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Original Article

The relationship between inflammatory marker levels and HBV-related cirrhosis severity

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Abstract: Haematological indices, including neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW), and red blood cell distribution width-platelet ratio (RPR) are used to assess the severity of various diseases. We aim to evaluate the relationship between these parameters and the severity of Hepatitis B Virus (HBV) related cirrhosis. The study consisted of 78 patients with HBV-related cirrhosis (32 compensated and 46 decompensated patients) and 54 healthy individuals. Clinical characteristics and laboratory parameters were recorded. The NLR, RDW and RPR were significantly increased in cirrhosis patients. The NLR in decompensated were significantly higher than compensated cirrhosis (3.84 ± 3.27 vs. 1.71 ± 0.65, P < 0.001). Moreover, RDW and RPR were significantly increased in decompensated patients compared to the compensated cirrhosis patients (all P < 0.001). The area under the curve of NLR was 0.801 and received a cutoff value of 2.06 (71.7% sensitivity and 78.1% specificity). The AUC values of RDW and RPR were 0.815 (cutoff value: 15.5%; sensitivity: 76.1%; specificity: 75.0%) and 0.876 (cutoff value: 0.166; sensitivity: 93.5%; specificity: 75.0%), respectively. The NLR, RDW and RPR were significantly increased and associated with disease severity in HBV-related cirrhosis patients.

Keywords: Neutrophil-lymphocyte ratio, red blood cell distribution width, red blood cell distribution width-platelet ratio, hepatitis B virus, cirrhosis

Introduction

Chronic hepatitis B virus (HBV) infection can result in HBV-related compensated cirrhosis and subsequently HBV-related decompensated cirrhosis, which is classified as advanced-stage disease. Chronic HBV infection is the main cause of cirrhosis in China, and advanced liver cirrhosis and hepatocellular carcinoma (HCC) are the main causes of mortality in chronic HBV patients [1, 2]. A liver biopsy is the gold standard for the diagnosis of hepatitis cirrhosis [3]. However, due to its invasive nature, it is not feasible in the dynamic monitoring of the severity in liver cirrhosis [4]. Complete blood count (CBC) has the advantages of convenient extraction of blood, rapid detection, and low price, which is used as a basic auxiliary test to assess the situation of various diseases. However, the additional functionality of neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW) and red blood cell distribution width-platelet ratio (RPR), may be largely overlooked.

The NLR can be readily calculated from the CBC. The NLR was used to predict the mortality of HBV-related decompensated cirrhosis patients [2]. The RDW is a numerical laboratory parameter that reflects the size heterogeneity of red blood cells (RBCs) and is commonly used in the classification of anemia [5]. A recent study suggested that an elevated RDW was a predictor of mortality in liver disease [6]. An elevated RPR was served as to predict severe liver fibrosis and cirrhosis in chronic HBV patients [7]. The RDW, RPR and NLR are economical, fast and convenient indicators that easily be obtained from the CBC. The number of studies evaluating the relationship between these parameters and compensated and decompensated cirrhosis patients is limited. The aim of the present study was to measure a number of indicators (NLR, RDW, RPR) in

Table 1. Demographic and laboratory characteristics of the participants

	Cirrhosis (n = 78)	Controls (n = 54)	*p*
[1]Age (years)	45.82 ± 9.94	44.82 ± 5.65	0.231
[2]Gender (male/female)	62/16	40/14	0.466
[1]WBC count ($\times 10^9$/L)	5.26 ± 2.72	6.66 ± 1.03	< 0.001
[1]Nc ($\times 10^9$/L)	3.22 ± 2.40	3.60 ± 0.88	0.001
[1]Lc ($\times 10^9$/L)	1.34 ± 0.69	2.42 ± 0.62	< 0.001
[1]Platelet count ($\times 10^9$/L)	89.97 ± 46.22	203.87 ± 28.49	< 0.001
[1]NLR	2.96 ± 2.74	1.60 ± 0.61	< 0.001
[1]RPR	0.27 ± 0.22	0.06 ± 0.01	< 0.001
[1]RDW (%)	18.62 ± 4.05	14.02 ± 1.81	< 0.001

[1]two-independent samples T-test; [2]Chi-square test. WBC, white blood cell; Nc, neutrophil count; Lc, lymphocyte count; NLR, neutrophil-lymphocyte ratio; RPR, red blood cell distribution width to platelet ratio; RDW, red blood cell distribution width.

patients with HBV-related cirrhosis and to evaluate the association between these markers and the severity of the disease.

Materials and methods

Information on HBV-related cirrhosis (1 March 2014 to 1 December 2015) was extracted from the electronic medical records of the first affiliated hospital of guangxi medical university. The diagnosis of HBV-related liver cirrhosis, including compensated and decompensated cirrhosis, was made according to the abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging), or surgical findings, and laboratory results [1]. The presence of jaundice, ascites, variceal bleeding, hepatorenal syndrome or hepatic encephalopathy in patients with cirrhosis was defined as decompensated cirrhosis [8]. The exclusion criteria were as follows: autoimmune (liver) diseases, such as rheumatoid arthritis, systemic lupus erythematosus; infectious diseases, inflammatory diseases, or other hepatic diseases, such as alcoholic liver disease; coinfection with other hepatitis viruses, such as the hepatitis C/D/G virus; malignancy, including HCC; previous blood transfusions; hematological diseases; atherosclerosis; hypertension; diabetes; renal diseases. Fifty-four healthy controls from health examination centers without HBsAg-positive and infection, and with normal liver and renal function, were also included in the study.

Demographic data on the patients, including their age and gender, were collected. Blood samples for CBC and biochemical parameters detection were drawn from the elbow after 8 hours of fasting. The CBC was analyzed using a Beckman Coulter LH780 hematology analyzer (Beckman Coulter Inc., Fullerton, CA, USA) within 1 hour of blood drawing. Biochemistry parameters were determined by a Hitachi 7600 autoanalyzer. Laboratory results, including data on white blood cells, neutrophils, lymphocytes, platelets, RDWs, prothrombin time (PTs), international normalized ratio (INRs), in addition to data on creatinine, total bilirubin (Tbil), total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and HBV DNA were collected from the electronic medical records. Data were also recorded on complications of HBV-related cirrhosis, including jaundice, ascites, variceal bleeding, hepatorenal syndrome and hepatic encephalopathy, on admission. The NLR was defined as the absolute value of the neutrophil count divided by the absolute value of the lymphocyte count. The RPR was defined as the RDW divided by the platelet count. This study was approved by the ethics committee of the first affiliated hospital of guangxi medical university.

Statistical analysis

Continuous variablesare reported as the mean ± standard deviation. Differences in normally distributed data between groups were analyzed using Student's *t*tests, and non-normally distributed data were evaluated by Mann-Whitney *U* tests. The X^2 test was used to analyze the categorical data. Spearman's correlation test was utilized to determine the relationship between NLR, RDW and RPR and MELD score. The diagnostic capacity of identifying decompensated cirrhosis in cirrhosis was performed by the receiver operating characteristic (ROC) curves. SPSS17.0 (SPSS Inc., Chicago, IL, USA) statistical software was used to analyze the data. $P < 0.05$ was considered statistically significant.

Results

Seventy-eight HBV-related cirrhosis patients (62 men and 16 women) and 54 controls (40

Table 2. Clinical and laboratory characteristics of patients with compensated and decompensated cirrhosis

	Compensated (n = 32)	Decompensated (n = 46)	*p*
[1]Age (years)	43.06 ± 9.17	47.74 ± 10.05	0.041
[2]Gender (male/female)	26/6	36/10	0.800
[1]Total protein (g/L)	65.28 ± 4.53	59.16 ± 5.99	< 0.001
[1]Albumin (g/L)	34.54 ± 5.02	26.61 ± 5.27	< 0.001
[3]Tbil (μmol/L)	21.57 ± 10.84	103.82 ± 132.02	< 0.001
[1]ALT (U/L)	47.67 ± 18.92	81.78 ± 151.14	0.265
[3]AST (U/L)	43.61 ± 16.36	115.25 ± 154.21	< 0.001
[1]Creatinine (μmol/L)	78.55 ± 14.64	74.59 ± 20.12	0.338
[3]PT (s)	12.67 ± 1.59	19.26 ± 5.95	< 0.001
[3]INR	1.09 ± 0.17	1.61 ± 0.51	< 0.001
[1]WBC count ($\times 10^9$/L)	5.19 ± 1.68	5.29 ± 3.27	0.337
[3]Nc ($\times 10^9$/L)	2.72 ± 1.03	3.57 ± 2.97	0.626
[1]Lc ($\times 10^9$/L)	1.74 ± 0.73	1.06 ± 0.55	< 0.001
[3]Platelet count ($\times 10^9$/L)	119.43 ± 46.05	68.75 ± 32.53	< 0.001
[3]NLR	1.71 ± 0.65	3.84 ± 3.27	< 0.001
[3]RDW (%)	15.01 ± 3.13	18.85 ± 3.99	< 0.001
[3]RPR	0.16 ± 0.13	0.35 ± 0.24	< 0.001
[3]MELD score	6.01 ± 3.01	13.81 ± 7.61	< 0.001
HBsAg positive (yes/no)	32/0	46/0	-
[2]HBeAg positive (yes/no)	6/26	7/39	0.726
[2]HBV DNA positive (yes/no)	25/7	39/7	0.451
Jaundice	-	21	-
Ascites	-	32	-
Variceal bleeding	-	9	-
Hepatorenal syndrome	-	2	-
Hepatic encephalopathy	-	2	-

[1]two-independent samples T-test; [2]Chi-square test; [3]Mann-Whitney *U* tests. Tbil, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; Nc, neutrophil count; Lc, lymphocyte count; NLR, neutrophil-lymphocyte ratio; RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet ratio; MELD, model for end-stage liver disease.

men and 14 women) were recruited in our study. Demographic and laboratory characteristics of the cirrhosis patients and controls were presented in **Table 1**. There were no significant differences in the age and gender of the cirrhosis patients and controls. The NLR, RDW, RPR were significantly increased, whereas white blood cells count, lymphocyte counts, and platelet counts were significantly decreased in cirrhosis patients, as compared to corresponding values in healthy individuals.

As shown in **Table 2**, there was no significant difference in the gender of the compensated and decompensated cirrhosis patients. The age of patients with decompensated was significantly higher than in the patients with compensated cirrhosis patients ($P = 0.041$). All the cirrhosis patients (78 cases) were positive for HBsAg, 13 patients were HBeAg positive (6 compensated and 7 decompensated), 64 patients were HBV DNA positive (25 compensated and 39 decompensated). In patients with decompensated patients, 21 patients had jaundice, 32 patients had ascites, 9 patients had variceal bleeding, 2 patients had hepatorenal syndrome, 2 patients had hepatic encephalopathy. The NLR, RDW, RPR values and MELD scores were significantly higher in decompensated cirrhosis compared to compensated cirrhosis (all $P < 0.001$), whereas total protein, albumin, lymphocyte and plateletcount values were significantly lower in decompensated cirrhosis compared to compensated cirrhosis (all $P < 0.001$). Correlation analysis showed that NLR, RDW and RPR were positively correlated with MELD scores, respectively ($r = 0.340$, $P = 0.002$; $r = 0.425$, $P < 0.001$; $r = 0.464$, $P < 0.001$) (Supplementary Table 1).

The diagnostic capability of parameters in identifying decompensated stage in patients with HBV-related cirrhosis was performed by the ROC curves. The AUC values of NLR and MELD score were 0.801 and 0.842, respectively. The cutoff value of NLR for decompensated cirrhosis patients was 2.06 and received a 71.7% sensitivity and 78.1% specificity. The AUC values of RDW and RPR were 0.815 (cutoff value: 15.5%; sensitivity: 76.1%; specificity: 75.0%) and 0.876 (cutoff value: 0.166; sensitivity: 93.5%; specificity: 75.0%), respectively (**Figure 1**).

Discussion and conclusion

Chronic HBV infection is considered to be one of the major global etiologies of liver cirrhosis

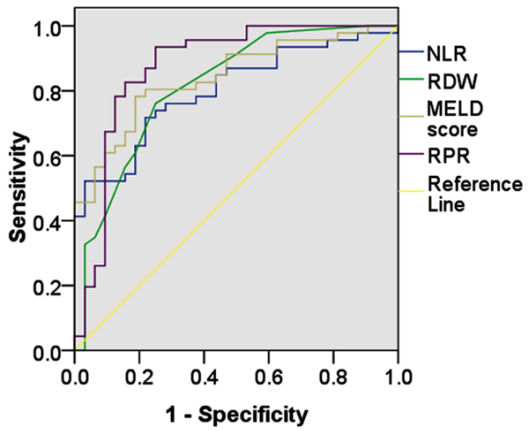

Figure 1. Receiver operator characteristic curve for NLR, RDW, RPR and MELD score. The cutoff values of the NLR, RDW, and RPR were 2.06, 15.5%, and 0.166, respectively. NLR, Neutrophil-lymphocyte ratio; RDW, red blood cell distribution width; MELD, model for end-stage liver disease; RPR, red blood cell distribution width to platelet ratio.

and subsequent development of decompensated cirrhosis and HCC [1, 9]. It is worth noting that the prevalence of HBV infection is high in the Asia Pacific region [3]. Apart from a liver biopsy, laboratory indicators, such as levels of albumin, Tbil, AST, and platelets, and platelet distribution width, are considered independent makers of the progression of hepatic fibrosis [4].

The RDW, an indicator of the heterogeneity of the size of RBCs, is easily obtained from the CBC. Recent studies indicated that RDW values could predict the severity of various liver diseases. Wang reported that increased RDW values might be related to the histological severity of primary biliary cirrhosis [10]. Karagoz indicated that the RDW could estimate the severity of hepatic fibrosis [11]. Lou investigated RDW values in patients with acute hepatitis B (AHB), CHB, and chronic severe hepatitis B (CSHB) [6]. They found that RDW values were slightly elevated in AHB, CHB, and CSHB patients. And they reported that the clinical manifestations of patients with elevated RDW values were more severe than those with lower RDW values, and their liver indices were worse. The mortality of patients with elevated RDW values was also increased. Huang found that RDW values in HBV-related cirrhosis were significantly higher than in CHB and healthy individuals and suggested that RDW values were positively correlated with MELD scores in cirrhosis patients [12]. Therefore, they suggested that the RDW might be a predictor of the severity of HBV-related hepatic disease. Furthermore, they found that the RDW could independently predict the presence of cirrhosis. Chen considered that elevated RDW and RPR could predict liver cirrhosis in chronic HBV [7]. They showed that RDW and platelet could strongly predict the presence of severe fibrosis or cirrhosis in chronic HBV patients. Few studies have reported the relationship between RDW, as well as RPR, and the stage of liver cirrhosis. In our study, an increased RDW value and thrombocytopenia can bring about an elevated RPR in cirrhosis patients. The RPR and RDW presented prominent performance in the prediction of decompensated cirrhosis.

The NLR, which can be calculated from the CBC using a simple test, served as an indicator of the inflammatory response [13-15]. Recently, the utility of the NLR as a marker in liver diseases was investigated. Alkhouri concluded that the NLR could be a new noninvasive predictor in advanced-stage nonalcoholic steatohepatitis (NASH) [16]. Yilmaz compared the utility of the NLR and C-reactive protein in NASH-related cirrhosis patients and found that the NLR was associated with the pathological grading and severity of fibrosis. They concluded that NASH might be a superior maker to C-reactive protein [17]. A few studies reported on the correlation between the NLR and HBV-related liver diseases. Chen indicated that the NLR could be utilized to forecast the mortality of patients with acute or chronic liver failure [18]. Zhang showed that the NLR was associated with disease severity in decompensated cirrhosis patients and suggested that the NLR could predict the mortality of patients with decompensated cirrhosis [2]. In our study, the NLR values in decompensated cirrhosis were significantly higher than those in compensated cirrhosis.

Neutrophils originate from bone marrow and can be an important inducer of inflammation of the liver and liver parenchymal cell injury [19, 20]. Zhang reported that neutrophils appeared to increase following inflammation of the liver and that lymphopenia of peripheral blood was involved in decompensated cirrhosis [2]. Lymphopeniais found in cases of malnutrition and a weak immune system, and immuno-incompe-

tence is relatively common in cases of chronic liver disease [21]. One study by Zhang reported that relatively decreased absolute value of lymphocyte while increased absolute value of monocyte was associated with elevated lymphocyte-monocyte ratio in patients with cirrhosis [22]. In our study of HBV-related cirrhosis patients, the levels of leukocytes and neutrophils of the patients with decompensated cirrhosis were higher than those of the patients with compensated cirrhosis, whereas lymphocyte counts were lower in decompensated cirrhosis than in compensated cirrhosis. Elevated neutrophils and reduced values of lymphocytes may result in increased NLR values.

The present study has some limitations. We did not measure the levels of various factors, such as vitamin B_{12} and iron, that might be associated with elevated RDW levels. We did not investigate subsequent treatment-induced changes in the biochemical data. Other non-invasive methods for assessing the severity of liver disease could also have been added to this study. This was a single centre, retrospective study. Further studies of larger sample sizes are needed.

Conclusions

We found that NLR, RDW, RRP were significantly increased and associated with the severity of HBV-related cirrhosis. These indices, in combination with other laboratory parameters, might be very useful in assessing the disease severity.

Disclosure of conflict of interest

None.

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