

Red Blood Cell Distribution Width Levels Correlate With Liver Fibrosis and Inflammation

A Noninvasive Serum Marker Panel to Predict the Severity of Fibrosis and Inflammation in Patients With Hepatitis B

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Abstract: We aimed to study whether red blood cell distribution width (RDW) could be one of the variables determining the extent of liver fibrosis and inflammation in patients with biopsy-proven hepatitis B.

A total of 446 hepatitis B virus-infected patients who underwent liver biopsy were divided into 2 groups: absent or mild and moderate–severe according to the severity of liver fibrosis and inflammation. The independent variables that determine the severity of liver fibrosis and inflammation were explored.

RDW values increased with progressive liver fibrosis and inflammation. After adjustments for other potent predictors, liver fibrosis (moderate–severe) was independently associated with RDW, platelet, and albumin (odds ratio = 1.121, 0.987, and 0.941, respectively), whereas increased odds ratios of significant inflammation were found for RDW, alanine aminotransferase, albumin, and PLT (odds ratio = 1.146, 1.003, 0.927, and 0.990, respectively). The sensitivity and specificity of model A were 70.0% and 62.9% for detection of significant liver fibrosis [area under the receiver-operating characteristic curve (AUC) = 0.713, $P < 0.001$]. The sensitivity and specificity of model B were 66.1% and 79.4% for predicting advanced liver inflammation (AUC = 0.765, $P < 0.001$). Compared with preexisting indicators, model A achieved the highest AUC, whereas model B showed a higher AUC than RDW to platelet ratio (0.670, $P < 0.001$) and FIB-4 (0.740, $P = 0.32$).

RDW may provide a useful clinical value for predicting liver fibrosis and necroinflammation in hepatitis B-infected patients with other markers.

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Abbreviations: ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate aminotransferase, AUC = the

area under the receiver operating characteristics curve, BMI = body mass index, CHBc = chronic hepatitis B, CIV = type IV collagen, HA = hyaluronic acid, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, LN = laminin, MCV = mean corpuscular volume, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, NPV = negative predictive value, PBC = primary biliary cirrhosis, PIIINP = N-terminal peptide of type III procollagen, PPV = positive predictive value, RDW = red blood cell distribution width, ROC = receiver operating characteristics, RPR = RDW to platelet ratio, TBIL = total bilirubin, WBC = white blood count.

INTRODUCTION

In China, an estimated 93 million people have been infected with the hepatitis B virus (HBV). Globally, more than 240 million people have suffered from chronic HBV infections and about 780,000 people died from HBV-related diseases each year.¹ It is well known that chronic infection with HBV will eventually lead to cirrhosis, hepatic failure, and primary hepatic carcinoma.² The nature of liver biopsy, such as invasiveness, cost, poor compliance, and contraindications, restricted the widespread utilization, particularly in the follow-up.³ Recently, candidate surrogates, including laboratory tests and algorithms based on laboratory and clinical variables, have gained popularity for diagnosis, staging, and evaluation of prognosis.^{4–6} Previously, we found that serum hyaluronic acid, N-terminal peptide of type III procollagen, type IV collagen, and laminin, combined with FibroTest index, improved the diagnostic efficiency and reduced the incidences of unnecessary liver biopsy.⁷ In the present study, we attempt to investigate a reliable and routine indicator for determining the progression of fibrosis or necroinflammation in patients with hepatitis B.

Red blood cell distribution width (RDW) reflects the heterogeneity of circulating red blood cell size. It has been widely applied for the differential diagnosis of anemia for decades. In recent years, RDW has been reported to be increased in cardiopulmonary vascular diseases (coronary artery disease, myocardial infarction, pulmonary hypertension),^{8–10} chronic kidney disease,^{11,12} and systemic lupus erythematosus,¹³ as well as liver diseases.^{14–17} It has been claimed that elevated RDW values positively correlate with MELD scores in different disease statuses of hepatitis B virus (HBV) infection.¹⁶ In addition, RDW increased with worsening of Child–Pugh grade in hepatic cirrhosis.¹⁴ Nevertheless, the relation between RDW levels and histopathological grades and stages in patients with chronic hepatitis B has not been fully elucidated.

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MATERIAL AND METHODS

Study Population

A retrospective analysis of liver biopsy was performed in 519 patients admitted to the Liver Disease Center at the First Affiliated Hospital of Fujian Medical University between January 2010 and December 2011. Patients were included if they were diagnosed with hepatitis B virus-related liver fibrosis in accordance with the Guideline of Prevention and Cure for Viral Hepatitis established by the Chinese Medical Association. Histopathological grades and stages were evaluated in accordance with 2000 Xi'an Viral Hepatitis Management Guidelines recommended by the Chinese Society of Infectious Diseases and Parasitology, and the Chinese Society of Hepatology, of the Chinese Medical Association.¹⁸ The exclusion criteria were as follows: first, patients coinfecting with hepatitis C, hepatitis G, human immunodeficiency virus, or other autoimmune liver diseases; second, patients who took medications that impaired red blood cell production or increased red cell destruction; third, patients diagnosed with comorbid diseases (ie, hematological diseases, systemic inflammation, renal failure, cardiovascular disease, and autoimmune disease); fourth, 28 patients without complete data were also excluded from the population. In addition, patients who had diabetes mellitus took medicines to stabilize the condition. Grades and fibrosis stages are categorized as 0–4 (G) and 0–4 (S), respectively.¹⁸ A total of 446 participants enrolled in this study gave written informed consent for the liver biopsy. The study was conducted in accordance with Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University Hospital.

Data Collection

Baseline characteristics were extracted from medical records. All laboratory measures were performed within 1 week before or after a liver biopsy, and the first laboratory results at admission were adopted. Laboratory tests were analyzed within 2 hours after obtaining blood samples.

Laboratory Measurements

Hematological variables were determined using the ADVIA 2120i automated analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). Serum levels of Hepatitis B surface antigen and E antigen were detected by ARCHITECT i2000SR (Abbott, IL). HBV DNA levels were measured using ABI 7500 real-time PCR equipment (USA, detection limit: 500 IU/mL). Biochemical parameters for liver function were determined using an automatic analyzer (Olympus AU 2700, Tokyo, Japan).

Histological Assessment of the Liver

A 16G Tru-Cut needle (TSK Laboratory, Tochigi-Ken, Japan) was applied in color Doppler ultrasound-guided liver biopsy (ACUSON, Aspen Advanced Ultrasound, Siemens Company, Forchheim, Germany). A minimum of 1.6 cm of liver tissue containing at least 6 portal tracts was required for diagnosis. The specimens were fixed in buffered formalin, embedded in paraffin and stained with haematoxylin and eosin (H&E), Masson's, and reticular fiber staining. The pathological diagnosis of each liver biopsy tissue was determined from the inflammation grade and fibrosis staging after a double-blind inspection by 2 specialists in the Pathological Diagnostic Center at Fujian Medical University in accordance with 2000 Xi'an Viral Hepatitis Management Guidelines.¹⁸ Fibrosis was evaluated on a 5-stage scale: S0 (no fibrosis), S1 (portal fibrosis

without septa), S2 (portal fibrosis with rare septa), S3 (portal fibrosis with many septa), and S4 (cirrhosis). Likewise, inflammatory activity was assessed on a 5-grade scale: G0 (no inflammation), G1 (portal inflammation with rare lobular necrosis), G2 (mild piecemeal portal necrosis, focal or spotty lobular necrosis), G3 (moderate piecemeal portal necrosis, bridging necrosis in lobule), G4 (severe piecemeal portal necrosis, multilobular necrosis). On the basis of the fibrosis stages, absent–mild (S0–S2) were defined as no significant fibrosis and moderate–severe (S3–S4) were termed advanced fibrosis. Similarly, patients were classified into 2 groups with respect to inflammatory activity grades: no significant inflammation (G0–G2) and significant inflammation (G3–G4).

Statistical Analysis

Continuous variables were displayed as mean \pm standard deviation or median (25th, 75th percentile). Categorical variables were shown as numbers and percentages. Student *t* test and Mann–Whitney nonparametric *U* test were used for comparison of continuous variables between 2 groups, as appropriate. Categorical data were analyzed by χ^2 test. Multivariate stepwise logistic regression analysis using the forward approach was carried out to investigate the independent variables predictive of the severity of liver disease. Formulae that developed from the logistic regression equation were constructed using coefficients of independent variables. Compared with preexisting formulas, models proposed by our study were assessed using the area under the receiver-operating curve (ROC). *Z* test was applied to compare differences between AUCs. All statistical analyses were performed in SPSS 17.0 (SPSS Inc, Chicago, IL). All *P* values given are 2-sided and a *P* value < 0.05 is statistically significant.

RESULTS

In total, 446 patients were enrolled in our study between January 2010 and December 2011. Age ranged from 13 to 66 years with the mean age 36.3 ± 10.5 years. Of these patients, 338 (75.8%) patients were men and 108 (24.2%) were women. RDW values ranged from 11% to 24% (median 13.98%). The advanced liver fibrosis (S3–S4) was present in 219 patients (49.1%) and significant hepatic inflammatory activity (G3–G4) in 254 patients (57.0%). Differences in clinical and laboratory parameters between 2 groups were summarized in Table 1. Patients in the progressive phase (ie, S3–S4 and G3–G4) were both more likely to have statistically higher levels of aspartate aminotransferase (AST), total bilirubin (TBIL), mean platelet volume (MPV), RDW, and lower values of albumin, platelet count. But, the level of hemoglobin was similar between groups. In addition, patients in S3–S4 stage were slightly older, whereas patients in G3–G4 grade had a higher likelihood of hepatitis B e antigen (HBeAg) positivity, HBV DNA positivity, and a lower level of mean corpuscular volume. Alanine aminotransferase (ALT) and white blood count (WBC) showed statistical differences between G0–G2 and G3–G4 rather than S0–S2 and S3–S4.

In univariate logistic regression analysis, age and laboratory parameters, including TBIL, ALT, AST, MPV, and RDW, increased with progressive fibrosis stages, whereas Alb and PLT count inversely related with stages. Significant variables were selected for a multivariate regression analysis. Finally, RDW, platelet count, and albumin were retained as independent predictors of liver fibrosis (odds ratio = 1.121, 0.987, and 0.941, respectively, Table 2).

TABLE 1. Demographics and Laboratory Measurements of Subjects Stratified According to Histological Grades and Stages

Variables	S0–S2 (n = 227)	S3–S4 (n = 219)	P Value	G0–G2 (n = 192)	G3–G4 (n = 254)	P Value
Age*, y	35.2 ± 10.6	37.5 ± 10.2	0.04	35.8 ± 10.2	36.6 ± 10.8	0.43
Male*, n (%)	165 (73%)	173 (79%)	0.12	138 (72%)	200 (79%)	0.10
ALT, U/L	74.0 (36.0, 212.5)	100.0 (42.0, 288.0)	0.05	53.0 (29.0, 98.0)	145.5 (58.0, 365.0)	<0.001
AST, U/L	45.5 (28.0, 100.5)	68.0 (38.0, 151.0)	<0.001	36.0 (26.5, 60.0)	91.5 (46.0, 189.0)	<0.001
Albumin, U/L	41.9 (38.6, 44.4)	39.3 (36.4, 42.6)	<0.001	42.5 (39.5, 44.7)	39.2 (36.4, 42.5)	<0.001
TBIL, μmol/L	15.1 (11.0, 19.4)	15.7 (11.8, 25.2)	0.01	14.1 (10.5, 18.7)	16.3 (12.0, 25.1)	<0.001
HBeAg positivity*, n (%)	135 (59.5%)	117 (53.4%)	0.31	89 (46.4%)	163 (64.2%)	<0.001
HBV DNA positivity*, n (%)	195 (85.9%)	192 (87.7%)	0.53	150 (78.1%)	237 (93.3%)	<0.001
WBC*, ×10 ⁹ /L	5.92 ± 1.58	5.74 ± 1.55	0.23	6.03 ± 1.59	5.68 ± 1.54	0.02
Hemoglobin*, g/L	144.2 ± 14.2	141.6 ± 15.8	0.07	143.5 ± 14.4	142. ± 15.5	0.47
PLT*, ×10 ⁹ /L	209.1 ± 53.0	172.2 ± 52.1	<0.001	208.2 ± 53.7	178.1 ± 53.8	<0.001
MCV, fl	91.3 (87.7, 94.8)	92.1 (88.6, 95.6)	0.12	90.7 (87.9, 93.4)	92.7 (88.5, 95.9)	0.001
MPV, fl	8.7(8.1, 9.4)	9.2(8.4, 9.8)	<0.001	8.7(8.0, 9.4)	9.1(8.4, 9.7)	0.002
RDW (%)	13.3 (12.7, 14.3)	13.6 (12.9, 14.7)	0.01	13.2 (12.7, 14.0)	13.7 (13.0, 14.9)	<0.001

Data are expressed as median (25th, 75th percentiles). ALT = alanine aminotransferase, AST = aspartate aminotransferase, HBeAg = hepatitis B e antigen, MCV = mean corpuscular volume, MPV = mean platelet volume, PLT = platelet, RDW = red blood distribution width, TBIL = total bilirubin, WBC = white blood cell.

* Values are expressed as mean ± standard deviation or number of patients (percentage).

Similarly, there was a stepwise increase in RDW values with the progression of inflammation. The risk for advanced inflammatory activity (G3–G4) went up by 25.9% for each 1% increase in RDW values as a continuous variable in the univariate logistic regression analysis. After adjustments for other potent predictors (TBIL, AST, Alb, WBC, PLT, mean corpuscular volume, HBV DNA positivity, HBeAg positivity), an increased odds ratio of significant inflammation was found for RDW and ALT (OR = 1.146 and 1.003, respectively, Table 3).

On the basis of these independent variables, 2 regression models were derived to predict the extent of liver fibrosis and inflammation. The models are listed as follows.

Regression model indicative of significant liver fibrosis (Model A):

$$p = \frac{1}{1 + e^{-(0.061Alb - 0.014PLT + 0.114RDW + 3.386)}}$$

Regression model predictive of advanced hepatic inflammation (Model B):

$$p = \frac{1}{1 + e^{-(0.003ALT - 0.076Alb - 0.010PLT + 0.136RDW + 2.761)}}$$

ROC curve analysis showed the optimal cutoff point of model A for the presence of advanced liver fibrosis (a sensitivity of 70.0% and a specificity of 62.9%, area under the ROC curve = 0.713) was 0.441. Moreover, model A provided a negative predictive value of 68.6% and a positive predictive value of 64.1% for the detection of significant fibrosis when the optimal cutoff was set at 0.441. On the contrary, the area under the ROC curve (AUC) of model B for the significant inflammation activity was 0.765 with a sensitivity of 66.1% and a specificity of 79.4%. A cut-off point of 0.528 for model B generated a positive predictive value of 80.7% and a negative predictive value of 64.2%.

TABLE 2. Univariate and Multivariate Regression Analysis Exploring the Predictors Determining the Severity of Fibrosis in Liver Biopsy

	Crude		Adjusted	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.019 (1.001–1.037)	0.04		0.46
TBIL	1.012 (1.002–1.023)	0.03		0.20
ALT	1.001 (1.000–1.002)	0.02		0.34
AST	1.002 (1.000–1.0030)	0.01		0.36
Albumin	0.918 (0.880–0.958)	0.02	0.941 (0.901–0.983)	0.01
PLT	0.987 (0.982–0.991)	<0.001	0.987 (0.982–0.991)	<0.001
MPV	1.374 (1.155–1.635)	<0.001		
RDW	1.140 (1.028–1.272)	0.01	1.121 (1.002–1.253)	0.04

Data are expressed as odds ratio (95% CI). ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, MPV = mean platelet volume, OR = odds ratio, PLT = platelet, RDW = red blood distribution width, TBIL = total bilirubin.

TABLE 3. Univariate and Multivariate Regression Exploring the Determinants Predicting the Inflammatory Activity Grades in Liver Biopsy

	Crude		Adjusted	
	OR (95% CI)	P Value	OR (95% CI)	P Value
TBIL	1.024 (1.008–1.041)	0.004		0.55
ALT	1.004 (1.002–1.005)	<0.001	1.003 (1.002–1.005)	<0.001
AST	1.006 (1.004–1.009)	0.01		0.95
WBC	0.848 (0.756–0.952)	0.01		0.79
Albumin	0.886 (0.846–0.927)	<0.001	0.927 (0.884–0.972)	0.002
PLT	0.990 (0.986–0.993)	<0.001	0.990 (0.986–0.994)	<0.001
MPV	1.231 (1.037–1.461)	0.02		
RDW	1.259 (1.112–1.425)	<0.001	1.146 (1.008–1.303)	0.04
MCV	1.031 (1.002–1.060)	0.03		0.10

Data are expressed as odds ratio (95% CI). ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, MCV = mean corpuscular volume, MPV = mean platelet volume, OR = odds ratio, PLT = platelet, RDW = red blood distribution width, TBIL = total total bilirubin, WBC = white blood cell.

In addition, we compared AUCs of AST-to-platelet ratio index (APRI), FIB-4, RDW to platelet ratio (RPR), and model A/B for the presence of significant fibrosis or inflammation. The AUC values of model A were the highest among 5 indexes for advanced fibrosis (AUC = 0.713, Table 4), although the difference is statistically insignificant when compared with FIB-4. RPR showed the poorest sensitivity (57.0%) and a good specificity (73.1%) for the detection of advanced fibrosis (AUC = 0.699). Considering significant inflammation, APRI showed the highest AUC value with the best specificity of 82.1% and a sensitivity of 66.4% (AUC = 0.802). Model B demonstrated better outcomes than FIB-4 (AUC = 0.765 vs. 0.740, *P* = 0.32), and a significantly higher AUC than RPR (AUC = 0.765 vs. 0.670, *P* < 0.001, Table 5). RPR had the poor predictive capability with a sensitivity of 52.2% and a specificity of 76.8% (AUC = 0.670).

The preexisting formulae are as follows:

$$RPR = \frac{RDW(\%)}{PLT(10^9/L)}$$

$$APRI = \frac{AST(U/LN^*)}{PLT(10^9/L)}$$

(*ULN = upper limit of normal for that laboratory)

$$FIB-4 = \frac{age(yr) * AST(U/L)}{PLT(10^9/L) * ALT(U/L)^{1/2}}$$

DISCUSSION

Chronic liver injury was elicited by a handful of mechanisms (eg, viral hepatitis, metabolic liver diseases, and chronic

alcohol consumption). Liver fibrosis is characterized by a continuous wound-healing response and chronic inflammation. Among patients with HBV-related liver cirrhosis, RDW levels positively related to Child–Pugh and MELD scores.^{14,19} In addition, an increasing correlation of RDW values with the Mayo risk score was also found in patients with primary biliary cirrhosis.¹⁴ Another study showed that elevated RDW was associated with advanced fibrosis in nonalcoholic fatty liver disease.¹⁵ However, Milic *et al.*¹⁷ found that statistically significant increase of RDW relevant to the disease severity was not observed in groups of patients neither with alcoholic cirrhosis nor with nonalcoholic cirrhosis. It is well known that RDW is elevated when there is ineffective red cell production. High RDW values represent greater variation in size. To date, the distinct role of RDW for the severity of liver pathology of various etiologies has been uncertain.

RDW is a parameter that may be influenced by multiple factors. Aging,²⁰ sex,²⁰ nutritional deficiency (eg, iron or folate deficiency), BMI,²¹ waist circumference,²² inflammation,²³ and oxidative stress²⁴ have been suggested to be determinants of RDW. The relation between HBV-related liver disease and RDW could be attributable to the possible explanations as follows. First, it is well appreciated that persistence of inflammation has been associated with progressive hepatic fibrosis and the development of cirrhosis.^{25,26} Previous studies demonstrated proinflammatory cytokines inhibited erythropoietin-induced erythrocyte maturation, and increased immature erythrocytes releasing into circulation resulted in higher RDW

TABLE 4. Diagnostic Accuracy of Different Formulae for the Prediction of Fibrosis Stages

	Cutoff	AUC (95% CI)	P Value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Model A	0.441	0.713 (0.667–0.761)	–	70.0	62.9	64.1	68.6
RPR	0.077	0.699 (0.653–0.742)	0.32	57.0	73.1	66.8	64.1
APRI	0.517	0.670 (0.623–0.714)	0.17	80.2	47.4	59.0	71.1
FIB4	1.065	0.711 (0.665–0.753)	0.99	73.2	62.8	65.0	71.1

APRI = aspartate aminotransferase-to-platelet ratio index, AUC = area under the receiver-operating characteristic curve, FIB4 = fibrosis index based on the 4 factors, NPV = negative predictive value, PPV = positive predictive value, RPR = red blood cell distribution width to platelet ratio.

* Compared with AUC of model A.

TABLE 5. Diagnostic Accuracy of Different Formulae for the Prediction of Inflammation Grades

	Cutoff	AUC (95% CI)	P Value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Model B	0.528	0.765 (0.723–0.805)	–	66.1	79.4	80.7	64.2
RPR	0.080	0.670 (0.624–0.714)	<0.001	52.2	76.8	74.3	55.6
APRI	0.884	0.802 (0.766–0.843)	0.03	66.4	82.1	82.6	65.6
FIB4	1.147	0.740 (0.698–0.783)	0.32	69.9	70.3	75.0	64.6

APRI = aspartate aminotransferase-to-platelet ratio index, AUC = area under the receiver-operating characteristic curve, NPV = negative predictive value, PPV = positive predictive value, RPR = red blood cell distribution width to platelet ratio.

* Compared with AUC of model B.

values.^{27,28} Second, increased RDW were found in overweight adolescents.²¹ It has been reported that metabolic syndrome was significantly more prevalent in patients with probable cirrhosis than those without cirrhosis in chronic hepatitis B.²⁹ Third, elevated RDW was linked to endothelial dysfunction independent of anemia and inflammation in patients with chronic kidney disease.¹² Thus, it is tempting to speculate that whether RDW could get involved in the regulation of hepatic stellate cell apoptosis in reversal of liver fibrosis.³⁰ Nonetheless, the mechanism by which elevated RDW values correlate with the degree of hepatic fibrosis remains elusive.

It is noteworthy that our study has several highlights. First, liver biopsy has been the gold standard for the liver fibrosis assessment in the last few decades, despite the sampling variability.³¹ However, liver disease severity at admission was mostly evaluated according to scoring systems in previous studies,^{14,16,17,19} including MELD score, Child–Pugh score, and Mayo risk score. Thus, there are limited data on the association between RDW and liver histology. Second, chronic inflammatory response drives the progression of liver fibrosis. But, little attention was focused on exploring predictors for fibrosis stages, as well as necroinflammation grades. Third, comparisons among RDW, FIB-4, RPR, APRI, and models suggested in our study were conducted to analyze the diagnostic values for predicting the severity of fibrosis and inflammation in HBV-infected patients.

Currently, FIB-4 has been identified as a potential index favorably for determining the extent of fibrosis in patients with HBV infection.^{5,6,32} A leading meta-analysis indicated that APRI showed limited value in identifying hepatitis B-related significant fibrosis and cirrhosis.³³ Chen³⁴ reported that RPR accurately predicted 63.1% of cases with significant fibrosis and 73.7% of cirrhosis in CHB patients. In our study, model A predictive of significant liver fibrosis was created, consisting of 3 readily available laboratory parameter variables (ie, RDW, PLT, and Alb). Until now, it has been well documented that serum Alb and PLT counts are determinants of liver fibrosis.^{5,35–37} In our findings, when RDW levels increased by 1%, the accompanying risk for progressive fibrosis rose by 12.1%, even after adjustments for other potent predictors. Moreover, previously published data also supported that RDW could be regarded as an independent predictive factor for HBV-related significant hepatic fibrosis.^{16,19,38} Compared with preexisting formulae such as FIB-4, APRI, and RPR, our model A demonstrated the highest AUC values (AUC = 0.713). Among 227 patients (50.9%) absence of significant fibrosis, 144 (63.4%) patients had a score of model A less than 0.441; whereas among 219 patients (49.1%) present with S3–S4, 153 patients (69.9%) could be identified as having advanced fibrosis with model A index >0.441. Overall, unnecessary liver biopsy would have been avoided in 297 patients

(66.6%) according to model A. The Asian Pacific Association for the Study of the Liver consensus on liver fibrosis has concluded that the utility of a stepwise algorithm of noninvasive markers may reduce the need for liver biopsy by 30%,³⁹ which is in agreement with our finding. On the contrary, 293 unnecessary biopsies (65.7%) would have been reduced at a cutoff of 1.065 for the FIB-4 index. Taken together, model A demonstrated a comparable predictive value to FIB-4 for significant fibrosis. Inconsistent with the previous study,³⁴ our finding indicated that RPR had a poor sensitivity of less than 60% for liver fibrosis. In addition, the APRI index failed to show the considerably high AUC values (AUC = 0.670) for distinguishing advanced fibrosis from mild counterparts.

With respect to hepatic inflammation, 4 laboratory parameters (ie, ALT, Alb, RDW, PLT count) constitute model B proposed in our study. Serum ALT was regarded as an accurate marker of liver necroinflammation in HBeAg-positive carriers of HBV.⁵ In our study, multivariate logistic regression analysis showed that serum ALT was found to be significantly elevated in advanced liver inflammation (G3–G4), but not in S3–S4 stage. This may be interpreted by a higher positive rate of HBeAg in G3–G4. Both Alb levels and PLT counts negatively correlated with hepatic inflammation grades, which gains some support from previous studies.^{5,40} In the literature, an acceleration of fibrosis progression with aging was found.⁴¹ In the present study, patients in S3–S4 stage were observed to be significantly older than those in S1–S2 stage, but there was no differentiation between G1–G2 and G3–G4. Maybe, it is because that most of asymptomatic patients with chronic hepatic inflammation were unaware of the disease until the symptom appeared. Regarding RDW, there are limited data with respect to the potential role of RDW as a marker for the progression of hepatic inflammation. In a large cohort of unselected outpatients, a strong graded association of RDW with plasma inflammation markers (eg, erythrocyte sedimentation rate, high-sensitivity C-reactive protein) independent of numerous confounders was found.²³ Unfortunately, we failed to analyze the correlation of RDW with inflammation markers as a result of the lost data from some inpatients in our study. Nevertheless, our result indicated that along with RDW levels increasing by 1%, the independent risk for the significant inflammation went up by 14.6%. Furthermore, we found that RDW values were more closely related to the inflammation grades than fibrosis stages ($r = 0.264$ vs. 0.177). However, in patients with biopsy-proven nonalcoholic steatohepatitis, there was no remarkable relation between RDW values and inflammation.⁴² In the present study, the likelihood of significant inflammation was correctly diagnosed with model B in 359 patients (80.5%), which implied that those patients could have been prevented from liver biopsy with a cutoff of model B set at 0.528.

There is, as yet, no robust evidence that APRI, FIB-4, and RPR could be regarded as predictors of hepatic inflammation. Hepatic inflammation is commonly associated with all stages of liver diseases independent of the etiology and eventually drives the development of hepatic fibrosis. Thus, the potential serum markers predictive of the progression of liver fibrosis may be applied for inflammation activity grading. The preexisting formulae (eg, RPR, FIB-4, and APRI) are composed of ALT, AST, RDW, PLT, and age. As stated above, those variables have been related to the extent of hepatic inflammation. Hence, we attempted to compare those panels with the suggested model B for detecting significant inflammation. Overall, both of the two models proposed in our study showed higher AUCs than FIB-4 and RPR for the presence of significant inflammation or fibrosis. RPR yield a poor AUC value with a lower sensitivity for predicting liver fibrosis or inflammation, which contrasts with the report by Chen.³⁴ In agreement with the published data,⁴³ APRI had the excellent capability of predicting significant liver necrosis and inflammation among 5 formulae, but exhibited a poor diagnostic value for the prediction of fibrosis. However, to what extent elevated level of these indicators because of inflammation alone without fibrosis is difficult to clarify at present. Complex interplay of fibrogenesis and inflammatory response in vivo makes it impossible that pure fibrosis separated from inflammation in a clinical setting. The integration of laboratory parameters into clinical application needs to be validated in multiple large and prospective studies.

In conclusion, our study shows that RDW could provide useful information with other serum markers for the detection of advanced hepatic fibrosis and necroinflammation in hepatitis B virus-infected patients, which may greatly help to reduce the need for liver biopsy.

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