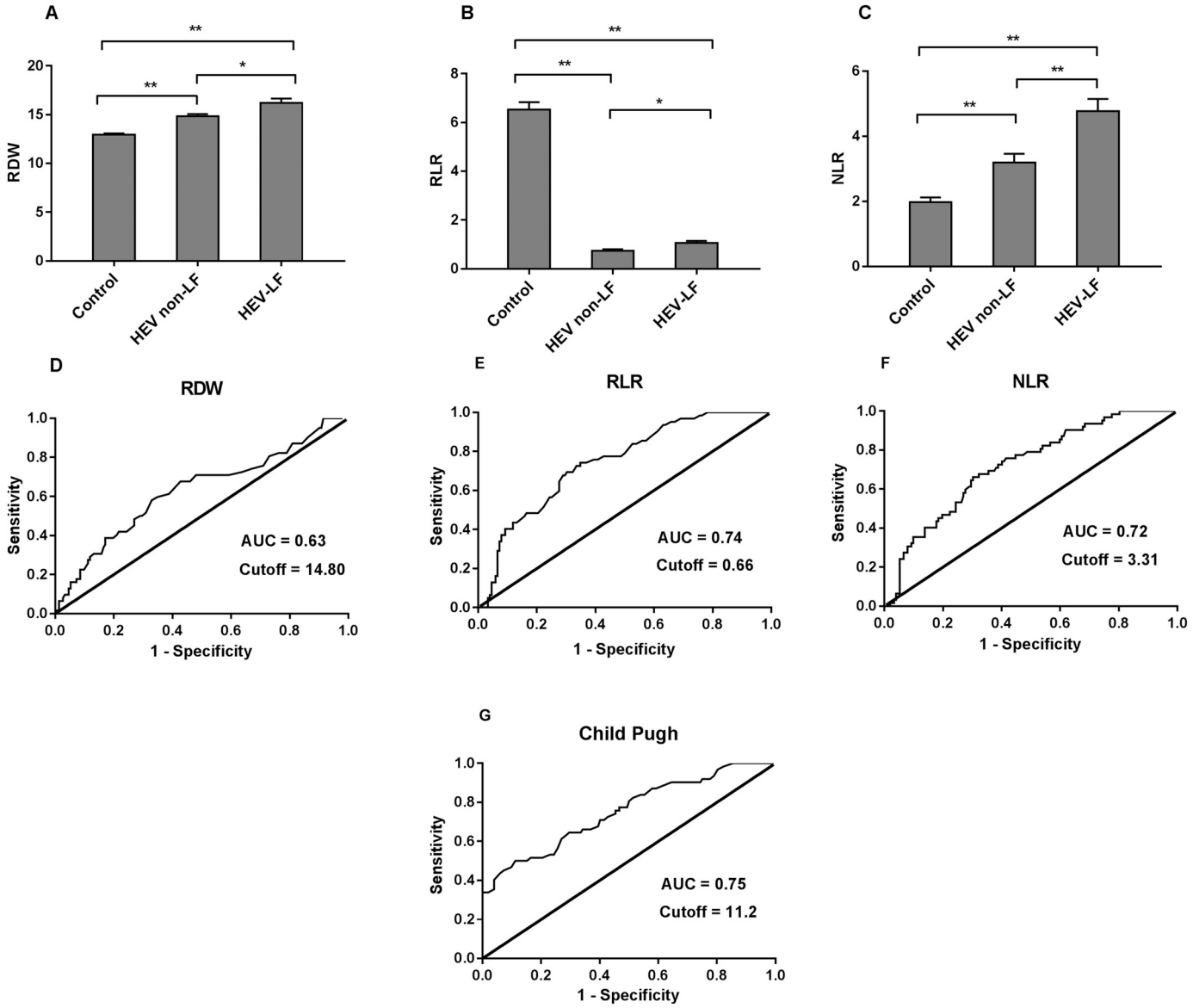

Fig. 1. The levels of RDW, RLR and NLR in different disease status of hepatitis E virus infection. *$P < .05$, **$P < .01$. CONTROL, healthy control group; RDW: red cell distribution width; NLR: neutrophil to lymphocyte ratio; RLR: RDW to lymphocte Ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. The ability of RDW, NLR and RLR in predicting liver failure in HEV infected patients

We firstly studied the levels of RDW, NLR and RLR in each group. The level of both RDW and NLR were gradually and significantly increased in control group, HEV-non-LF group and HEV-LF group (Fig. 1A and Fig. 1C). The level of RLR was remarkably lower in acute HEV infected patients, regardless of the presence of HEV-LF, than healthy controls ($P < .05$; Fig. 1B). Among the 152 HEV infected patients without developing liver failure, 78 were followed up and all of them achieved anti-HEV seronegative conversion, indicating viral clearance. Further analysis with the 78 subjects revealed that the level of RDW, RLR and NLR were all completely restored to the level comparable with that in healthy controls after HEV clearance (Fig. 2). Thus the alterations of these parameters seem to be triggered by HEV infection, other than the causes that increase the susceptibility for severe HEV infections.

AUC analysis was then performed by using RDW, RLR, NLR and Child-Pugh scores (CPS) to predict the development of liver failure in HEV infected patients. The AUC of RLR for predicting HEV-related liver failure was 0.74, which was superior to NLR (0.72) and RDW (0.63), but inferior to CPS (0.75). The sensitivity of RLR for predicting HEV-related liver failure was 0.74, which was superior to NLR (0.66), RDW (0.58) and Child-Pugh scores (0.47), while the specificity of CPS for predicting HEV-related liver failure was 0.73, which was superior to RLR (0.65),NLR (0.70) and RDW (0.67) (Fig. 1D–G).

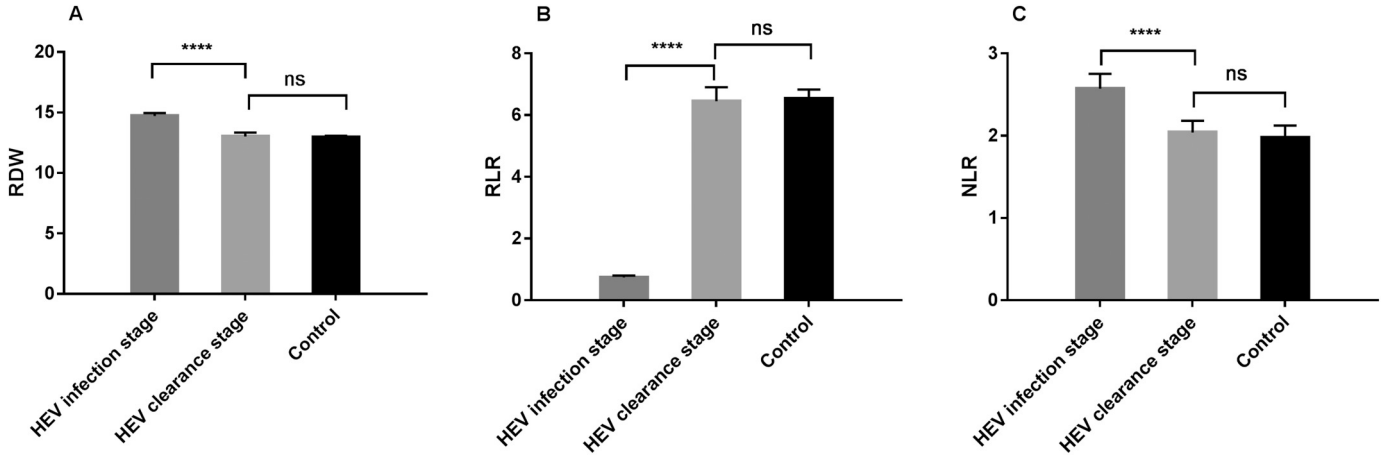

Fig. 2. The levels of RDW, NLR and RLR in HEV-non-LF patients at HEV infection stage and HEV clearance stage, and in healthy controls. *$P < .05$, **$P < .01$, ns, no statistical significance; Control, healthy control group; RDW: red cell distribution width; NLR: neutrophil to lymphocyte ratio; RLR: RDW to lymphocte ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Association of RDW, NLR and RLR with risk of liver failure in HEV infected patients: OR (95%CI) using binary logistic regression.

		HEV non-LF	HEV-LF	Crude OR (95%CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value[a]
RDW	Dichotomies [n (%)]						
	Low (< 14.35 ng/mL)	87 (57.24)	20 (32.26)	1.0 (reference)		1.0 (reference)	
	High (≥14.35 ng/mL)	65 (42.76)	42 (67.74)	2.81 (1.51–5.24)	0.001	1.75 (0.77–3.96)	0.181
	Quartile [n (%)]						
	Q1 (< 13.40 ng/mL)	41 (26.97)	12 (19.35)	1.0 (reference)		1.0 (reference)	
	Q2 (13.40–14.35 ng/mL)	46 (30.26)	8 (12.90)	0.59 (0.22–1.60)	0.302	0.86 (0.25–2.93)	0.812
	Q3 (14.35–16.00 ng/mL)	35 (23.03)	18 (29.03)	1.76 (0.75–4.15)	0.198	1.36 (0.43–4.29)	0.603
	Q4 (> 16.00 ng/mL)	30 (19.74)	24 (38.71)	2.73 (1.18–6.32)	0.019	1.96 (0.63–6.07)	0.243
RLR	Dichotomies [n (%)]						
	Low (< 0.63 ng/mL)	92 (60.53)	15 (24.19)	1.0 (reference)		1.0 (reference)	
	High (≥0.63 ng/mL)	60 (39.47)	47 (75.81)	4.80 (2.47–9.35)	< 0.001	5.02 (2.01–12.58)	< 0.001
	Quartile [n (%)]						
	Q1 (< 0.45 ng/mL)	50 (32.89)	3 (4.84)	1.0 (reference)		1.0 (reference)	
	Q2 (0.45–0.63 ng/mL)	42 (27.63)	12 (19.35)	4.76 (1.26–18.00)	0.022	21.90 (1.87–256.64)	0.014
	Q3 (0.63–0.86 ng/mL)	36 (23.68)	18 (29.03)	8.33 (2.28–30.42)	0.001	34.50 (3.00–396.44)	0.005
	Q4 (> 0.86 ng/mL)	24 (15.79)	29 (46.77)	20.14 (5.57–72.74)	< 0.001	67.93 (5.92–779.44)	0.001
NLR	Dichotomies [n (%)]						
	Low (< 2.81 ng/mL)	91 (59.87)	16 (25.81)	1.0 (reference)		1.0 (reference)	
	High (≥2.81 ng/mL)	61 (40.13)	46 (74.19)	4.29 (2.23–8.26)	< 0.001	4.81 (1.93–12.02)	< 0.001
	Quartile [n (%)]						
	Q1 (< 1.71 ng/mL)	48 (31.58)	5 (8.06)	1.0 (reference)		1.0 (reference)	
	Q2 (1.71–2.81 ng/mL)	43 (28.29)	11 (17.74)	2.46 (0.79–7.64)	0.121	2.47 (0.54–11.30)	0.242
	Q3 (2.81–4.13 ng/mL)	34 (22.37)	20 (32.26)	5.65 (1.93–16.53)	0.002	7.13 (1.68–30.37)	0.008
	Q4 (> 4.13 ng/mL)	27 (17.76)	26 (41.94)	9.24 (3.18–26.87)	< 0.001	9.40 (2.22–39.75)	0.002

[a] Adjusted for alcoholic liver damage (ALD), HBV, cirrhosis.

Table 3
Validation of RDW, NLR and RLR in diagnosis of 48 HEV patients with or without liver failure.

		HEV-LF (*N* = 24)	HEV-non-LF (N = 24)	Sensitivity	Specificity
RDW (ng/mL)	> 14.8	15	8	0.63	0.67
	≤14.8	9	16		
RLR (ng/mL)	> 0.66	17	9	0.71	0.63
	≤0.66	7	15		
NLR (ng/mL)	> 3.31	16	7	0.67	0.71
	≤3.31	8	17		

We subsequently assessed the correlations between RDW, RLR, NLR and the incidence of HEV-LF by binary logistic regression analysis (Table 2). According to the median values of RDW (14.35 ng/mL), NLR (2.81 ng/mL) and RLR (0.63 ng/mL), participants were divide in to "Low" and "High" groups. After adjusting for background liver status, including alcoholic liver damage (ALD), HBV infection and liver cirrhosis, HEV patients with higher levels of RLR and NLR were significantly associated with increased risk of liver failure, respectively. Furthermore, a clear relationship between increased serum RLR, NLR levels and liver failure risk were observed with the elevation of adjusted OR by quartile analyses (Table 2).

We then validated the diagnostic efficacy of the three parameters with additional 24 HEV-LF patients and 24 HEV-non-LF patients from Beijing 302 hospital between Octobers in 2017 and September in 2018.

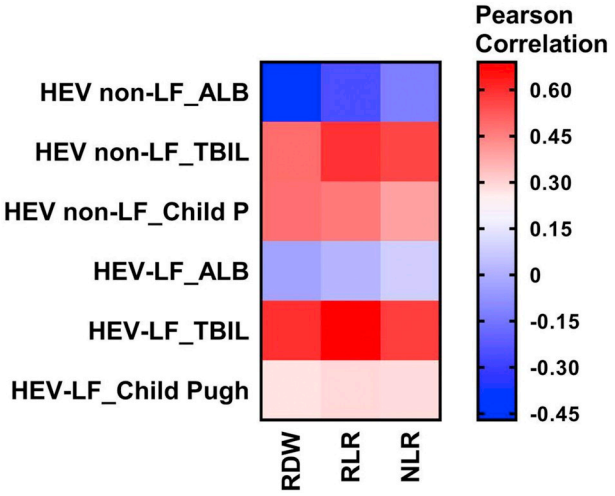

Fig. 3. Overall profile of the correlations between ALB, TBIL, Child-Pugh score and RDW, RLR, NLR in HEV patients with or without liver failure. ALB: serum albumin concentration (g/L); TBIL: total billirubin (umol/L); RDW: red cell distribution width; NLR: neutrophil to lymphocyte ratio; RLR: RDW to lymphocte ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

According to the CUT OFF values of RDW (14.8 ng/mL), NLR (3.31 ng/mL) and RLR (0.66 ng/mL), the predicting abilities of RDW, NLR and RLR for HEV-related liver failure were similar to the results obtained in original cohort (Table 3).

3.3. Correlations between RDW, NLR and RLR levels and other liver function parameters

To clarify the role of RDW, NLR and RLR in predicating liver function, we then analyzed the correlations between RDW, NLR, RLR levels and other liver function parameters in HEV-non-LF and HEV-LF groups, respectively (Fig. 3).

In HEV-non-LF group, RDW, NLR and RLR levels were all negatively correlated with serum albumin (ALB) (all $P < .05$) and positively correlated with serum TBIL and CPS (all $P < .001$; Fig. 4). In HEV-LF group, positive correlation was only observed between RDW, NLR, RLR levels and serum TBIL, but not ALB and CPS (Fig. 5).

3.4. RDW, NLR and RLR in predicting the prognosis of liver failure in HEV patients

In order to investigate the ability of RDW, NLR and RLR in predicting the prognosis of HEV-related liver failure, we divided the HEV-LF patients into two groups according to treatment outcomes: Recovery/Improvement group and Treatment failure/Death group. No significant correlations were found between favorite/poor prognosis and any of the three parameters after adjusting for TBIL, prothrombin time, ascites, hepatic encephalopathy (Table 4).

4. Discussion

In this study, we analyzed the role of RDW, RLR and NLR in predicting the occurrence and prognosis of liver failure in HEV patients. RDW, NLR and RLR were found higher in HEV patients developing liver failure, compared with HEV-non-LF patients. There are positive associations of increased RDW, RLR, NLR and incidence of liver failure, respectively. Among these, RLR has a good sensitivity and specificity for predicting liver failure in HEV patients. However, no correlations between any of the three parameters and prognosis of HEV-LF were observed. In addition, the three parameters were all correlated to ALB, TBIL and CPS in HEV-non-LF subjects, other than in HEV-LF patients.

The association between RDW and liver diseases has been investigated in several studies. It has been reported that the level of RDW was elevated in HBV patients and correlated with the severity of liver damage [13]. It has also been suggested that RDW may be a potential marker for diagnosis of liver fibrosis in HCV patients [6]. Similarly, our study found a significant increase of the RDW values in HEV patients with the highest value in HEV-LF population, compared with healthy controls. Moreover, serum RDW correlates with the severity of liver damage in HEV-non-LF individuals. It is uncertain why the level of RDW is associated with liver diseases. Most of HEV patients who developed liver failure generally undergo a process of inflammation. Elevation of RDW reflecting systemic inflammation, which is a hallmark of acute-on-chronic liver failure (ACLF), may explain their alteration in HEV patients. Alternatively, the change of RDW is associated with anemia, which is a common complication of hepatitis E, suggesting another potential mechanism of RDW elevation in patients with HEV infection. Similar to RDW, RLR is also an inflammatory marker [14,15]. Comparing to the increased RDW in patients with HEV-related liver diseases, the level of RLR was remarkably lower. Binary logistic regression analysis showed that RLR was an independent predicting factor for liver failure in HEV patients, but not for prognosis in HEV patients.

In previous studies, NLR was reported to be an independent predicting factor for the mortality rate in HBV-related ACLF or liver decompensated patients [16,17]. In the current study, binary logistic regression analysis showed that NLR was an independent predicting factor for liver failure in HEV patients, but not for prognosis in HEV patients. Both lymphocytes and neutrophils are important components of white blood cells, which participate in the pathogenesis of various diseases, and play an important role in the immune defense system of the body [18]. Peripheral blood neutrophils are significantly elevated during infection. The level of neutrophils is capable to reflect the inflammatory state in the course of disease progression, while lymphocytes represent the outcome of regulated immunity [19]. The pathogenesis of HEV-LF is indeed complex. The release of pathogen-associated-molecular patterns (PAMPs) by viral infection is a possible mechanism. In addition, excessive inflammation may also result from nonbacterial endogenous mediators [20,21]. Hence, the initial level of systemic inflammation following HEV infection could lead to organ dysfunction and subsequent deregulated NLR.

In the current study, we also compared the predicating abilities of the 3 parameters with conventional parameter, CPS. Although CPS displayed a mildly superior predicting efficacy to RLR (0.75 vs. 0.74),

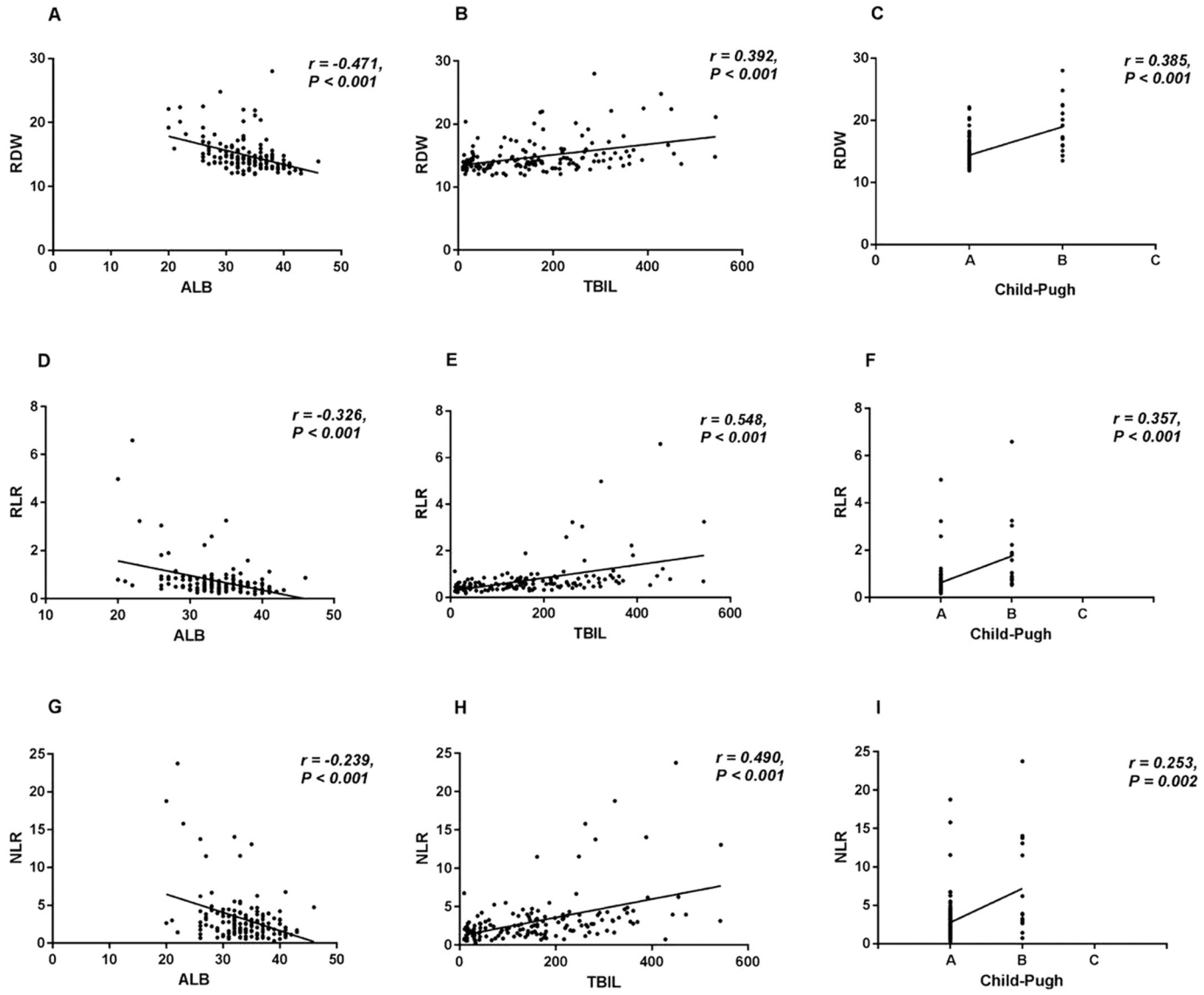

Fig. 4. Correlations between RDW, RLR, NLR and ALB, TBIL, CPS in patients with HEV-LF. ALB: serum albumin concentration (g/L); TBIL: total billirubin (umol/L); RDW: red cell distribution width; RLR: RDW to lymphocte Ratio; NLR: neutrophil to lymphocyte ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the sensitivity of CPS for predicting HEV-related liver failure was only 0.47. The sensitivity and specificity of RLR for predicting HEV-related liver failure were 0.74 and 0.65, respectively. The much better sensitivity of RLR suggested a promising role in screening and early prediction to identify potential patients with risk of liver failure.

Overall, our study has pioneered to evaluate the role of RDW, NLR and RLR in predicating the development and prognosis of liver failure following HEV infection. We found that RDW, NLR and RLR are useful to predicate the development of liver failure in HEV patients, among which RLR has the best efficacy. RDW, NLR and RLR shall be considered as new diagnosis preliminarily diagnostic markers for liver failure in HEV patients with advantages of non-invasiveness, easy access, cost-efficiency and timeliness.

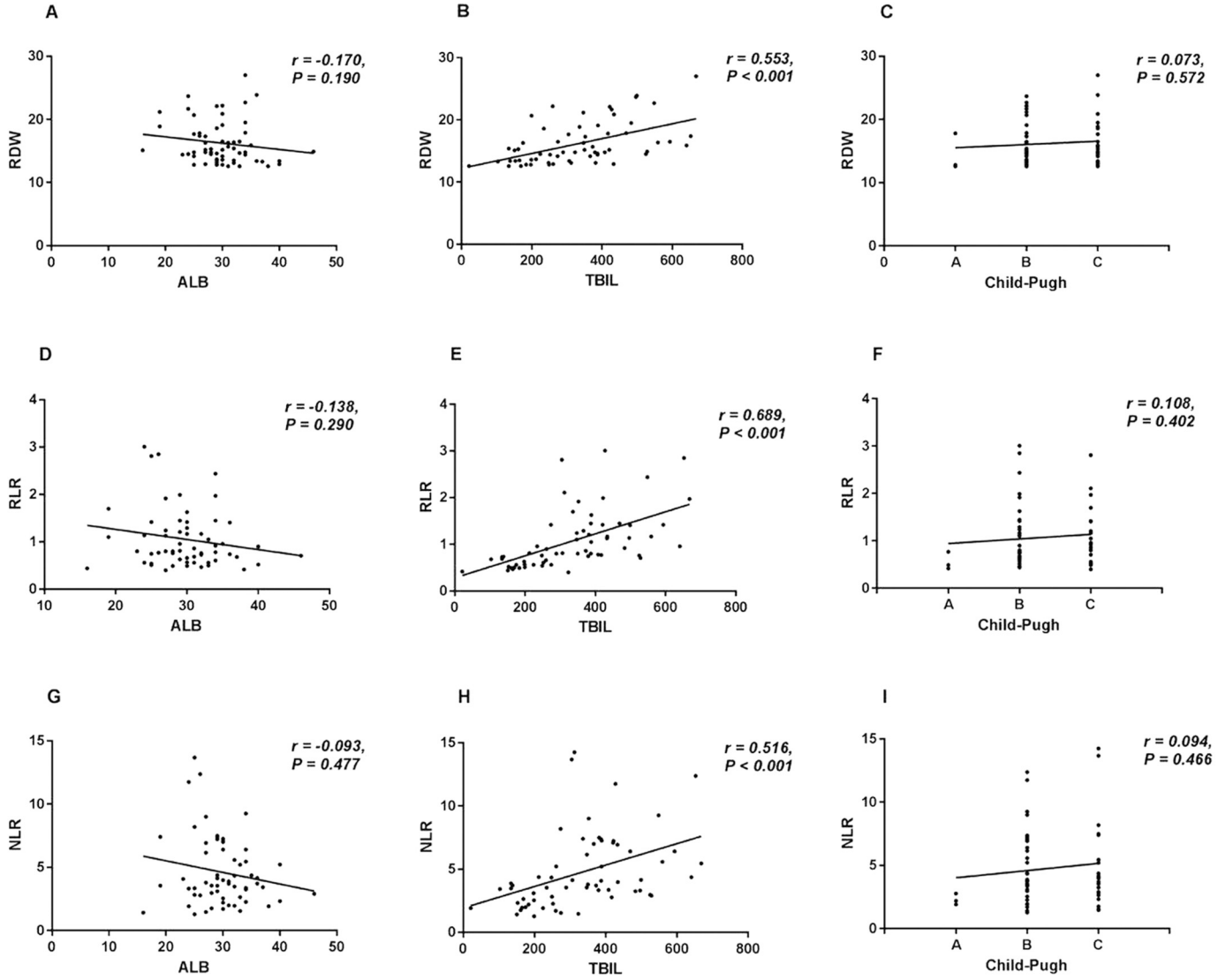

Fig. 5. Correlations between RDW, RLR, NLR and ALB, TBIL, CPS in HEV patients without liver failure. ALB: serum albumin concentration (g/L); TBIL: total billirubin (umol/L); RDW: red cell distribution width; RLR: RDW to lymphocte Ratio; NLR: neutrophil to lymphocyte ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Competing interests

The authors have declared that no competing interests exists.

Author contributions

J.W. contributed to study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; X.Z contributed to statistical analysis; H.L.contributed to acquire clinical data; N.G. contributed to study concept, study supervision and critical revision of the manuscript; Y·W and Q.P. contributed to study concept and design, study supervision and critical revision of the manuscript.

Grant support

This research was supported by the Youth Medical Talent of Jiangsu Province (grant no. QNRC2016475) to (J.W.).

Table 4
Association of RDW, NLR and RLR with prognosis of liver failure in HEV infected patients: OR (95%CI) using binary logistic regression.

		Recovery/improvement	Treatment failure/death	Crude OR (95%CI)	*P*-value	Adjusted OR (95% CI)[a]	*P*-value[a]
RDW	Dichotomies [n (%)]						
	Low (< 15.00 ng/mL)	20 (50.00)	11 (50.00)	1.0 (reference)		1.0 (reference)	
	High (≥15.00 ng/mL)	20 (50.00)	11 (50.00)	1.00 (0.35–2.83)	1.0	0.51 (0.13–1.98)	0.329
	Quartile [n (%)]						
	Q1 (< 13.50 ng/mL)	9 (22.50)	6 (27.27)	1.0 (reference)		1.0 (reference)	
	Q2 (13.50–15.00 ng/mL)	11 (27.50)	5 (22.73)	0.68 (0.16–2.99)	0.612	0.46 (0.08–2.63)	0.381
	Q3 (15.00–17.80 ng/mL)	11 (27.50)	5 (22.73)	0.68 (0.16–2.99)	0.612	0.23 (0.04–1.55)	0.132
	Q4 (> 17.80 ng/mL)	9 (22.50)	6 (27.27)	1.00 (0.23–4.31)	1.000	0.48 (0.06–3.90)	0.490
RLR	Dichotomies [n (%)]						
	Low (< 0.81 ng/mL)	22 (55.00)	9 (40.91)	1.0 (reference)		1.0 (reference)	
	High (≥0.81 ng/mL)	18 (45.00)	13 (59.09)	1.77 (0.62–5.06)	0.290	1.25 (0.32–4.96)	0.747
	Quartile [n (%)]						
	Q1 (< 0.63 ng/mL)	9 (22.50)	6 (27.27)	1.0 (reference)		1.0 (reference)	
	Q2 (0.63–0.81 ng/mL)	13 (32.50)	3 (13.64)	0.35 (0.07–1.76)	0.201	0.25 (0.04–1.66)	0.152
	Q3 (0.81–1.41 ng/mL)	8 (20.00)	8 (36.36)	1.50 (0.36–6.23)	0.577	0.78 (0.12–5.15)	0.795
	Q4 (> 1.41 ng/mL)	10 (25.00)	5 (22.73)	0.75 (0.17–3.33)	0.705	0.33 (0.04–2.56)	0.287
NLR	Dichotomies [n (%)]						
	Low (< 3.76 ng/mL)	21 (52.50)	10 (45.45)	1.0 (reference)		1.0 (reference)	
	High (≥3.76 ng/mL)	19 (47.50)	12 (54.55)	1.33 (0.47–3.77)	0.596	0.88 (0.25–3.11)	0.836
	Quartile [n (%)]						
	Q1 (< 2.78 ng/mL)	10 (25.00)	5 (22.73)	1.0 (reference)		1.0 (reference)	
	Q2 (2.78–3.76 ng/mL)	11 (27.50)	5 (22.73)	0.91 (0.20–4.10)	0.901	0.77 (0.13–4.51)	0.767
	Q3 (3.76–6.41 ng/mL)	9 (22.50)	7 (31.81)	1.56 (0.36–6.69)	0.553	0.94 (0.14–6.14)	0.949
	Q4 (> 6.41 ng/mL)	10 (25.00)	5 (22.73)	1.00 (0.22–4.56)	1.000	0.57 (0.09–3.68)	0.550
	High (≥0.81 ng/mL)	18 (45.00)	13 (59.09)	1.77 (0.62–5.06)	0.290	1.25 (0.32–4.96)	0.747

[a] Adjusted for TBIL, prothrombin time (PT), ascites, hepatic encephalopathy.

Acknowledgements

None.

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