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Red Blood Cell Distribution Width to Platelet Ratio is Related to Histologic Severity of Primary Biliary Cirrhosis

Huan Wang, PhD, Hongqin Xu, PhD, Xiaomei Wang, PhD, Ruihong Wu, MD, Xiuzhu Gao, MD, Qinglong Jin, PhD, and Junqi Niu, PhD

Abstract: We aimed to investigate whether red blood cell distribution width (RDW) and RDW to platelet ratio (RPR) were related to the histologic severity of primary biliary cirrhosis (PBC).

Seventy-three treatment-naïve PBC patients who had undergone a liver biopsy between January 2010 and January 2015 were enrolled in our study. The patients' histological stages were based on the classifications of Ludwig and Scheuer. The patients were divided into early stage (Stage I) and advanced stage (Stage II, III, and IV) hepatic fibrosis according to their histological stage. All common patient demographics, clinical characteristics, hematological parameters, liver biochemistry, and antimitochondrial M2 antibody levels (AMA-M2) were retrospectively analyzed, and RDW, RPR, aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis index based on the 4 factors (FIB-4) were calculated.

A total of 28 (38.4%) patients had early stage PBC, whereas 45 (62.6%) were classified as advanced stage. Regarding age, no significant differences between the early and advanced stages were observed. Patients with advanced stage PBC had significantly higher RDW (13.6 vs 14.4; $P = 0.019$), conjugated bilirubin (10.1 vs 23.4; $P = 0.029$), and significantly lower cholinesterase (7901.1 vs 6060.8; $P = 0.001$) and platelets (212.6 vs 167.0; $P = 0.006$). However, no significant differences ($P > 0.05$) in other routine parameters previously evaluated in PBC, including aspartate aminotransferase (AST) and mean platelet volume, were found between the groups. The sensitivity and specificity of RDW were 33.3% and 92.9%, respectively, and the area under the receiver-operating characteristic curve (AUROC) was 0.66. However, the sensitivity and specificity of RPR were 46.7% and 96.4%, respectively, and the corresponding AUROC was 0.74 ($P < 0.001$). Hence, compared with preexisting indicators, RPR showed a higher AUROC than APRI (0.648; $P = 0.035$) and FIB-4 (0.682; $P = 0.009$).

RDW and RPR may be a new noninvasive marker for predicting histologic severity of PBC.

Abbreviations: AIH = autoimmune hepatitis, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AMA = antimitochondrial antibody, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, AUROC = area under the receiver-operating characteristic curve, CB = conjugated bilirubin, CBC = complete blood count, CHB = chronic hepatitis B, CHE = cholinesterase, CHO = cholesterol, FIB-4 = fibrosis index based on the 4 factors, GGT = gamma-glutamyl transpeptidase, HB = hemoglobin, HBV = hepatitis B virus, HCV = hepatitis C virus, MPV = mean platelet volume, NASH = nonalcoholic steatohepatitis, PBC = primary biliary cirrhosis, PLT = platelet, RBC = red blood cell, RDW = red blood cell distribution width, RPR = red blood cell distribution width to platelet ratio, TBIL = total bilirubin, TG = triglyceride, ULN = upper limit of normal, WBC = white blood cell.

INTRODUCTION

Primary biliary cirrhosis (PBC) is a progressive autoimmune cholestatic liver disease that is characterized by the detection of the highly specific serum antimitochondrial antibody (AMA) and by the destruction of small and medium bile ducts, which results in chronic cholestasis, portal inflammation, fibrosis, cirrhosis, and eventually liver failure or liver cancer.[1] Typically, patients meeting 2 of the 3 following conditions are diagnosed with PBC: serum AMA or AMA-M2 positive; unexplained, elevated alkaline phosphatase (ALP) ≥1.5 times the normal upper value for over 24 weeks; and liver histology consistent with PBC, specifically nonsuppurative cholangitis and interlobular bile duct injury.[2,3] Liver biopsy remains the gold standard for assessment of hepatic fibrosis, but biopsies are limited by sampling error, invasiveness, cost, poor compliance, and contraindications, particularly in the follow-up.[4] However, evaluation of the histologic severity provides valuable information with respect to the stage of the disease and aids in monitoring the response to treatment, which in turn provides information related to the prognosis.[5] Hence, the need to establish noninvasive methods to replace liver biopsy in the assessment of hepatic fibrosis has become urgent because noninvasive approaches are associated with lower risk and are often less expensive than liver biopsy. Several noninvasive methods to predict hepatic fibrosis have been proposed over the past decades, including transient elastography, FibroTest, aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis index based on the 4 factors (FIB-4).[6–12] Accordingly, our objective in the present study was to investigate a reliable and routine indicator corresponding to the histologic severity of PBC.

Red blood cell (RBC) distribution width (RDW) is a measure of the range of variation of RBC volume. In our hospital, the normal reference range of RDW in humans is 11.0% to 14.0%. Further, RDW has been shown to be an independent marker of mortality in renal disease, multiple cardiovascular diseases and interventions (such as percutaneous coronary interventions), multiple sclerosis, and inflammatory bowel disease.[13–17] Likewise, recent studies have shown that RDW is related to fibrosis caused by nonalcoholic steatohepatitis (NASH) and hepatitis B virus (HBV).[18–20] As well, other studies have shown that the RDW to platelet ratio (RPR) can be a predictor of significant fibrosis and cirrhosis in patients with chronic hepatitis.[21] To our knowledge, only a limited number of studies have investigated RDW and RPR values in patients with PBC; hence, the relationship between RDW levels and histopathological severity in patients with PBC has not been fully elucidated. Therefore, we aimed to investigate if RDW and RPR were related to the histologic severity of PBC.

MATERIALS AND METHODS

Study Population

This retrospective study was performed in the First Hospital of Jilin University between January 2010 and January 2015. A total of 93 patients with PBC confirmed by a liver biopsy were included. Patients with PBC-autoimmune hepatitis or with PBC-chronic hepatitis B overlap syndrome, patients who had undergone prior treatment, or patients with a portal vein diameter $\geq$15 mm were excluded from the study. After exclusion criteria, 73 patients were included in the final analysis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the First Hospital of Jilin University Ethics Committee.

Clinical and Laboratory Assessments

Demographic information, clinical symptoms, and laboratory data were collected and documented on a form by a clinician who was blinded to prevent bias. Prior to the performance of the liver biopsy, venous blood samples were collected from each patient between 5:30 and 6:00 AM on the day of the procedure after the patient had fasted for at least 8 to 12 h. The demographics collected included age and sex of the patients. The clinical symptoms recorded for each patient included fatigue, pruritus, jaundice, xerostomia, ascites, and edema. The laboratory analyses included complete blood count including RDW, hemoglobin, white blood cell, RBC, neutrophil counts, lymphocytes, platelets (PLT), and mean platelet volume (MPV). Liver biochemistry analyses included aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, gamma-glutamyl transpeptidase (GGT), total bilirubin (TBIL), conjugated bilirubin (CB), and cholinesterase (CHE). Other assessments included AMA-M2, triglycerides, and cholesterol.

Histological Assessment

For the performance of all liver biopsies, a 16-gauge Tru-Cut biopsy needle was applied using color-Doppler ultrasonography. A minimum of 1.5 cm of liver tissue containing at least 5 portal tracts was required for diagnosis. The specimens were fixed in buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin, and Masson trichrome stain. The pathological diagnosis of each liver biopsy tissue was determined based on the classifications provided by Ludwig and

Scheuer after a double-blinded inspection by 2 specialists in the First Hospital of Jilin University Pathological Diagnostic Center. Based on the histological staging system, the stage of disease can be categorized into 4 stages. Typically, florid duct lesions are seen in Stage I, whereas proliferating ductular structures are evidenced in Stage II, scarring is apparent in Stage III, and cirrhosis is detected in Stage IV. Accordingly, the subjects enrolled in the study were divided into 2 groups that were defined as early stage (Stage I) and advanced stage (Stages II, III, and IV).

Formulas

$$APRI = (AST/ULN) \times 100/PLT \ (10^9/L)^{10}$$
$$FIB-4 = (Age \times AST)/[PLT \times (ALT)^{1/2}]^{22}$$
$$RPR = RDW/PLT \ (10^9/L)^{19}$$

Statistical Analysis

Continuous variables were shown as mean (25th and 75th percentiles), whereas categorical variables were displayed as numbers and percentages. The Student t test and Mann–Whitney nonparametric U test were used for comparison of continuous variables between the 2 groups, as appropriate. Categorical data were analyzed using the chi-squared (χ^2) test. The values for RDW, RPR, APRI, and FIB-4 were assessed using the area under the receiver-operating characteristic curve (AUROC) and the sensitivity and specificity to detect PBC stage were calculated by the optimal cut-off value of RDW, RPR, APRI, and FIB-4. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL). All P values provided are 2-sided and a P value <0.05 was considered statistically significant.

RESULTS

Baseline demographic characteristics of the study population are presented in Table 1. A total of 73 treatment-naïve PBC patients were enrolled in the study, of which 62 (75.8%) were women and 11 (24.2%) were men. The percentage of patients in Stage I, II, III, and IV hepatic fibrosis were 28 (38.4%), 27 (37.0%), 16 (21.9%), and 2 (2.7%), respectively. Table 2 provides the clinical characteristics of the PBC patients. The incidence of fatigue, pruritus, jaundice, xerostomia, ascites, and edema upon admission were 57 (78.1%), 35 (47.9%), 13 (17.8%), 21 (28.8%), 0 (0.0%), and 2 (2.7%), respectively, and the number of AMA-M2 positive patients was 62 (84.9%).

Table 3 shows the laboratory data and the differences between the 2 groups in each of the clinical measurements. Twenty-eight patients had early stage hepatic fibrosis (Group 1, 38.4%), whereas 45 patients had advanced stage hepatic fibrosis (Group 2, 62.6%). Patients in the advanced stage group had statistically higher RDW and CB levels but statistically lower CHE and PLT levels. However, there were no differences between the groups in terms of other routine parameters that were previously evaluated in PBC, including AST and MPV. Diagnostic accuracy of different formulae for the prediction of histologic severity is shown in Table 4. The sensitivity and specificity of RDW were 33.3% and 92.9%, respectively, and the AUROC was 0.66. The sensitivity and specificity of RPR were 46.7% and 96.4%, respectively, and the AUROC value was 0.74 ($P < 0.001$). Compared with preexisting indicators, RPR yielded a higher AUROC than APRI (0.648; $P = 0.035$) and FIB-4 (0.682; $P = 0.009$). The ROC analysis of RDW, RPR, APRI, and FIB-4 for the identification of early and advanced stage hepatic fibrosis is shown in Figure 1.

TABLE 1. Baseline Characteristics of Study Population

Variables	Total (n = 73)	Normal Range
Demographic		
Age, y	52.4 (48.0, 60.0)	
Female	62 (84.9%)	
Hematological parameters		
WBC count, 10^9/L	5.1 (4.0, 6.0)	(4.0, 10.0)
RBC count, 10^{12}/L	4.2 (3.9, 4.5)	(3.5, 5.0)
Hemoglobin, g/L	121.2 (112.5, 134.0)	
PLT, 10^9/L	184.5 (145.0, 219.5)	(100.0, 300.0)
RDW, %	14.1 (13.1, 14.8)	(11.0, 14.0)
MPV, fL	11.6 (11.0, 12.0)	(7.0, 11.0)
Liver function markers		
AST (8−40 IU/L)	89.3 (42.2, 102.4)	(8.0, 40.0)
ALT (8−40 IU/L)	116.0 (43.5, 110.5)	(8.0, 50.0)
ALP (15−112 IU/L)	314.9 (150.5, 417.0)	(15.0, 112.0)
GGT (5−54 IU/L)	407.9 (166.0, 564.9)	(5.0, 54.0)
TBIL (6.8−30.0 μmol/L)	32.5 (12.1, 37.1)	(6.8, 30.0)
CB (0.0−8.6 μmol/L)	18.2 (4.00, 22.00)	(0.0, 8.6)
CHE (4300−12,000 U/L)	6766.7 (5082, 8516)	(4300.0, 12,000.0)
Histological stages		
I	28 (38.4%)	
II	27 (37.0%)	
III	16 (21.9%)	
IV	2 (2.7%)	

Data are expressed as median (25th, 75th percentiles).
ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CB = conjugated bilirubin, CHE = cholinesterase, GGT = gamma-glutamyl transpeptidase, MPV = mean platelet volume, PLT = platelet, RBC = red blood cell, RDW = red blood distribution width, TBIL = total bilirubin, WBC = white blood cell.

DISCUSSION

PBC is a progressive autoimmune cholestatic liver disease that is characterized by the presence of serum AMA, the destruction of small and medium bile ducts, and by other secondary clinical indications, including chronic cholestasis, portal inflammation, fibrosis, and cirrhosis, which eventually lead to liver failure or liver cancer.[1] In our study, 84.9% of the patients were women, which was lower than a previous report in which 91% of the study participants were female.[23] An explanation for this discrepancy is the possibility that it is easier to diagnose PBC in women than in men, and thus, fewer females require a liver biopsy.

Fatigue and pruritus are the most common symptoms of PBC, affecting up to 80% and 20% to 70% of patients,[24]

respectively. In our study, the percentages of fatigue and pruritus were 78.1% and 47.9%, respectively, which were approximately the same. Edema was noted in only a limited number (2.7%) of patients, and no patients in our study population presented with ascites. Clinicians in our department seldom perform liver biopsies on patients with esophageal varices, serious thrombocytopenia, or ascites implying cirrhotic liver disease, which is a probable reason why only 16 (21.9%) patients in the study population exhibited Stage III hepatic fibrosis and only 2 (2.7%) patients had Stage IV fibrosis. Patients who were serum positive for AMA or AMA-M2 and had unexplained elevated ALP upon admission were definitively diagnosed with PBC, whereas patients who were AMA negative or who were suspected to have another liver disease

TABLE 2. Clinical Characteristics of Patients

Symptoms	N (%)	Laboratory Results	N (%)
Fatigue	57 (78.1)	AMA-M2 positive	62 (84.9)
Pruritus	35 (47.9)	ALP elevation	64 (87.7)
Jaundice	13 (17.8)	GGT elevation	68 (93.2)
Xerostomia	21 (28.8)	TBIL elevation	20 (27.4)
Ascitis	0 (0.0)	TG elevation	16/61 (26.2)*
Edema	2 (2.7)	CHO elevation	18/61 (29.5)*

ALP = alkaline phosphatase, AMA = antimitochondrial antibody, CHO = cholesterol, GGT = gamma-glutamyl transpeptidase, TBIL = total bilirubin, TG = triglyceride.
* Only 61 patients have the data of TG and CHO.

TABLE 3. Analysis of Factors Associated With the Advanced Stage

Variables	Early Stage (n = 28)	Advanced Stage (n = 45)	P Value
Age, y	50.0 (43.2, 58.0)	54.0 (49.0, 60.5)	0.114
AST, IU/L	76.1 (38.5, 104)	97.5 (44.0, 102.4)	0.734
ALT, IU/L	93.3 (36.0, 93.6)	130.1 (49.3, 114.0)	0.404
ALP, IU/L	281.3 (142.3, 397.3)	335.8 (157.0, 430.5)	0.507
GGT, IU/L	326.9 (176.3, 365.3)	458.3 (144.0, 627.5)	0.240
CB, μmol/L	10.1 (4.0, 11.6)	23.4 (4.5, 30.8)	0.029
CHE, μmol/L	7901.1 (5894.8, 9322.8)	6060.8 (4525.0, 6925.0)	0.001
WBC, 10^9/L	5.5 (4.8, 6.5)	4.9 (3.9, 5.7)	0.038
RBC, 10^{12}/L	4.2 (3.9, 4.5)	4.0 (3.7, 4.4)	0.128
PLT, 10^9/L	212.6 (168.3, 238.0)	167.0 (118.5, 193.0)	0.006
Hemoglobin, g/L	124.6 (113.5, 138.8)	119.1 (112.0, 130.5)	0.202
MPV, fL	11.4 (11.0, 12.0)	11.7 (11.0, 12.5)	0.178
RDW, %	13.6 (12.9, 14.4)	14.4 (13.3, 15.3)	0.019
RPR	0.07 (0.05, 0.08)	0.10 (0.07, 0.12)	<0.001
APRI	0.93 (0.49, 1.33)	1.54 (0.67, 2.00)	0.035
FIB-4	2.18 (1.28, 2.29)	3.27 (1.73, 4.64)	0.009

Data are expressed as median (25th, 75th percentiles).
ALP = alkaline phosphatase, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CB = conjugated bilirubin, CHE = cholinesterase, FIB4 = fibrosis index based on the 4 factors, GGT = gamma-glutamyl transpeptidase, MPV = mean platelet volume, PLT = platelet, RBC = red blood cell, RDW = red blood distribution width, RPR = red blood cell distribution width to platelet ratio, WBC = white blood cell.

underwent a liver biopsy. Consequently, the number of AMA-M2 positive patients was 62 (84.9%), which was less than a previous report of 95%.[25] The number of patients with elevated ALP and GGT upon admission was 64 (87.7%) and 68 (93.2%), respectively. However, 20 patients (27.4%) had elevated TBIL, indicating that most patients were diagnosed when the ALP and GGT levels appeared abnormal, which often occurs before the onset of clinical symptoms. Conversely, TBIL is typically normal in the early stages of disease, whereas an abnormal value raises concerns of advanced stage disease.[2]

It is established that despite inherent sampling errors, invasiveness, cost, poor compliance, and contraindications, a liver biopsy is the gold standard for assessing all types of liver fibrosis.[26] However, the severity of liver disease at admission was predominantly evaluated by clinical symptoms, laboratory analyses, and imaging results. Therefore, there is a need to identify a good prediction model that can evaluate the stage of liver fibrosis as reliably as the performance of a liver biopsy. In recent years, an increasing number of exploratory predictors for fibrosis have been suggested, including APRI and FIB-4. However, most of the proposed indicators are also used to assess hepatitis C virus (HCV) and HBV. Further, studies

investigating the relationship between biochemical markers and histological stages of fibrosis are limited in PBC. Recently, Tahtaci et al[27] found that increased MPV is related to the histologic severity of PBC, but their sample size of 39 patients was small. Hence, the need to identify a noninvasive diagnostic marker that is indicative of the histological severity observed in PBC in a large population is urgent. In our study, we enrolled 73 patients with biopsy-proven PBC and found that patients with advanced stage fibrosis were more likely to have statistically higher RDW levels. However, we did not detect significant increases in MPV levels between early and advanced stage fibrosis. In addition, another study demonstrated that RDW was correlated with conventional prognostic markers of PBC.[28]

There have been several studies of the relationship between RDW or RPR and liver diseases.[18–21,28] Xu et al[19] found that RDW levels were correlated with liver fibrosis and inflammation and could be a noninvasive serum marker to predict the severity of fibrosis and inflammation in patients with hepatitis B. Similarly, Cengiz et al[18] reported that RDW is associated with histological severity and could be used to screen for advanced liver fibrosis in patients with NASH confirmed by a liver biopsy. Further, Hu et al[28] found that RDW was

TABLE 4. Diagnostic Accuracy of Different Formulae for the Prediction of Histologic Severity

	AUROC (95% CI)	P Value	Cut Off	Sensitivity, %	Specificity, %
RDW, %	0.66 (0.54, 0.79)	0.019	14.9	33.3	92.9
RPR	0.74 (0.63, 0.85)	<0.001	0.1	46.7	96.4
APRI	0.65 (0.52, 0.78)	0.035	0.6	88.9	39.3
FIB-4	0.68 (0.56, 0.81)	0.009	2.4	57.8	78.6

APRI = aspartate aminotransferase-to-platelet ratio index, AUROC = area under the receiver operating characteristic curve, CI = confidence interval, FIB-4 = fibrosis index based on the 4 factors, RDW = red blood cell distribution width, RPR = red blood cell distribution width to platelet ratio.
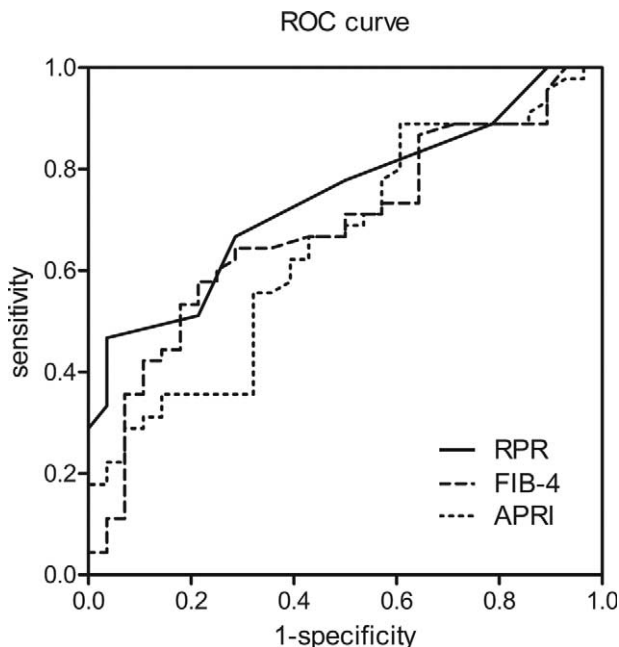
FIGURE 1. Receiver-operating characteristic curve of RPR, APRI, and FIB-4 for the identification of PBC patients with advanced stage fibrosis. APRI = aspartate aminotransferase-to-platelet ratio index, FIB-4 = fibrosis index based on the 4 factors, PBC = primary biliary cirrhosis, RPR = red blood cell distribution width to platelet ratio.

correlated with the conventional prognostic markers of PBC. However, the primary mechanisms that cause increased RDW in these different conditions remain largely unknown, although some pathways that might explain the elevated RDW levels have been suggested. First, a recent study by Allen et al[29] showed that elevated RDW might be an indicator of inflammatory stress and impaired iron mobilization. As well, Lippi et al[30] found that RDW has a strong and graded correlation with the degree of inflammatory marker expression. A possible explanation is that inflammatory cytokines might suppress erythrocyte maturation and accelerate the entry of newer, larger reticulocytes into the peripheral circulation, therefore causing increased RDW. PBC is an autoimmune liver disease that has been characterized by a predominant type I cytokine pattern including increased levels of interferon gamma, interleukin-5 (IL-5), IL-6, IL-10, IL-12, and IL-15 in the blood and liver of patients with PBC.[31] Hence, inflammatory cytokines could be the primary reason behind elevated RDW in PBC patients. Second, nutritional deficiencies are common in patients with liver disease and it has been shown that these patients have lower folic acid levels compared with healthy controls. Decreased folic acid could affect hematopoiesis, and thus amplify the heterogeneity of RBC. Third, portal hypertension can cause hypersplenism and thus accelerate the destruction of RBCs. A shortened RBC life span might promote the release of immature RBCs that are larger than mature RBCs from bone marrow into circulation, thus leading to increased RDW.

To date, both transient elastography and FibroTest have been reported as useful not only for the noninvasive assessment of liver fibrosis stage[32,33] but also in the prediction of long-term prognosis through longitudinal follow-up.[34,35] At present, some studies have found that transient elastography, which has more than 90% sensitivity and specificity for detecting advanced fibrosis in patients with PBC,[36,37] could be an easy and accurate tool for evaluating the stage of PBC.[6,7] Unfortunately, only a limited number of the patients underwent transient elastography, and therefore, we did not analyze the data. Nonetheless, RDW and RPR results can be obtained more easily than corresponding transient elastography or FibroTest results.

APRI and FIB-4 have successfully predicted hepatic fibrosis in large cohorts of patients infected with HCV and HBV.[38,39] These prior studies suggest that APRI and FIB-4 are suitable markers for detecting the stage of liver fibrosis with moderate sensitivity and accuracy; thus, they have been used in clinical practice, as well as in epidemiological research. For example, APRI has been recommended as the preferred noninvasive test to assess for the presence of cirrhosis (APRI score > 2 in adults) in resource-limited settings,[40] and another study in Japan found that APRI is correlated positively with the histological stage of fibrosis in PBC patients.[41] However, there were no significant differences between early stage and advanced stage fibrosis in terms of AST in our study. In addition, the AUROC of APRI and FIB-4 were lower than the corresponding value for RPR. Possible explanations for these differences are that APRI might not be sensitive enough to detect fibrosis related to PBC or that our staging system was different from the system used in Japan.

There were a few limitations in our study, including the fact that the sample size representing Stage IV fibrosis was limited to 2 cases, and thus, the patients in our study were divided into early stage (Stage I) and advanced stage (Stage II, III, and IV) fibrosis, which differs from other studies. As well, the factors that increase RDW and RPR levels, such as iron deficiency anemia and vitamin B12 deficiency, were not evaluated in this study.

In conclusion, our study findings indicated that RDW and RPR could provide useful information for the prediction of histologic severity in PBC patients when iron deficiency anemia and vitamin B12 deficiency were ignored, which could aid in reducing the need for liver biopsy. As well, the treatment and follow-up of AMA positive patients who have been definitively diagnosed with PBC can be optimized based on RDW and RPR values.

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