Novel noninvasive indices for the assessment of liver fibrosis in primary biliary cholangitis

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Abstract. The present study aimed to investigate the accuracy of new noninvasive markers in predicting liver fibrosis among individuals with primary biliary cholangitis (PBC). This retrospective analysis included subjects with PBC who had liver biopsies. Scheuer's classification was used to determine the fibrosis stage. The bilirubin to albumin (Alb) ratio (BAR), fibrosis index based on the four factors (FIB-4), γ-glutamyl transpeptidase to platelet (PLT) ratio (GPR), red cell distribution width to PLT ratio (RPR), aspartate aminotransferase (AST) to alanine aminotransferase ratio (AAR), AST to PLT ratio index (APRI) and total bilirubin to PLT ratio (TPR) were calculated based on the laboratory parameters. A novel index called BARP was conceived as BAR x RPR. A total of 78 individuals with PBC were included in the study, 84.6% of whom had significant fibrosis, 30.8% had advanced fibrosis and 15.4% had cirrhosis. In the multivariate analysis, Alb was determined to be an independent predictor of advanced fibrosis (odds ratio=0.823, P=0.034). The area under the receiver operating characteristic curves (AUROCs) of the BAR, GPR, TPR and BARP were statistically significant in predicting severe fibrosis (P<0.05) and were 0.747, 0.684, 0.693 and 0.696, respectively. In assessing advanced fibrosis, the AUROCs for the AAR, APRI, BAR, FIB-4, RPR, TPR and BARP were 0.726, 0.650, 0.742, 0.716, 0.670, 0.735 and 0.750, respectively. The AUROCs for the APRI, BAR, FIB-4, RPR, TPR and BARP for cirrhosis prediction were 0.776, 0.753, 0.821, 0.819, 0.808 and 0.832, respectively. By comparing the AUROCs, it was demonstrated that the diagnostic capabilities of the BARP (P=0.021) and TPR (P=0.044) were superior to those of the APRI in predicting advanced fibrosis. In conclusion, the BAR, BARP and TPR were of predictive value for the grade of liver fibrosis in PBC and Alb had a diagnostic value in identifying early fibrosis. The aforementioned noninvasive indices may be used for predicting histologic stages of PBC.

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Introduction

The chronic cholestatic liver illness known as primary biliary cholangitis (PBC), previously referred to as primary biliary cirrhosis, is characterized by a cycle of immune-mediated destruction of intrahepatic bile ducts. At least two of the following criteria can be used to diagnose PBC in patients: Tests indicating cholestasis in the serum [such as unexplained increase of alkaline phosphatase (ALP) or γ-glutamyl transferase (GGT) levels], positivity for antimitochondrial antibodies (AMA) or PBC-specific antinuclear antibodies, and the presence of cholangitis and nonsuppurative interlobular bile duct damage on histopathology (1). The gold standard for measuring histologic lesions and determining the stage of liver fibrosis remains liver biopsy. However, it has several significant drawbacks, including invasiveness, sampling errors, unpredictability in histological evaluation, risk of severe procedure-related consequences and high cost (2). Considering the benefits-to-risk ratio, liver biopsy is seldom required for diagnosing PBC (1), unless the cases are unusual or it is essential to rule out concurrent liver diseases such as autoimmune hepatitis. PBC has the same potential for progression as other chronic liver disorders, including fibrosis, cirrhosis and consequences of portal hypertension. The major worldwide health issue of liver cirrhosis, which has high morbidity and mortality rates, may be prevented by detecting liver fibrosis early (3). Given the limitations of liver biopsy, there is substantial clinical value in exploring noninvasive, cost-effective, accurate, readily available and reproducible indicators for assessing hepatic fibrosis in individuals with PBC. Hematological parameters are considered reliable indicators of prognosis in PBC (4). Blood indices may be highly informative in evaluating concurrent conditions linked to non-alcoholic fatty liver disease (NAFLD), including atherosclerosis (5). Serum lipid levels are often markedly elevated in PBC, although it has remained uncertain whether this hyperlipidemia is linked to an accelerated development of atherosclerosis. This question was initially inconclusive due to the disease's progressive nature but has gained clinical significance in light of improved survival rates (6).

Various studies have demonstrated the influence of numerous noninvasive markers (7-9) and the application

potential of serum indices in the prediction of (10-12) the fibrosis degree, particularly for NAFLD and viral hepatitis. Examples include the aspartate aminotransferase (AST) to platelet (PLT) ratio index (APRI), magnetic resonance elastography, ultrasound elastography and the fibrosis index based on four variables (FIB-4). However, there are fewer options available for PBC. The diagnostic performances of these noninvasive predictors are diversiform and need to be further confirmed. It is widely recognized that an increase in serum bilirubin and a decrease in serum albumin (Alb) indicate exacerbation and poor prognosis of PBC (1,13). Currently, the bilirubin to Alb ratio (BAR) is mainly used to predict hemolytic disease in a newborn (14) and assess the prognosis of hepatic encephalopathy (15). The association between PBC and BAR has rarely been reported. In order to forecast the phases of liver fibrosis in individuals with PBC, laboratory parameters were analyzed in the present study and the diagnostic value of noninvasive serum indicators was investigated.

Materials and methods

Patient population. Patients with PBC treated at the Affiliated Hospital of Qinghai University (Xining, China) from January 2015 to September 2022 were gathered for this retrospective analysis. The diagnostic criteria are based on recommendations for PBC identification and treatment (1). Adults with PBC were included in the study if they had undergone a liver biopsy with at least 10 portal tracts visible in the pathological examination. Patients were excluded from the study if they met any of the following criteria: i) Concurrent presence of other factors causing chronic liver diseases, such as hepatitis viruses, drug-induced liver damage or other autoimmune hepatitis, and ii) the presence of hematological system disorders or other systemic illnesses.

Data collection. The demographic and laboratory data acquired during the preceding week before the biopsy included age, gender, AST, red cell distribution width, PLT count, alanine aminotransferase (ALT), ALP, GGT, total bilirubin (TBil) and Alb.

Liver biopsy. Informed consent was obtained from all of the patients before liver biopsy. Under computerized tomography or ultrasonographic supervision, a needle biopsy was carried out using a 16G disposable needle. The liver specimens were pierced and at least 1.5 cm of the length was required. The liver specimens were then collected, fixed with 4% formaldehyde solution, embedded in paraffin, sliced into 2-3 mm slices and stained for pathological analysis using hematoxylin-eosin and Masson's trichrome stains. Two qualified pathologists used Scheuer's classification to analyze the results of liver histology as follows: F1, periportal fibrosis; F2, a few fibrotic septa; F3, several septa; and F4, cirrhosis. Staging as F1 was considered to indicate significant fibrosis; otherwise, it suggested minimal fibrosis. Staging as F3 was used to identify advanced fibrosis; otherwise, it denoted early fibrosis.

Index computation without intervention. The following formulae were used to determine the AST to ALT ratio (AAR), APRI (ULN:upper limit of normal value), bilirubin to Alb ratio (BAR), FIB-4, GGT to PLT ratio (GPR), red blood cell distribution width (RDW) to PLT ratio (RPR) and TBil to PLT ratio (TPR):

i) AAR=AST (IU/l)/ALT (IU/l)
ii) APRI=[AST (IU/l)/ULN (IU/l)/PLT (10^9/l)]x100
iii) BAR=TBil (mg/dl)/Alb (g/dl)
iv) FIB-4=age (years) x AST (IU/l)/[PLT (10^9/l) x ALT (IU/l)$^{1/2}$]
v) GPR=GGT (IU/l)/PLT (10^9/l)
vi) RPR=RDW (%)/PLT (10^9/l)
vii) TPR=TBil (μmol/l)/PLT (10^9/l)

Statistical analysis. All statistical analyses were conducted using the MedCalc statistical program version 20.0.4 (MedCalc Software Ltd.) and SPSS software version 22.0 (IBM Corp.). The mean and standard deviation were used to describe quantitative data with a normal distribution, while the median (interquartile range) was used to express continuous data with a non-normal distribution. Numbers (percentages) were used for presenting categorical data. Student's t-tests were used for normally distributed variables, Mann-Whitney U-tests for non-normally distributed continuous variables and the Chi-squared test for categorical variables to compare groups. To identify fibrosis predictors, single-variable logistic regression analysis was performed. Subsequently, multiple logistic regression models were constructed by incorporating fibrosis-related variables. The receiver operating characteristic (ROC) curve was utilized to calculate the diagnostic accuracies of noninvasive indices. The highest sum of specificity and sensitivity was used to determine the best cut-off values for the fibrosis diagnosis. Using DeLong's test, the area under the ROC curve (AUROC) was used to assess the diagnostic performance and compare the AUROCs of various noninvasive markers. A 2-sided $P<0.05$ was considered to indicate statistical significance.

Results

Characteristics of the study population. The present study included 78 patients with PBC who underwent liver biopsies. Their average age was 54.0±9.3 years and the cohort comprised 68 (87.2%) women and 10 (12.8%) men. Among them, 67 (85.9%) were positive for AMA. In terms of the Scheuer fibrosis staging, there were 12 (15.4%) patients with F1, 42 (53.8%) patients with F2, 12 (15.4%) patients with F3 and 12 (15.4%) patients with F4. Significant variations in TBil, BAR, GPR and TPR were observed between negligible fibrosis (<F2) and considerable fibrosis (≥F2). Patients with advanced fibrosis (≥F3) showed decreased PLT and Alb and elevated levels of TBil, AAR, APRI, BAR, FIB-4, RPR and TPR compared to those with early fibrosis (F3). Lowered PLT and Alb and elevated RDW, TBil, APRI, BAR, FIB-4, RPR and TPR were seen in patients with cirrhosis (F4). Table I displays the demographic and laboratory characteristics of the patients.

Logistic regression analysis. First, univariate analysis was used to evaluate variables related to cirrhosis, advanced fibrosis and substantial fibrosis. In the univariate analysis, none of the factors was significantly linked with fibrosis ($P\geq0.05$). PLT

Table I. Demographical and laboratory parameters of the subjects with primary biliary cholangitis (n=78).

Variable (normal range)	Insignificant fibrosis (F1; n=12)	Significant fibrosis [F2+F3+F4; n=66 (86.4%)]	P-value	Early fibrosis (n=54)	Advanced fibrosis [F3+F4; n=24 (30.8%)]	P-value	Non cirrhosis (n=66)	Cirrhosis [F4; n=12 (15.4%)]	P-value
Female sex	10 (83.3)	58 (87.9)	0.665	46 (85.2)	22 (91.7)	0.429	57 (86.4)	11 (91.7)	0.613
Age, years	55.2±8.2	53.7±9.5	0.628	53.3±1.2	55.5±2.0	0.319	53.6±1.2	55.9±2.2	0.364
PLT, 10^9/l (125-350)	187.0±141.8	118.0±117.5	0.259	145.5±127.0	96.0±92.0	0.019	145.5±122.5	61.0±49.8	<0.001
RDW, % (12.3-14.8)	13.6±2.5	13.7±3.5	0.961	13.5±2.0	14.5±3.7	0.109	13.5±2.1	15.8±2.7	0.029
ALT, IU/l (7-40)	71.0±53.3	54.0±48.0	0.724	59.0±39.5	45.5±62.8	0.346	59.0±41.8	45.5±61.8	0.648
AST, IU/l (13-35)	47.0±59.5	62.0±49.8	0.372	54.0±43.3	82.5±68.3	0.211	54.0±44.8	85.0±51.3	0.205
GGT, IU/l (7-45)	176.5±294.3	292.5±409.5	0.083	282.0±379.8	242.5±411.3	0.991	282.0±392.0	197.5±238.3	0.430
ALP, IU/l (50-135)	217.5±273.5	265.0±260.5	0.315	261.5±267.5	260.0±222.3	0.717	261.5±273.8	253.5±116.8	0.901
Alb, g/l (40-55)	40.5±3.2	37.6±6.5	0.110	39.9±5.0	35.8±7.7	0.001	39.5±6.1	35.8±7.8	0.008
TBil, mg/dl (<1.35)	0.6±0.2	1.1±1.7	0.004	0.8±1.0	1.6±3.1	0.001	0.9±1.1	1.8±3.5	0.011
AAR	1.03±0.42	1.06±0.53	0.497	0.97±0.39	1.41±0.88	0.002	1.04±0.42	1.19±1.31	0.114
APRI	0.71±2.00	1.37±1.64	0.250	1.10±1.60	2.03±2.91	0.035	1.07±1.64	2.52±1.74	0.002
BAR	0.16±0.04	0.30±0.40	0.007	0.21±0.26	0.47±0.72	0.001	0.23±0.33	0.51v1.39	0.006
FIB-4	2.20±4.83	3.77±5.20	0.184	2.79±3.68	6.64±6.78	0.002	2.96±3.95	8.44±4.44	<0.001
GPR	1.77±5.34	6.05±6.62	0.043	4.83±6.44	6.88±7.16	0.135	4.83±6.60	7.44±9.07	0.124
RPR	0.07±0.12	0.11±0.13	0.601	0.09±0.11	0.16±0.19	0.017	0.09±0.11	0.24±0.14	<0.001
TPR	0.07±0.16	0.17±0.46	0.034	0.13±0.21	0.35±0.87	0.001	0.13±0.24	0.53±1.02	0.001

Values are expressed as n (%) or the mean ± standard deviation. PLT, platelets; RDW, red blood cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; Alb, albumin; Tbil, total bilirubin; AAR, aspartate aminotransferase to alanine aminotransferase ratio; APRI, aspartate aminotransferase to platelet ratio index; BAR, bilirubin to albumin ratio; FIB-4, fibrosis index based on the four factors; GPR, γ-glutamyl transpeptidase to platelet ratio; RPR, red cell distribution width to platelet ratio; TPR, total bilirubin to platelet ratio.

Table II. Factors influencing progressive fibrosis in subjects with primary biliary cholangitis.

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	P-value	OR (95% CI)	P-value
Female sex	1.913 (0.375-9.770)	0.436		
Age	1.027 (0.975-1.083)	0.316		
PLT	0.993 (0.986-0.999)	0.035	0.997 (0.990-1.005)	0.482
RDW	1.266 (0.969-1.653)	0.084		
ALT	0.996 (0.984-1.009)	0.584		
AST	1.006 (0.997-1.016)	0.183		
GGT	1.000 (0.998-1.002)	0.873		
ALP	1.000 (0.998-1.002)	0.960		
Alb	0.802 (0.705-0.912)	0.001	0.833 (0.725-0.957)	0.010
TBil	1.414 (1.069-1.869)	0.015	1.205 (0.892-1.627)	0.225

PLT, platelets; RDW, red blood cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; Alb, albumin; Tbil, total bilirubin; OR, odds ratio.

Table III. Factors connected to cirrhosis in subjects with primary biliary cholangitis.

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	P-value	OR (95% CI)	P-value
Female sex	1.737 (0.199-15.128)	0.617		
Age	1.028 (0.961-1.099)	0.427		
PLT	0.975 (0.958-0.993)	0.006	0.979 (0.956-1.002)	0.070
RDW	1.470 (1.050-2.059)	0.025	1.042 (0.624-1.740)	0.874
ALT	0.995 (0.978-1.012)	0.573		
AST	1.001 (0.991-1.012)	0.811		
GGT	0.999 (0.996-1.001)	0.311		
ALP	0.999 (0.995-1.002)	0.487		
Alb	0.823 (0.719-0.941)	0.004	0.877 (0.755-1.019)	0.086
TBil	1.275 (1.012-1.607)	0.040	1.047 (0.784-1.398)	0.755

PLT, platelets; RDW, red blood cell distribution width; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ALP, alkaline phosphatase; Alb, albumin; Tbil, total bilirubin; OR, odds ratio.

[odds ratio (OR)=0.993, P=0.035], Alb (OR=0.802, P=0.001) and TBil (OR=1.414, P=0.015) exhibited negative correlations with advanced fibrosis, whereas the latter had a positive correlation. In the multivariate analysis, only Alb (OR=0.833, P=0.010) was an independent negative predictor of advanced fibrosis (Table II). In addition, cirrhosis was inversely linked with PLT (OR=0.975, P=0.006) and Alb (OR=0.823, P=0.004). Positive correlations were found between RDW (OR=1.470, P=0.025) and TBil (OR=1.275, P=0.040) and cirrhosis. In the multivariate analysis, none of the factors was an independent predictor of cirrhosis (Table III).

Development of a novel index called BAR x RPR (BARP). From the above results, PLT, RDW, Alb and TBil were statistically significant laboratory parameters among different degrees of fibrosis. Consequently, a novel index was envisioned that combined the BAR with RPR. The novel index called BARP was conceived, calculated as BAR x RPR. The BARP was compared among different fibrosis stages and it was found that there were statistically significant differences between significant fibrosis and insignificant fibrosis (P=0.032), advanced fibrosis and early fibrosis (P<0.001), and cirrhosis and non-cirrhosis (P<0.001), respectively (Table IV).

Diagnostic performances of noninvasive indices. The diagnostic performance of each noninvasive index was estimated using ROC curves. Table IV displays the AUROC, sensitivity, specificity and cutoff values. The AUROCs for BAR, GPR, TPR and BARP demonstrated statistically significant coefficients for predicting substantial liver fibrosis (≥F2) with P<0.05. Their respective values were 0.747 (95% CI: 0.598-0.897), 0.684 (95% CI: 0.510-0.858), 0.693 (95% CI:

Table IV. Ability of each non-invasive marker to diagnose cirrhosis, advanced fibrosis and severe fibrosis.

	Significant fibrosis					Advanced fibrosis					Cirrhosis				
Non-invasive index	AUROC (95% CI)	Cut-off	Sensitivity	Specificity	P-value	AUROC (95% CI)	Cut-off	Sensitivity	Specificity	P-value	AUROC (95% CI)	Cut-off	Sensitivity	Specificity	P-value
AAR	0.562 (0.399-0.724)	1.469	22.7	100.0	0.497	0.726 (0.597-0.855)	1.360	54.2	88.9	0.002	0.644 (0.466-0.822)	1.716	41.7	89.4	0.114
APRI	0.604 (0.408-0.799)	0.551	81.8	50.0	0.256	0.650 (0.508-0.792)	1.818	62.5	70.4	0.035	0.776 (0.652-0.899)	1.833	83.3	69.7	0.002
BAR	0.747 (0.598-0.897)	0.176	75.8	83.3	0.007	0.742 (0.622-0.863)	0.286	79.2	68.5	0.001	0.753 (0.601-0.904)	0.341	83.3	65.2	0.006
FIB-4	0.621 (0.430-0.812)	2.536	69.7	66.7	0.184	0.716 (0.587-0.845)	2.731	87.5	50.0	0.002	0.821 (0.720-0.921)	3.598	100	57.6	<0.001
GPR	0.684 (0.510-0.858)	1.467	86.4	50.0	0.043	0.606 (0.473-0.740)	1.963	87.5	31.5	0.135	0.640 (0.487-0.793)	2.449	91.7	36.4	0.124
RPR	0.597 (0.406-0.787)	0.077	71.2	58.3	0.289	0.670 (0.537-0.802)	0.149	58.3	74.1	0.017	0.819 (0.721-0.918)	0.136	91.7	66.7	<0.001
BARP	0.696 (0.535-0.857)	0.009	90.9	41.7	0.032	0.750 (0.635-0.865)	0.031	79.2	57.4	<0.001	0.832 (0.729-0.935)	0.034	100	59.1	<0.001
TPR	0.693 (0.530-0.857)	0.097	66.7	66.7	0.034	0.735 (0.618-0.852)	0.075	91.7	42.6	0.001	0.808 (0.699-0.917)	0.141	100	56.1	0.001

AAR, aspartate aminotransferase to alanine aminotransferase ratio; APRI, aspartate aminotransferase to platelet ratio index; BAR, bilirubin to albumin ratio; FIB-4, fibrosis index based on the four factors; GPR, γ-glutamyl transpeptidase to platelet ratio; RPR, red cell distribution width to platelet ratio; BARP, BARxRPR, TPR, total bilirubin to platelet ratio; AUROC, area under the receiver operating characteristic curve.

0.530-0.857) and 0.696 (95% CI: 0.535-0.857), as illustrated in Fig. 1. Except for GPR (P=0.135), all of the noninvasive indicators' AUROCs for differentiating advanced fibrosis (F3) exhibited statistically noteworthy results (P<0.05; Fig. 2). The AUROCs of AAR, APRI, BAR, FIB-4, RPR, TPR and BARP were 0.726 (95%CI: 0.597-0.855), 0.650 (95%CI: 0.508-0.792), 0.742 (95%CI: 0.622-0.863), 0.716 (95%CI: 0.587-0.845), 0.670 (95%CI: 0.537-0.802), 0.735 (95%CI: 0.618-0.852) and 0.750 (95%CI: 0.635-0.865), respectively. For the prediction of cirrhosis (=F4), the AUROCs of APRI, BAR, FIB-4, RPR, TPR and BARP were 0.776 (95%CI: 0.652-0.899), 0.753 (95%CI: 0.601-0.904), 0.821 (95%CI: 0.720-0.921), 0.819 (95%CI: 0.721-0.918), 0.808 (95%CI: 0.699-0.917) and 0.832 (95%CI: 0.729-0.935), respectively, all of which were statistically significant (P<0.05; Fig. 3). When predicting significant fibrosis, there were no statistically significant differences among the BAR, GPR, TPR and BARP (P≥0.05; Fig. 1). To diagnose advanced fibrosis, the AUROCs of the BARP and TPR outperformed those of the APRI (P=0.021 and 0.044, respectively; Fig. 2). However, when assessing cirrhosis, there were no statistically significant differences between APRI, BAR, BARP, FIB-4, TPR and RPR (P≥0.05; Fig. 3).

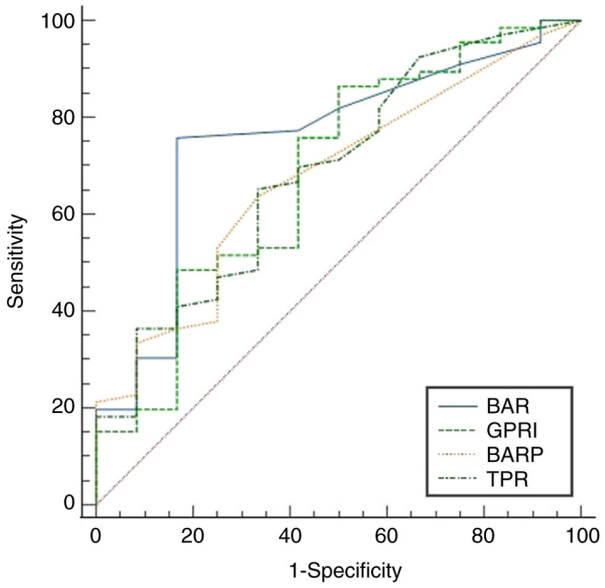

Figure 1. Receiver operating characteristic curves for the prediction of substantial fibrosis using the BAR, GPR, TPR and BARP. BAR, bilirubin to albumin ratio; GPR, γ-glutamyl transpeptidase to platelet ratio; TPR, total bilirubin to platelet ratio; BARP, BAR x red cell distribution width to platelet ratio.

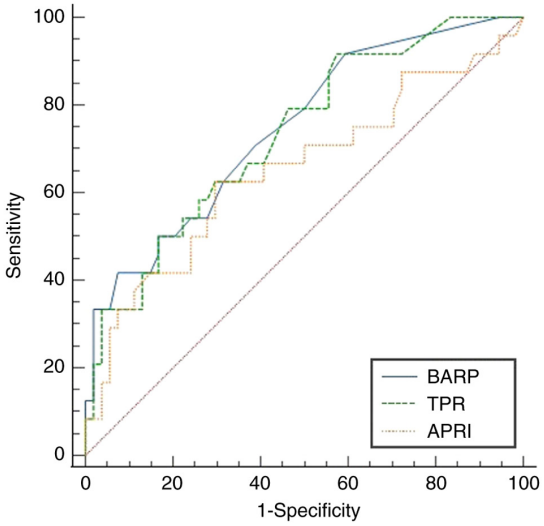

Figure 2. Receiver operating characteristic curves for advanced fibrosis prediction using the BARP, TPR and APRI. BARP, bilirubin to albumin ratio xRPR; TPR, total bilirubin to platelet ratio; APRI, aspartate aminotransferase to platelet ratio index.

Discussion

PBC is an autoimmune cholestasis of the liver that primarily affects females. Cholestatic biochemistry along with the presence of AMA or other PBC-specific autoantibodies can typically lead to a precise diagnosis of PBC in the majority of patients. Liver biopsy is no longer recommended as a diagnostic technique, with the exception of atypical cases, such as those with low antibody levels or no PBC-specific autoantibodies, because of its invasive nature, cost, potential for sampling errors, and the risk of severe complications (1). Effective treatments can facilitate slower progression and better prognosis (16). However, the majority of individuals with PBC are often asymptomatic and the condition is undetectable in the early stages. If no effective treatment is available, the condition tends to progress in most patients. PBC is a chronic autoimmune cholestatic liver disease that can deteriorate rapidly in the end stage and culminate in biliary cirrhosis and complications related to portal hypertension over time (17). Therefore, a condition with a lower overall survival rate than that of the general population may substantially reduce the quality of life for those affected and require long-term monitoring. Early diagnosis, risk assessment, treatment and long-term management are vital for patients with PBC (18). Histological progression is closely related to prognosis in PBC. Therefore, identifying liver fibrosis at an early stage is of critical importance for preventing cirrhosis and improving the prognosis of patients with PBC.

The present study aimed to explore new indices and evaluate their diagnostic performance in predicting the stages of liver fibrosis in patients with PBC. The results revealed that individuals with severe fibrosis exhibited elevated levels of TBil and GGT in their blood. Furthermore, advanced fibrosis was associated with higher TBil levels and lower levels of PLT and Alb. There were statistically significant differences in PLT, RDW, Alb and TBil levels between the cirrhosis and non-cirrhosis groups. Based on these results, it was hypothesized that a novel noninvasive indicator called BARP, derived from BAR x RPR, could be a valuable tool for predicting liver fibrosis in PBC. Alb was found to be a distinct, unfavorable predictor of advanced fibrosis in the multivariate analysis. Of note, unlike other noninvasive indices, the BAR, TPR and BARP exhibited statistically significant differences in their diagnostic performance for significant fibrosis, advanced fibrosis and cirrhosis. The present result suggested that BAR, with the highest AUROC value (0.747, 95%CI: 0.598-0.897), is a reasonable predictor of significant fibrosis. Furthermore, the TPR and BAPR also showed definite advantages in assessing advanced fibrosis (AUROC: 0.735, 0.750; 95%CI: 0.618-0.852,

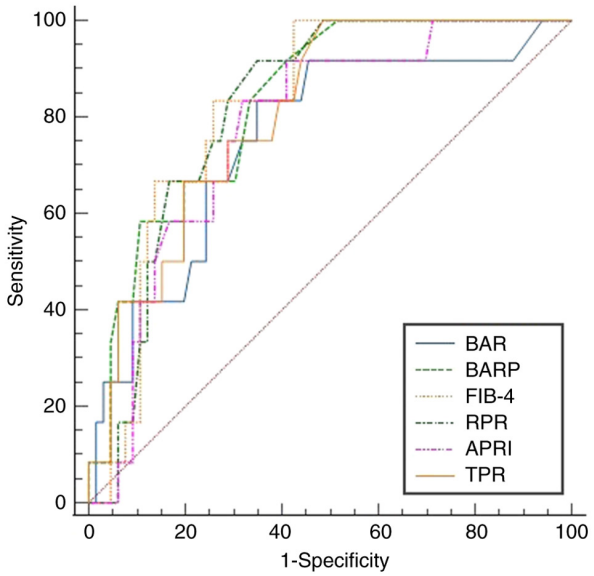

Figure 3. ROC curves for predicting cirrhosis using the APRI, BAR, BARP, TPR, FIB-4 and RPR. APRI, aspartate aminotransferase to platelet ratio index; BAR, bilirubin to albumin ratio; BARP, BAR x red cell distribution width to platelet ratio; TPR, total bilirubin to platelet ratio; FIB-4, fibrosis index based on the four factors.

0.635-0.865, respectively) and cirrhosis (AUROC: 0.808, 0.832; 95% CI: 0.699-0.917, 0.729-0.935, respectively). The AUROCs for identifying advanced fibrosis were greater for BARP and TPR compared to APRI (P=0.021, 0.044, respectively). The AAR, APRI, FIB-4, GPR and RPR had AUROCs that were either slightly inferior to or comparable to those of the BAR, TPR and BARP. To the best of our knowledge, the present study was the first to use both the BAR index and the new BARP index to predict the stages of PBC fibrosis.

Various studies have reported on the value of ultrasound elastography in predicting liver fibrosis (19,20). Consistent with previous research, transient elastography has a higher ability to diagnose the liver fibrosis stage than liver stiffness measurement (21,22). The ideal cutoff value for each liver condition varies depending on the etiology of the condition. However, the accuracy of the results is influenced by factors such as liver inflammation, cholestasis, congestion and the patient's somatotype, and it is not suitable for patients with ascites around the liver. Of note, it is difficult to distinguish the differentiation between adjoining liver fibrosis stages because of the extensive overlap of cutoff values. The clinical use of blood biomarkers or indices in predicting the degree of liver fibrosis has also been the subject of several investigations (23,24). Serum indices such as RDW, RPR, AAR, APRI and GPR have a certain utility for evaluating liver fibrosis. The TPR was found to more reliably predict early liver fibrosis in PBC in the study by Jiang *et al* (25), and its AUROC was greater than that of the AAR, APRI, FIB-4 and RPR. The outcomes of their study are comparable to those of the present study. The histologic stage of individuals with PBC is associated with RDW, RPR and the RDW to lymphocyte ratio, and these tests demonstrate superior diagnostic capabilities compared to typical indices such as APRI, FIB-4 and AAR (26-28). In prior reports, the GPR (29) and mean platelet volume (30) were found to have certain utility for identifying advanced fibrosis in PBC. However, the diagnostic capabilities of those studies could not be fully examined due to their small size or absence of a 95% CI for the AUROC. Compared to the AAR, FIB-4 and APRI, the current investigation demonstrated that the growth arrest-specific gene 6 protein to Alb ratio was more likely to accurately diagnose advanced fibrosis (31). The diagnostic performances and cutoff values of these noninvasive procedures and markers are multifarious. To date, no consensus has been reached regarding the most effective noninvasive procedure, serum index or the optimal cutoff value. Given the limitations of liver biopsy, noninvasive measurement of hepatic fibrosis has become the standard. This field of study is ongoing and the current findings require further confirmation.

The present study has certain limitations. First, it is a retrospective study without sampling and lacks a validation cohort. Furthermore, certain patients included in the study had received ursodeoxycholic acid treatments and therefore, the accuracy of the results needs to be verified in further investigations. Finally, the diagnostic performance of FibroScan was not assessed, as only a limited number of individuals had undergone the test. Larger, more diverse studies with robust methodologies are needed to validate these markers and determine their clinical relevance in managing PBC-related liver fibrosis.

In conclusion, the present study demonstrated that Alb is useful for early fibrosis prediction, while the BAR, BARP and TPR offer benefits in assessing liver fibrosis in PBC. All of these can be easily calculated using standard blood counts and inexpensive biochemical markers. However, the accuracy of these results needs to be substantiated through multicenter collaboration and randomized trials.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Data curation: YL and MJZ. Formal analysis: YL. Data analysis: YL, MJZ, XHW and SHL. Writing-original draft: YL. Writing-review and editing: SL. All authors have read the final version of the manuscript and checked and approved the authenticity of the raw data.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Affiliated Hospital of Qinghai University (Xining, China). All procedures followed were in accordance with the

declaration of Helsinki as revised in 2008. All participants provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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